Short term pulmonary function trends are predictive of mortality in interstitial lung disease associated with systemic sclerosis

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Abstract

Objective: To determine the prognostic value of pulmonary function test (PFT) trends at one and two years in interstitial lung disease associated with systemic sclerosis (SSc-ILD), (should we also add the aim of defining optimal outcomes for clinical trials here at the start?).

Methods: The prognostic significance of PFT trends at one year (n=162), and two years (n=140) was examined against 15 year survival. PFT trends, expressed as continuous and categorical change in separate analyses, were examined against mortality in univariate and multivariate models. SSc-ILD was defined at presentation as limited or extensive using the UKRSA staging system.

Results: At one year, PFT trends were predictive of mortality only in patients with extensive SSc-ILD: categorical FVC change, alone or in combination with categorical change in DLco, had greater prognostic significance than continuous FVC change or trends in other PFT variables. Taking into account both prognostic value and sensitivity to change, the optimal definition of progression for trial purposes was an FVC and DLco composite, consisting of *either* an FVC decline from baseline≥10% *or* an FVC decline of 5-9% in association with a DLco decline of ≥15%. At two years, DLco (? Or have you said gas transfer because you want to include both DLco and Kco?)) trends (is this both categorical and continuous?) had the greatest prognostic significance, in the whole cohort and in limited disease. However, in extensive disease, the composite end-point defined above was the strongest prognostic determinant. Larger changes were required in the FVC/DLco ratio than in Kco to achieve prognostic significance.

Conclusion: Our findings provide support for routine spirometric and gas transfer monitoring in SSc-ILD, based on linkages to long-term outcome, with further evaluation of a composite FVC and DLco end-point warranted for trial purposes.

Introduction

At presentation, the broad approach to prognostic evaluation differs little between systemic sclerosis-associated interstitial lung disease (SSc-ILD) and idiopathic pulmonary fibrosis (IPF). In both diseases, mortality is linked to baseline disease severity, variably quantified using pulmonary function tests and HRCT (1-5). However, prognostic evaluation in IPF is more nuanced than in SSc-ILD in one important regard. It has been demonstrated in a large number of IPF studies that serial decline in forced vital capacity (FVC) over six to 12 months is a powerful predictor of mortality (6-15).Based on these findings, FVC is now universally regarded as central to routine monitoring in IPF (16). Furthermore, links between short term FVC change and mortality provide support for the choice of FVC as the primary end-point in current IPF trials (17;18). .

In SSc-ILD, limited (19) data currently exist examining the relationship between short-term pulmonary function trends and intermediate to long-term survival. Although conventional pulmonary function thresholds have been explored for clinical practice (19), little is known about the optimal measure for use in clinical trials. Monitoring strategies in clinical practice and the choice of FVC as a primary end-point in treatment trials in SSc-ILD have largely been based upon IPF studies. However, important caveats in extrapolating from IPF data include the fact that SScILD is less progressive than IPF (potentially influencing the optimal expression of FVC trends in prognostic evaluation) and the existence of disproportionate pulmonary vasculopathy in many SSc-ILD patients (20).

We have evaluated relationships in SSc-ILD between pulmonary function trends at one year and at two years against 15 year survival in a large cohort with definitive follow-up information. Our findings have implications both for routine clinical monitoring and future study design in SSc-ILD.

Methods

Patients

Data were reviewed from 215 SSc-ILD patients from a previously published cohort (in which baseline variables were examined against outcome) (3). Exclusion criteria comprised of: 1) death within nine months of follow up (n=15); no serial lung function measurements within the first 12 months [because of a shared model of care (n=38)]. The remaining 162 patients made up the study population. The study cohort of 162 patients was compared to the 38 excluded patients with more than nine months of follow up in order to exclude major selection bias.

Clinical data

Smoking status was defined as never, former (>1 cigarette/day for >1 year) or current smoking. Treatment was defined as corticosteroid (prednisolone ≥1mg/day) and/or immunosuppressant (cyclophosphamide, azathioprine, mycophenolate, cyclosporin) therapy. Treatment status was sub-categorised as "intention to treat" (treatment instituted within three months of presentation or continuation of pre-existing treatment) or "intention to observe" (the remaining patients on no therapy at three months of follow-up). Trans-thoracic echocardiography and high resolution computed tomography (HRCT) of the chest were performed as previously reported (21). The presence of pulmonary hypertension (PHT) on echocardiography was defined as a pulmonary arterial systolic pressure of ≥40mmHg (22). The UKRSA severity staging system, integrating disease extent on HRCT and forced vital capacity (FVC) levels, was used to sub-classify disease severity at presentation as "limited" or "extensive" (3)

Pulmonary function data

Standard pulmonary function tests (PFTs) (expressed as absolute values and percentage predicted) were

performed (23), including a) forced vital capacity (FVC) levels, b) gas transfer (DLco) levels, c) gas transfer co-efficient (Kco) levels, d) the FVC/ DLco ratio. PFT measurements were obtained at a) baseline, b) 12 months (range 9 to 18 months) from baseline, and c) 24 months (range 18 to 30 months) from baseline. Pulmonary function trends were analyzed as continuous and categorical change in separate models. PFT change was computed as a percentage relative change from baseline absolute values, i.e.. a 10% relative decline in FVC equates to an FVC change from a baseline value of 2.0 litres to 1.8 litres.

Categorical PFT trends at 12 months were defined as: a) FVC decline $\geq$10%; b) FVC decline $\geq$15%; c) DLco decline $\geq$15%; d)FVC decline $\geq$10% or DLco decline $\geq$15%; e) FVC decline $\geq$10% and DLco decline $\geq$15%; f) Kco decline $\geq$10% (why was the threshold of 10% chosen? Even if less variable than DLco, is there a reason for not looking at 15%?); g) FVC/DLco ratio rise $\geq$10%; h) FVC/DLco ratio rise $\geq$15%; i) FVC/DLco ratio rise $\geq$ 20%. Trends examined at 24 months consisted of a), c) and f)-i). In addition, composite categorical decline (CCD), utilized in an IPF trial (24), was defined as *either* FVC decline $\geq$10% *or* FVC decline of 5 -9% in combination with a DLco decline $\geq$15%.

Data analysis

Analyses were performed using STATA software (Stata data analysis software; Computing Resource Centre, Santa Monica, CA). Data were expressed as means (SD) or medians (range), depending on distribution. Groups were compared using Student's *t* test, Wilcoxon rank sum, chi-squared statistics and Fisher's exact test, as appropriate. A p-value of <0.05 was considered significant. 15-year survival was examined using univariate proportional hazards analysis against baseline variables, change in individual PFTs at 12 months and change in individual PFTs at 24 months.

Stepwise multivariate models were constructed in order to identify the determinants of mortality after 12 months of follow-up and, separately, after 24 months of follow-up. In both models, key covariates included baseline stage of interstitial lung disease (limited versus extensive disease), baseline severity of pulmonary vascular limitation (percent predicted Kco), progression of interstitial lung disease (categorical decline in FVC) and progression of pulmonary vascular limitation (categorical decline in Kco). Other covariates

consisted of age, gender, treatment status (“intention to treat” versus “intention to observe”), smoking status and the presence or absence of pulmonary hypertension, as judged by echocardiography.

RESULTS

Baseline data

Demographic data and baseline pulmonary function tests are summarised in Table 1. The cohort was characterised by a female predominance and the presence of "limited disease" in 70% of cases. There were 84 deaths (52%) during a median follow-up of 155 months. There were no significant differences between the study cohort (n=162) and excluded patients (n=38) in gender (p=0.33), smoking status (p=0.57), baseline pulmonary function tests [FVC levels (p=0.77), DLco levels (p=0.32), Kco levels (p=0.55)] or survival (p=0.65). Patients in the excluded cohort were older [mean age 53 years versus 48 years (p=0.03)].

At baseline, FVC levels (hazards ratio [HR] = 0.98; 95% confidence intervals [CI] = 0.97, 1.00; p<0.01), DLco levels (HR = 0.96; 95% CI = 0.94, 0.97; p<0.0005), Kco levels (HR=0.97; 95% CI=0.96, 0.99; p<0.0005), FVC/DLco ratio (HR=2.73; 95% CI=1.79, 4.18; p<0.0005), disease stage (HR=3.01; 95% CI=1.90, 4.74; p<0.0005) and age (HR = 1.04; 95% CI = 1.02, 1.05; p<0.0005) were independent determinants of mortality, whereas gender and smoking status were not.

Pulmonary function trends at 12 months and their prognostic significance:

The prognostic significance of 12 month trends in FVC and DLco are shown in Table 2. Continuous change in FVC and DLco was not predictive of outcome, with the exception of continuous FVC change in patients with extensive disease. By contrast, categorical decline in FVC and/or DLco (using different thresholds) was predictive of mortality in all analyses in the whole cohort and in patients with extensive disease (see Figure 1 for FVC 10% change threshold data), although never predictive of mortality in patients with limited disease , regardless of threshold used (is this what you mean?) Categorical decline was most strongly predictive of mortality, both in whole cohort and in the extensive disease subgroup, when quantified as a) rise (why rise? Isn't this the categorical decline category? Even if this is derived from a score which increases the greater the decline, may be worth explaining, as when you look at the figure, it seems it is the decline and therefore strange to speak of rise…)in the CCD (Figure 2); or b) decline in both FVC (>10%?) and/or DLco (>15%?), (found to be a relatively insensitive measure of decline) in the whole cohort, and this finding was replicated in patients with extensive disease (Table 2)

Kco decline (analysed as continuous change and as a decline of 10% in separate models) and increases in the

FVC/DLco ratio (analysed as continuous change and as rises of 10%, 15% or 20% in separate models) were not predictive of mortality in the whole cohort, in limited disease or extensive disease (data not shown).

In patients with extensive disease (and how about in the whole group?), the prognostic value of individual variables was unchanged when analysis was confined to patients in the "intention to treat" sub-group (n=35): continuous change in FVC, p=0.03; 10% decline in FVC, p<0.01; a 15% decline in FVC, p<0.05; a 10% decline in FVC and a 15% decline in DLco, p=0.04; rise in CCD, p<0.001.

Multivariate analysis at 12 months

On stepwise proportional hazards analysis of the whole cohort, the independent determinants of mortality were age (HR = 1.03; 95%CI = 1.01, 1.05; p<0.005), baseline stage of disease (HR = 2.30; 95%CI = 1.43, 3.70; p<0.001), baseline Kco (HR = 0.98; 95%CI = 0.96, 0.99; p<0.005), rise in CCD at 12 months? (HR = 2.25; 95%CI = 1.39, 3.63; p<0.001) and the (at baseline?) presence of pulmonary hypertension (HR = 2.05; 95%CI = 1.07, 3.91; p=0.03) . and what about the decline in FVC > 10%, I imagine it does not hold ? Covariates discarded from the model consisted of gender, treatment status ("intention to treat" versus "intention to observe", smoking status and decline in Kco ≥10%.

Pulmonary function trends at 24 months and their prognostic significance:

As shown in Table 3, prognostically significant pulmonary function trends in the whole cohort consisted of change in DLco (categorical decline, Fig3a), change in Kco (both continuous change and categorical decline, Fig3b) and change in the FVC/DLco ratio (categorical rise? by 15% and 20%, Fig3c). Changes in FVC and the CCD had no prognostic value. Prognostically significant trends in patient severity sub-groups were confined to categorical changes in Kco and the FVC/DLco ratio in limited disease and change in the CCD in extensive disease.

Analyses were repeated separately in the intention to treat (n=66) and intention to observe (n=74) sub-groups. A categorical decline in DLco of 15% was the only variable to have prognostic significance both in

the intention to treat sub-group (HR=2.06; 95% CI 1.03 to 4.12, p=0.04) and the intention to observe sub-group (HR = 2.07, 95%CI 1.05 to 4.08, p=0.04). A categorical decline in Kco of 10% remained significant in the intention to observe sub-group (p<0.005) but was only marginally significant in the intention to treat sub-group (p=0.11).

Multivariate analysis at 24 months

On stepwise proportional hazards analysis of the whole cohort, the independent determinants of mortality were age? (HR = 1.04; 95%CI = 1.02, 1.06; p<0.0005), baseline stage of disease (HR = 2.54; 95%CI = 1.52, 4.24; p<0.0005), baseline Kco (HR = 0.97; 95%CI = 0.95, 0.98; p<0.0005), decline in Kco ≥10% (HR = 2.88; 95%CI = 1.62, 5.10; p=0<0005) and decline in FVC ≥10% (HR = 1.83; 95%CI = 1.07, 3.12; p=0.03). You don't mention DLCO, does it not hold on multivariate? Covariates discarded from the model consisted of gender, treatment status (intention to treat versus intention to observe), smoking status and pulmonary hypertension. You don't mention the multivariate of extensive disease subgroup, but in the abstract you mention that CCD is the strongest determinant in this subgroup, does it hold on multivariate?

Discussion

We report that in an SSc-ILD cohort followed for over 15 years, pulmonary function trends at one and two years were predictive of intermediate to long-term mortality. At one year, changes in FVC provided the most accurate prognostic information, with optimal expression of FVC change consisting of either a ≥10% decline in FVC from baseline or a marginal (5-9%) decline in FVC in association with a definite (i.e.≥15%) decline in DLco. The prognostic value of pulmonary function trends in the whole cohort was entirely ascribable to disease progression in patients with extensive SSSc-ILD. At two years, serial gas transfer trends predicted survival much more accurately than FVC trends.

Pulmonary function trends in the routine monitoring of SSc-ILD

These findings support the view that the same broad approach to routine clinical monitoring is appropriate in SSc-ILD and in IPF. In the 2011 international guideline for the diagnosis and management of IPF (16), the importance of monitoring both FVC and DLco was emphasized. In the current cohort, categorical decline

in both variables at one year, both in isolation and in combination, were predictive of increased long-term mortality. The fact that gas transfer trends at two years had much greater prognostic significance than FVC trends may seem surprising but this observation is consistent with the prognostic value of three year gas transfer trends in a previous smaller SSc-ILD cohort (25). One possible explanation is that progression of SSc-ILD at two years may carry a greater threat to life expectancy when it has an impact on the pulmonary vasculature. In principle, this might also apply to IPF but at present, the prognostic impact of two year pulmonary function trends in IPF is not known. Importantly, a multivariate analysis of baseline data and pulmonary function trends at two years against subsequent survival established that baseline and serial variables relevant to both interstitial lung disease (i.e. baseline disease stage, CCD) and pulmonary vascular disease (i.e. baseline Kco, serial Kco) were all independently predictive of mortality, underlining the importance of continuing to monitor both FVC and DLco in the longer term.

Implications for trial design: cohort enrichment

The findings in the present study support a policy of "cohort enrichment" (i.e. selective recruitment of SSc-ILD patients with extensive disease). The growing consensus that SSc-ILD patients with mild lung involvement should not be recruited in treatment trials is based on the low prevalence of disease progression in that patient sub-group in the scleroderma lung study trial of oral cyclophosphamide (26) and also in the present cohort, although reported only as an integrated statement of "progression-free survival" in our earlier report and not analysed for individual variables (the preceding sentence not very clear) (3). The current findings present an additional argument for "cohort enrichment" for extensive disease in clinical trial recruitment: serial FVC trends (irrespective of the method of quantification) had no long-term prognostic value in patients with limited disease and, thus, lack credibility as clinically relevant end-points in this patient sub-group. Whilst the low prevalence of disease progression in limited disease was a contributing factor, the absence of marginally significant relationships between disease progression and mortality in patients with limited disease suggest that factors other than under-powering are likely to be at play. One possible explanation is that when disease is limited, there is a higher prevalence of transient disease progression than in extensive disease and, therefore, short-term disease progression is less predictive of

longer-term disease behaviour than in extensive disease (in which, by definition, there is a "track record" of repeated disease progression). It is also possible that in limited SSc-ILD, anti-inflammatory therapies (whether given for pulmonary or systemic indications) are more efficacious in stabilizing disease and, thus, more likely to confound linkages between short-term disease progression and long-term outcome.

Implications for trial design: how should FVC change be expressed?

Equally important with regard to study design was the observation that FVC change had no prognostic significance when quantified as a continuous variable. This observation contrasts with findings in IPF (6) and calls into question extrapolation of current practice in IPF trials, in which the most frequent primary end-point is continuous change in FVC. The less progressive nature of SSc-ILD, compared to IPF, may be the most important consideration. It is generally accepted that in IPF, disease progression is the rule, although the rate of progression is variable and decline is interspersed with periods of stability. By contrast, long term stabilization is seen in a significant proportion of SSc-ILD patients, even in extensive disease, and in other patients, progression is much more insidious than typically observed in IPF. As a consequence, it appears likely that a greater proportion of continuous FVC change at one year in SSc-ILD is ascribable to measurement variation, compared to IPF, whereas major FVC change captured by threshold analyses is much less likely to be spurious.

The mode of expression of categorical change in FVC is a contentious area. In clinical cohorts, a relative change of 10% from baseline has been shown to predict mortality in the majority of IPF studies (6;8;11-13;15). An absolute change in FVC of 10% of the predicted normal value also predicts mortality (7;9;27) but this larger amplitude of change is less prevalent than relative change in a given time period (28)). In the current study, mortality was less strongly linked to a 10% decline in FVC than to a) a 15% decline in FVC; or b) both a 10% change in FVC and a 15% change in DLco. However, the low prevalence of these alternative expressions of categorical decline mitigates against their use as trial end-points. Our findings suggest that when the prevalence and the prognostic significance of decline are both taken into account, the optimal definition of categorical decline in FVC for trial purposes may consist of ***either*** a $\geq$10% decline in

FVC ***or*** a 5-9% "marginal" decline in FVC in association with a ≥15% decline in DLco. The use of DLco trend data to indicate that marginal FVC change is likely to be clinically significant in individual patients (i.e. may represent an understatement of FVC change due to measurement variation in those cases) justifies amalgamation of trends in this way(29) and was the basis for an integrated FVC/DLco end-point in a recent IPF trial (24). Our findings support a recent expert group recommendation for use of this end point in future SSc-ILD trials (30).

Change in Kco versus change in the FVC/DLco ratio

Our findings suggest that with regard to monitoring, serial change in the FVC/DLco ratio is inferior to Kco trends. In recent years, the FVC/DLco ratio has been advocated as a marker of pulmonary vasculopathy in systemic sclerosis (31-33). However, the growth in use of this index can only be viewed as surprising. The gas transfer coefficient (Kco) (also known as "DLco/VA") has been used for many decades to quantify uptake in carbon monoxide per unit of alveolar volume (VA). Reduced Kco levels have an inverse correlation with the FVC/DLco ratio and both variables quantify reductions in DLco that are disproportionate to lung volumes. However, Kco has the critically important advantage of the measurement variability of a single variable (measured Kco is used in combination with measured VA to compute DLco). By contrast, the FVC/DLco ratio has the measurement variability of three variables (FVC, VA and Kco). Substantially greater measurement variability is likely to explain the fact that a very large (20%) rise in the FVC/DLco ratio is required to provide the same prognostic guidance as a 10% decline in Kco.

It should be stressed that in all prognostic evaluations of SSc-ILD cohorts, there are important but unavoidable confounding factors. There is no current method of controlling definitively for treatment status as this often changes radically during both short-term and long-term follow-up. We adopted a simplified approach to adjustment for treatment, as in previous work (3), cactegorising patients as being in "intention to observe" or "intention to treat" sub-groups, based on treatment decisions at presentation and during the first three months of follow-up. Taking this dichotomy into account had no influence on our findings when included in multivariate modelling but this does not alter the fact that linkages between pulmonary function

change and mortality might have been much stronger had a robust method of adjusting for treatment effects been possible. Similarly, a reliable means of distinguishing between respiratory and non-respiratory mortality might conceivably have strengthened our findings but in common with previous authors in this field, we viewed this distinction as highly unsafe, especially given the fact that very few deaths occurred at our institution.

In summary, we have examined relationships between short term pulmonary function trends and long term outcome in interstitial lung disease associated with systemic sclerosis. Disease severity at baseline and subsequent pulmonary function trends were independent prognostic determinants. At one year, categorical FVC trends provide the most accurate prognostic information, especially when integrated with DLco trends. At two years, changes in gas transfer are more informative, with Kco trends more accurate prognostically than rises in the FVC/DLco ratio.

Table 1

Age (years)	47.8 ± 12.7
Gender Male:Female	29:133
Smoking status	never=96, ex=53,current=13
Survival	Alive = 78; Dead = 84
Length of follow up (months)	154.6 (9.0 to 180.0)
Disease stage	Limited = 113; Extensive =49
"Intention to treat" at baseline	limited disease 39/113; extensive disease 35/49
Presence of PHT	18/162
Pulmonary function:	
Baseline FEV_1	78.5± 18.3 (% predicted)
Baseline FVC	79.6 ± 21.1 (% predicted)
Baseline DLco	56.2± 16.6 (% predicted)
Baseline Kco	78.0 ± 16.2 (% predicted)
Baseline FVC/DLco	1.48 ± 0.42

Definition of abbreviations: FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; DLco = gas transfer; PHT = pulmonary hypertension

Table 2

Pulmonary function trends at 12 months (prevalence of change stated for categorical thresholds)	**Prognostic significance in the whole cohort (n=162)**	**Prognostic significance in limited disease (n= 113)**	**Prognostic significance in extensive disease (n=49)**
Change in FVC stated as continuous data	HR = 1.00 95% CI = 0.98, 1.01 p=0.56	HR = 1.00 95% CI = 0.99, 1.01 p=0.56	**HR = 0.98** **95% CI = 0.95, 1.00** **p<0.05**
Decline in FVC ≥10% n=34, 21%: Limited disease 17/113, 15% Extensive disease 17/49, 35 %	**HR = 1.84** **95% CI = 1.14, 2.97** **p=0.01**	HR = 1.10 95% CI = 0.52, 2.33 p=0.81	**HR = 2.31** **95% CI = 1.16, 4.60** **P=0.02**
Decline in FVC ≥15% (n=20, 12%) Limited disease 7/113, 6% Extensive disease 13/49, 27%	**HR = 2.36;** **95% CI = 1.35, 4.14** **P<0.005**	HR = 1.05 95% CI = 0.33, 3.37 p=0.94	**HR = 2.32** **95% CI = 1.14, 4.73** **p=0.02**
Change in Dlco stated as continuous data	HR =1.00; 95% CI = 0.99, 1.01 P=0.68	HR = 1.00 95% CI = 0.99, 1.01 p=0.57	HR = 0.98 95% CI = 0.96,1.00 P=0.12
Decline in DLco ≥15% (n=36, 22%) Limited disease 16/113, 14% Extensive disease 20/48, 42%	**HR = 1.84** **95% CI = 1.15, 2.95** **p=0.01**	HR = 1.23 95% CI = 0.60, 2.53 p=0.57	HR = 1.89 95% CI = 0.94, 3.78 p=0.07
Decline in FVC ≥10% AND Dlco ≥15% (n=18, 11%) Limited disease 7 /113, 6% Extensive disease 11/48, 23%	**HR = 2.40** **95% CI = 1.35, 4.26** **P<0.005**	HR = 0.91 95% CI = 0.28, 2.93 p=0.88	**HR = 3.14** **95% CI = 1.51, 6.54** **P<0.005**
Decline in FVC ≥10% OR Dlco ≥15% (n=51, 32%) Limited disease 26 /113, 23% Extensive disease 25 /48, 52%	**HR = 1.69** **95% CI = 1.09, 2.62** **p=0.02**	HR = 1.27 95% CI = 0.69, 2.36 p=0.44	HR = 1.68 95% CI = 0.83, 3.40 p=0.15
CCD (n=42, 26%) Limited disease 22/113, 19% Extensive disease 20/49 41%	**HR = 1.96** **95% CI = 1.25, 3.08** **P<0.005**	HR = 1.17 95% CI = 0.60, 2.27 p=0.65	**HR = 2.86** **95% CI = 1.44, 5.71** **P<0.005**

Table 3

Pulmonary function trends at 24 months (prevalence of change stated for categorical thresholds)	**Prognostic significance in the whole cohort (n=140)**	**Prognostic significance in limited disease (n= 100)**	**Prognostic significance in extensive disease (n=40)**
Change in FVC stated as continuous data	HR = 1.00 95% CI = 0.99, 1.01 p=0.88	HR = 1.00 95% CI = 1.00, 1.01 p=0.34	HR = 0.98 95% CI = 0.96, 1.00 p=0.07
Decline in FVC ≥10% (n=42, 30%) Limited disease 30/100, 30% Extensive disease 12/40, 30%	HR = 1.25 95% CI = 0.77, 2.04 p=0.37	HR = 1.10 95% CI = 0.58, 2.05 p=0.79	HR = 1.68 95% CI = 0.77, 3.68 p=0.20
Decline in FVC ≥12% (n=35, 25%) Limited disease 23/100, 23% Extensive disease 12/40, 30%	HR = 1.28 95% CI = 0.77, 2.15 p=0.35	HR = 0.99 95% CI = 0.49, 2.01 p=0.99	HR = 1.68 95% CI = 0.77, 3.68 p=0.20
Decline in FVC ≥15% (n=27, 19%) Limited disease 16/100, 16% Extensive disease 11/40, 28%	HR = 1.08 95% CI = 0.60, 1.93 p=0.80	HR = 0.62 95% CI = 0.24, 1.57 p=0.32	HR = 1.45 95% CI = 0.65, 3.23 p=0.37
Change in Dlco stated as continuous data	HR = 1.00 95% CI = 0.99, 1.01 p=0.85	HR = 1.00 95% CI = 0.99, 1.01 p=0.46	HR = 0.99 95% CI = 0.96, 1.01 p=0.19
Decline in DLco ≥15% (n=39, 28%) Limited disease 20/100, 20% Extensive disease 19/39, 49%	**HR = 2.03** **95% CI = 1.25, 3.29** **p<0.005**	HR = 1.47 95% CI = 0.75, 2.91 p=0.26	**HR = 2.16** **95% CI = 0.99, 4.73** **p=0.05**
Change in Kco stated as continuous data	**HR = 0.98** **95% CI = 0.96, 1.00** **p=0.04**	HR = 0.98 95% CI = 0.95, 1.00 p=0.09	HR = 0.99 95% CI = 0.97, 1.01 p=0.31
Decline in Kco ≥10% (n=27, 19%) Limited disease 15/100, 15% Extensive disease 12/39, 31%	**HR = 2.35** **95% CI = 1.40, 3.95** **p<0.001**	**HR = 2.57** **95% CI = 1.30, 5.09** **p<0.01**	HR = 1.67 95% CI = 0.74, 3.75 p=0.22
Change in the FVC/DLco ratio stated as continuous data	HR = 1.01 95% CI = 0.99, 1.03 p=0.26	HR = 1.01 95% CI = 0.99, 1.03 p=0.38	HR = 1.00 95% CI = 0.98, 1.02 p=0.79
Increase in FVC/DLco ≥10% (n=47, 36%) Limited disease 29/100, 29% Extensive disease 18/39, 46%	HR = 1.19 95% CI = 0.73, 1.94 p=0.50	HR = 1.34 95% CI = 0.71, 2.52 p=0.37	HR = 0.79 95% CI = 0.35, 1.75 p=0.56
Increase in FVC/DLco ≥15% (n=30, 22%) Limited disease 17/100, 17% Extensive disease 13/39, 33%	**HR = 2.06** **95% CI = 1.19, 3.37** **p<0.01**	**HR = 2.12** **95% CI = 1.07, 4.22** **p=0.03**	HR = 1.53 95% CI = 0.68, 3.46 p=0.30
Increase in FVC/DLco ≥20% **(n=23, 17%)** **Limited disease 12/100, 12%** **Extensive disease 11/39, 28%**	**HR = 2.45** **95% CI = 1.41, 4.23** **p<0.001**	**HR = 2.70** **95% CI = 1.29, 5.63** **p<0.01**	HR = 1.66 95% CI = 0.72, 3.86 p=0.24
CCD (n=48, 35%) Limited disease 33/100, 33% Extensive disease 15/39 38%	HR = 1.43 95% CI = 0.89, 2.30 p=0.14	HR = 1.06 95% CI = 0.57, 1.97 p=0.86	**HR = 2.52** **95% CI = 1.16, 5.49** **p=0.02**

Table legends:

Table 1: Demographic and clinical data in the study population (n=162)

Table 2: The prevalence of categorical change and relationships between 12 month changes in pulmonary function variables (FVC, DLco, Kco, the FVC/DLco ratio, the CCD) and mortality in the whole cohort and, separately, in the limited and extensive disease sub-groups. Pulmonary function trends are expressed as continuous data or as categorical change to pre-defined thresholds (with prevalence stated in parentheses). Prognostic significance is expressed as hazards ratios (HR) with 95% confidence intervals (CI) and p values.

Table 3: The prevalence of categorical change and the relationships between 24 month changes in pulmonary function variables (FVC, DLco, Kco, the FVC/DLco ratio, the CCD) and mortality in the whole cohort and, separately, in the limited and extensive disease sub-groups. Pulmonary function trends are expressed as continuous data or as categorical change to pre-defined thresholds (with prevalence stated in parentheses). Prognostic significance is expressed as hazards ratios (HR) with 95% confidence intervals (CI) and p values.

Figure legends:

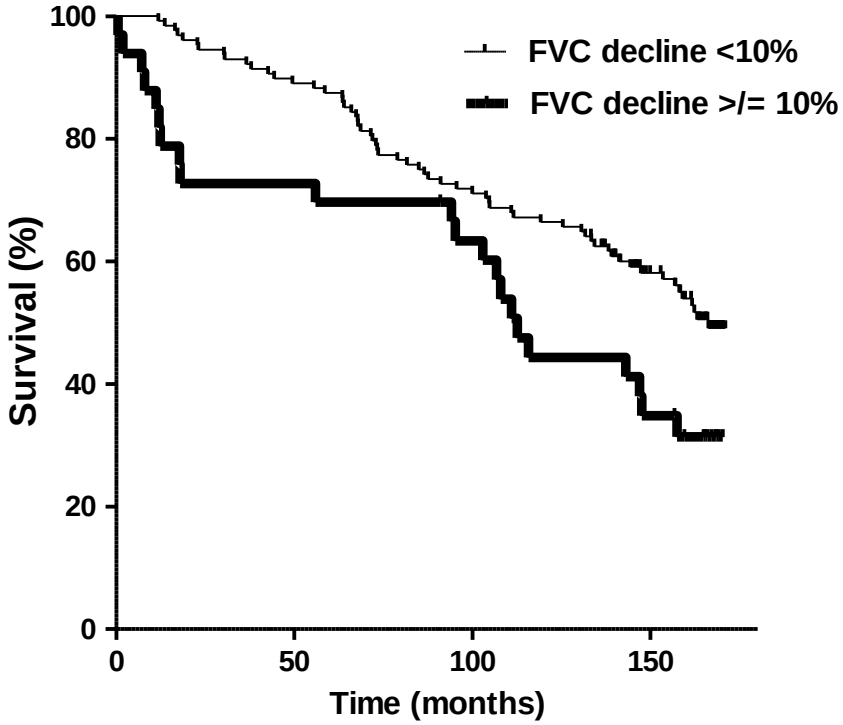
Figure 1: FVC decline at 10% threshold at 12 months is predictive of mortality in a) the whole cohort (n=162) (HR=1.84; 95% CI 1.14, 2.97; p=0.01); b) the extensive subgroup (n=49) (HR=2.31; CI 1.16, 4.6; p=0.02)

Figure 2: CCD at 12 months is predictive of mortality in a) the whole cohort (n=162) (HR=1.96; CI 1.25, 3.08; p<0.005) ; b) the extensive subgroup (n=49) (HR=2.86; CI 1.44, 5.71; p<0.005)

Figure 3: The prognostic significance of PFT trends at different thresholds at 24 months in the whole cohort (n=113)): a) DLco decline at 15% threshold (HR=2.03, 95% CI 1.25, 3.3, p<0.005); b) Kco decline at 10% threshold (HR=2.35, 95% CI 1.40, 3.95; p<0.001); and c) FVC/DLco ratio rise at 20% threshold (HR=2.45, 95% CI 1.41, 4.23, p<0.001).

Figure 1.

a)


100
80
60
40
20
0
Survival (%)
0
50
100
150
Time (months)
FVC decline <10%
FVC decline >/= 10%

b)

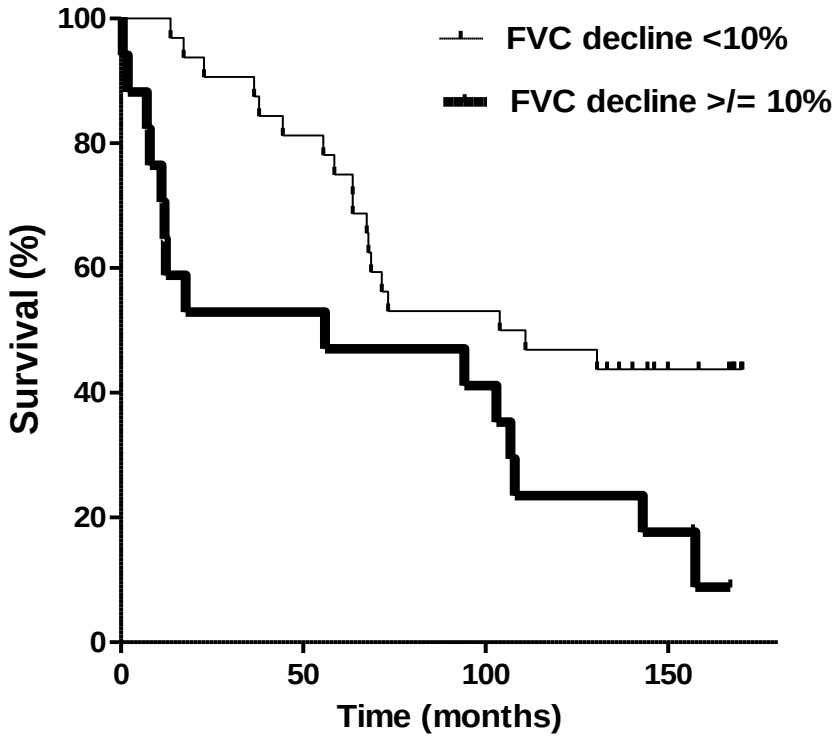
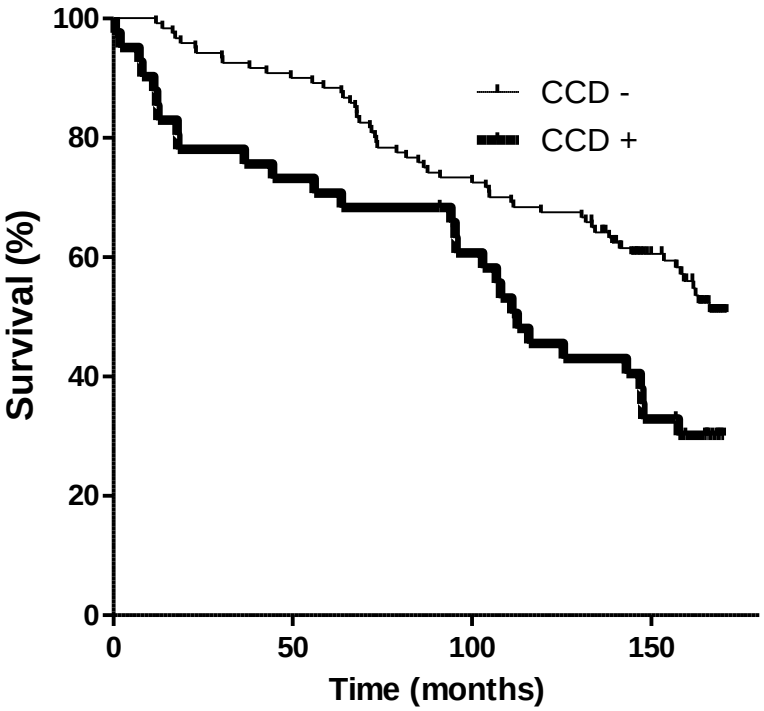

100
80
60
40
20
0
Survival (%)
0
50
100
150
Time (months)
FVC decline <10%
FVC decline >/= 10%

Figure 2.

a)


100
80
60
40
20
0
Survival (%)
0
50
100
150
Time (months)
CCD -
CCD +

b)

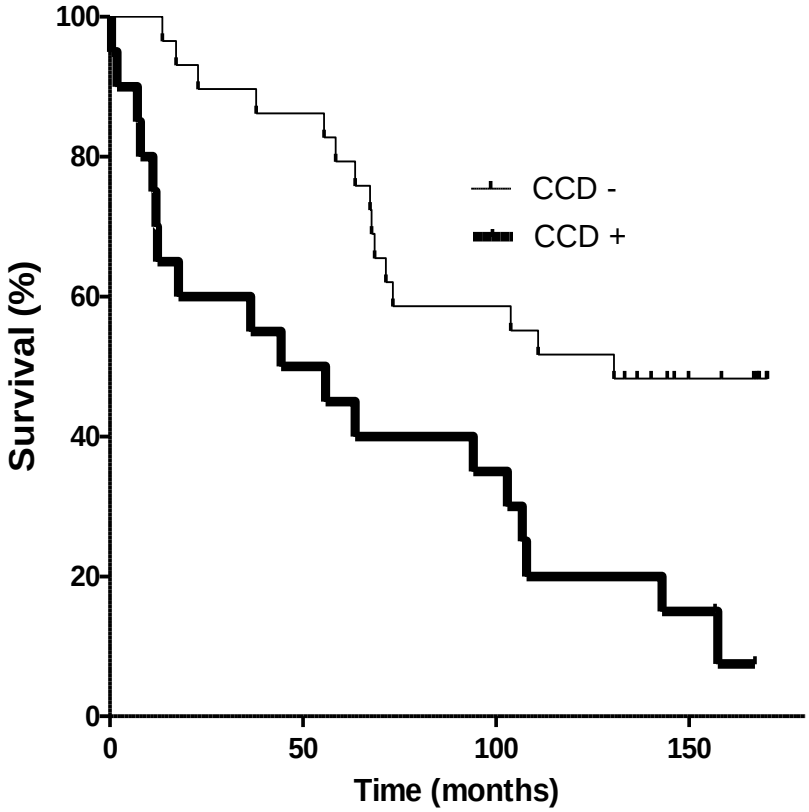
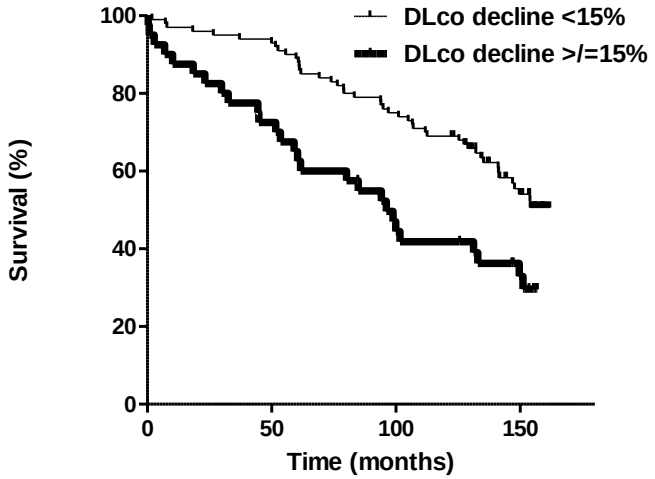
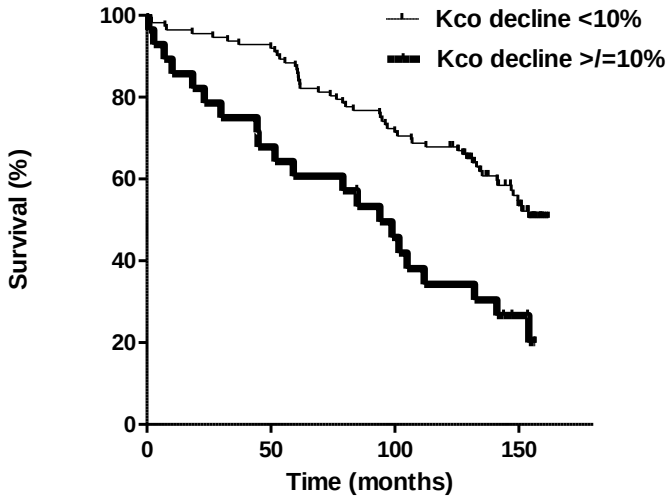

100
80
60
40
20
0
Survival (%)
0
50
100
150
Time (months)
CCD -
CCD +

Figure 3.

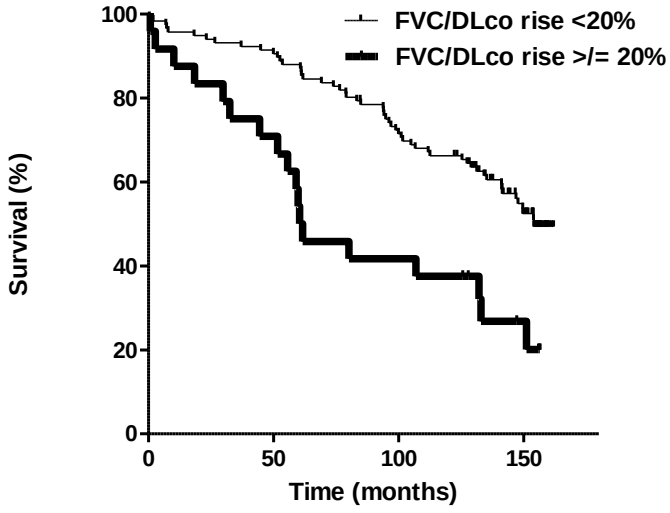
a)


DLco decline <15%
DLco decline >/=15%
Survival (%)
100
80
60
40
20
0
0
50
100
150
Time (months)

b)


Kco decline <10%
Kco decline >/=10%
Survival (%)
100
80
60
40
20
0
0
50
100
150
Time (months)

c)


FVC/DLco rise <20%
FVC/DLco rise >/= 20%
Survival (%)
100
80
60
40
20
0
0
50
100
150
Time (months)

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