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MARGINAL DECLINE IN FVC IS ASSOCIATED WITH A POOR OUTCOME IN IDIOPATHIC PULMONARY FIBROSIS

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ABSTRACT

In therapeutic studies in idiopathic pulmonary fibrosis (IPF), the low prevalence of significant change in pulmonary functional tests (PFT) has been a major constraint. We evaluated the prognostic value of "marginal" changes in PFT in IPF and fibrotic non-specific interstitial pneumonia (NSIP).

In patients with biopsy-proven IPF (n=84) and NSIP (n=72), FVC and DL_{CO} trends at six months were categorised as "significant" (FVC>10%; DL_{CO}>15%) or "marginal" (FVC 5-10%; DL_{CO} 7.5-15%). Proportional hazards analysis and time-dependent ROC methodology were used to examine PFT trends against mortality.

In IPF, FVC reductions were "significant" in 22 cases (26%) and "marginal" in 19 cases (23%). Mortality was higher with significant FVC decline [HR = 2.80 (1.54, 5.06), p<0.001] and with marginal FVC decline [HR = 2.31 (1.19, 4.50), p=0.01] than with stable disease. Progression-free survival was lower when FVC decline was marginal than in stable disease (HR = 2.34 (1.19, 4.60), p=0.01). Marginal changes in DL_{CO} in IPF and marginal changes in FVC and DL_{CO} in fibrotic NSIP did not provide useful prognostic information.

Marginal FVC change in IPF denotes a poor outcome. These findings are applicable to clinical practice and to the selection of patients with more progressive disease for therapeutic studies.

INTRODUCTION

In IPF and fibrotic NSIP, serial changes in pulmonary function tests (PFTs) at six or 12 months have had greater prognostic value than baseline data [1-6]. The current threshold values, used to define "significant decline", are a reduction from baseline values of 10% for FVC and 15% for DL_{CO} [1]. Decline of a lesser magnitude (marginal) may indicate real disease progression, especially when accompanied by increased symptoms or other evidence. If real disease progression can be defined in terms of marginal PFT thresholds, then their inclusion in clinical decision-making and in therapeutic trial end-points would allow increased recognition of clinically relevant disease behaviour.

The paucity of signal offered by current significant PFT thresholds has been a limitation in trials of new agents. The IFIGENIA group, investigating N-acetylcysteine in IPF, found a difference of 8% predicted in FVC and 14% in DL_{CO} at 12 months between the treatment and placebo groups [7]. Similarly, Azuma et al, investigating Pirfenidone in IPF, found only a preservation of FVC by 0.1L between treatment and placebo groups, though this was statistically significant [8]. Controversially, both groups interpreted these marginal results as positive and relevant to clinical practice.

Our hypothesis was that marginal change in lung function parameters would predict survival and allow a more sensitive signal to be used in clinical decision-making and therapeutic trials. We therefore determined the prognostic significance of relative marginal change in FVC and DL_{CO} at six months in patients with IPF and fibrotic NSIP.

Some of the results of this study have been presented in abstract form [9].

MATERIAL AND METHODS

Between 1978 and June 30th 2005, 191 patients met histological criteria at surgical biopsy for IPF (n=103) or fibrotic NSIP (n=88). IPF patients met ATS/ERS diagnostic criteria [10]. Clinical criteria for NSIP comprised: (1) bilateral predominantly basal or widespread crackles, (2) radiographic evidence of predominantly basal bilateral lung infiltrates with ground glass or reticular opacities on either chest radiograph or high resolution CT scan from 1991 onwards, (3) a restrictive functional defect or isolated reduction in diffusing capacity, (4) absence of features suggestive of hypersensitivity pneumonitis or organising pneumonia, (5) no other known cause of pulmonary fibrosis of associated disease.

Patients without serial PFT data were excluded [IPF, n=19; fibrotic NSIP, n= 16]. Excluded IPF patients were characterised by greater baseline impairment of FVC and DL_{CO} levels and higher mortality (data not shown). The remaining 156 patients (IPF, n=84; fibrotic NSIP, n= 72) comprised the study cohort. Part of the cohort has been reported in outcome studies [2, 11, 12].

Histological diagnoses of UIP or fibrotic NSIP were made by two histopathologists, blinded to clinical data (Kappa = 0.53) with diagnostic divergences resolved by consensus. In six cases, a final diagnosis (IPF, n=2; excluded, n=4) was made in formal multidisciplinary review (by a histopathologist, radiologist and clinician) [13, 14]. Vital status at October 31st 2006 was determined. Transplanted patients (n=4) were censored as alive at the date of transplant. Treatment regimens included (1) combination immunosuppressive treatment including low dose prednisolone (10mg), or (2) high-dose prednisolone initially (40-60mg) reducing to a maintenance average dose of 10mg.

Baseline disease severity was quantified using DL_{CO} and composite physiologic index (CPI) levels, based on their superior prognostic value in previous analyses [2, 4, 5, 15, 16] and in preliminary analyses in the current cohort (data not shown).

Serial PFT trends at six months (+/- two months), expressed as percentages of baseline values, were evaluated for FVC (PKM spirometer, P. K. Morgan, Kent, UK, or Jaeger Compact, Viasys Healthcare, Warwickshire, UK) and DL_{CO} (single breath or re-breathing technique, PK Morgan respirometer) [17]. Relative trends were defined a priori as significant [(FVC > 10%; DL_{CO} > 15%)] [2] or marginal [FVC 5-10%; DL_{CO} 7.5-15%], compared to baseline. Criteria for marginal decline were chosen to allow rapid computation in clinical practice, reflecting the rationale of current American Thoracic Society criteria for significant PFT change.

Data Analysis

Group comparisons were made using unpaired t tests or chi-squared statistics. PFT trends were evaluated against mortality using proportional hazards analysis [18], with findings re-examined in multivariate models including adjustment for age, gender, smoking status and baseline disease severity (CPI and DL_{CO} levels in separate models), as follows:

1) Outcome was evaluated from the date of the six month follow-up pulmonary function tests. Mortality was compared between patient sub-groups (significant decline; marginal decline; stable disease) in IPF and NSIP. Progression-free survival (i.e. duration of follow-up to a significant decline in FVC or death) was compared between patient sub-groups in IPF.

2) Alternative threshold values for PFT decline were examined against mortality in IPF, comparing patients with marginal decline and those with stable disease. In post hoc analysis, the FVC threshold of 5% in IPF, corresponding to marginal decline, was compared with alternative thresholds (3%, 4%, 6%, 7%) using proportional hazards analysis. This analysis were performed to identify the optimal FVC trend threshold for possible use in pharmaceutical studies, with regard to recruitment of patients with more progressive disease and end-point definition.

3) Survival analyses were repeated in the entire cohort of both IPF and NSIP patients (n=156), with baseline DL_{CO} <40% predicted (n=71) and, separately, with DL_{CO} > 40% values (n=85). This sub-analysis was performed to explore the hypothesis that the prognostic value of PFT trends is influenced by the severity of baseline functional impairment.

RESULTS

BASELINE DEMOGRAPHICS AND DETERMINANTS OF OUTCOME

Patients with IPF were older, more often male and more often current or ex-smokers, as shown in Table 1. Mortality was higher in IPF (five year survival 19%) than in NSIP (five year survival 65%).

PREVALENCE OF SERIAL DECLINE IN DLCO AND FVC

As shown in Table 2, declines in DL_{CO} and FVC at six months were more prevalent in IPF than in NSIP. In IPF, a high proportion of patients had either significant or marginal decline (DL_{CO} 55%; FVC 49%). In NSIP, fewer patients showed marginal decline, such that the overall proportion with significant or marginal decline was only 24% for DL_{CO} and 28% for FVC.

In IPF patients, marginal decline in FVC was confirmed when pulmonary function tests were next measured in 16 of 18 cases (88.9%). One patient died without repeat pulmonary function tests.

MORTALITY IN RELATION TO PFT TRENDS

Mortality was compared between patient sub-groups with significant decline, marginal decline and stable disease. Median survival was 29 months in patients with stable or improved serial FVC trends at 6 months (n=38), 14 months in patients with a marginal decline in FVC at 6 months (n=23), and 7 months in patients with a significant decline in FVC at 6 months (n=23). In IPF, mortality was higher with marginal FVC decline [HR = 2.31 (1.19, 4.50), p=0.01] and with significant FVC decline [HR = 2.80 (1.54, 5.06), p<0.001] than in stable disease (Figure 1). As shown in Table 3, this finding was robust with adjustment for disease severity (marginal decline versus stable disease, p<0.005).

Mortality did not differ between patients with marginal FVC decline and patients with significant FVC decline.

By contrast, a marginal decline in DL_{CO} was not associated with increased mortality in IPF (Figure 2). Similarly, marginal PFT decline (both in FVC and in DL_{CO}) was not associated with increased mortality in NSIP. Significant decline in DL_{CO} and FVC in both disease cohorts was predictive of increased mortality.

In the combined cohort (n=156), a marginal decline in FVC was associated with a poor outcome, both in 71 patients with severe disease (baseline DLCO < 40%: HR = 2.27 [1.28, 4.02]; p<0.005) and in 85 patients with less severe disease (baseline DLCO > 40%: HR 2.98 [1.08, 3.60] p=0.03).

PROGRESSION FREE SURVIVAL IN IPF

As shown in Figure 3, progression free survival was highest in patients with stable disease and higher in patients with a 5-10% decline in FVC than in those with significant FVC decline (HR 2.24, CI 1.63, 3.08, p<0.001). When compared with stable disease, patients with a 5-10% decline in FVC had a marginal reduction in progression free survival (HR 1.82 [CI 0.97-3.40] p=0.06), which became statistically significant with adjustment for baseline DL_{CO} (HR = 2.56, CI 1.17, 4.38, p=0.02) and CPI levels (HR = 2.34, CI 1.19, 4.60, p=0.01).

Parallel analyses of DL_{CO} trends in IPF revealed that progression free survival did not differ between patients with stable disease and those with a marginal DL_{CO} decline (p = 0.88).

THRESHOLD VALUES

Alternative threshold values for marginal change of between 3% and 7% were evaluated for FVC decline in IPF, with the exclusion of patients with a significant decline in FVC. The prognostic significance of thresholds of 4%, 5% or 6% were broadly similar, (Table 4). By contrast, a 3% or 7% threshold was non-discriminatory.

The sensitivity and specificity of marginal and significant decline, in identifying mortality within one year and within two years are shown in table 5. Marginal change offered advantages over significant change in predicting death within two years, although the rise in sensitivity from 37% to 65% was partially offset by a smaller fall in specificity from 85% to 72%.

DISCUSSION

We report that marginal (5-10%) declines in FVC at six months are linked to increased mortality in IPF. This finding was robust after adjustment for baseline disease severity (using CPI and DL_{CO} levels in separate models) in sub-group analysis, and when progression-free survival was evaluated as an alternative end-point. The amalgamation of marginal and significant decline in FVC provided an outcome end-point that was positive at six months in almost 50% of IPF patients.

The low prevalence of marginal FVC change in fibrotic NSIP removed any possibility of demonstrating a linkage between marginal change and outcome in that disease. However, it can be argued along Bayesian principles that such a linkage is, in any case, less likely in patients with fibrotic NSIP. A decline in FVC of 5-10% may represent either technical variation in measurement or progression of disease. In IPF, the pre-test probability of disease progression is high and, thus, marginal decline is relatively more likely to denote true deterioration in individual cases, a conclusion that is strongly supported by our findings. By contrast, because NSIP is less progressive than IPF [1, 2, 19], marginal change in NSIP is necessarily more likely to represent measurement variation.

RELEVANCE TO CLINICAL PRACTICE

It should be stressed that in isolation, marginal FVC trends are not sufficiently prognostically accurate to determine management. However, our findings suggest that marginal reductions in serial FVC provide important ancillary support for true disease progression in the context of symptomatic deterioration or equivocal change on chest radiography. In other cases, marginal FVC trends provide a logical indication for more intense evaluation including the performance of HRCT, or repetition of pulmonary

function tests. In that regard, marginal trends were reproduced in the great majority of patients when pulmonary function tests were next performed.

There are also possible implications for routine prognostic evaluation. The use of marginal trend thresholds may identify patients with real disease progression at higher risk of mortality who are not captured by traditional thresholds based on "significant decline" [1, 2, 4, 5]. Clinicians are often confronted with diagnostic ambiguity between fibrotic NSIP and IPF, in the absence of surgical lung biopsy. Serial PFT trends at 6-12 months provide useful prognostic information, with stability indicative of a better outcome [2, 3, 5, 15]. However, our results indicate that patients with IPF should be regarded as stable only if the FVC has declined by less than 5% at 6 months, although it should also be stressed that long term outcome remains poor, even in stable IPF, and that a single study is an insufficient basis on which to change routine clinical recommendations [20].

Relevance to Clinical Trials

The criteria used to define marginal decline in the present study were based on the principle that selected cut-off values should facilitate rapid computation in clinical practice. The current ATS criteria for significant change do not exactly capture the reproducibility of individual indices but are a close and user-friendly approximation. However, in pharmaceutical studies in which average population effects are defined, rather than change in individual patients, clinical convenience is a lesser consideration and this prompted us to explore lower threshold values for marginal decline in the hope of amplifying outcome signal. We demonstrated that threshold values of 4%, 5% and 6% provided equivalent predictive power, whereas threshold values of 3% and 7% were non-discriminatory.

These findings have implications for the selection of end-points. In therapeutic trials of pirfenidone [8] and N acetylcysteine [7] in IPF, average treatment effects were not definitive. With pirfenidone treatment, the relative FVC benefit was only 0.13L at nine months [8]. N-acetylcysteine therapy was associated with a relative improvement of 8% in FVC and 14% in DL_{CO} [7]. These average effects are deceptive because they are not uniform but represent a clear benefit in some but not all cases. Our findings underline the possibility that even marginal FVC benefits in individuals may represent a worthwhile therapeutic effect (although the degree to which the six month trends in our study can be equated to 12 month trends in clinical trials is unclear). However, surrogate end points are not fully validated by a single study [20], and independent verification of disease progression may be required. Serial HRCT, which has yet to be validated as an independent outcome variable in IPF, may have a valuable role in providing collateral morphologic evidence of disease progression. A combined end-point of marginal FVC decline and progression of disease on HRCT (or, alternatively, declining exercise tolerance) merits further study.

More importantly, our findings have implications for the selection of patients for enrolment in clinical trials. Current end-points in therapeutic studies may not be sufficiently sensitive. In a retrospective analysis of a placebo-controlled trial of interferon-gamma, the primary end-point (change in FVC, change in A-a gradient or death) was met in less than 30% of cases [22]. By implication, a prohibitively large number of patients would be required to demonstrate a worthwhile partial treatment effect. It can be argued that patients with more indolent disease tend to be selectively enrolled in placebo-controlled studies in diffuse lung disease [23-25]. Our results indicate that an enrolment criterion of marginal or significant decline in FVC during the

six months before entry into a clinical trial selects patients more likely to meet a progression-free survival end-point during a treatment period of one to two years. However, as in the detection of disease progression in clinical practice, it appears likely that the optimal algorithm for patient selection, when refined in future studies, will consist of a combination of marginal FVC trends and other ancillary evidence of disease progression, including symptomatic decline and/or evidence of disease progression on HRCT.

LIMITATIONS OF THE STUDY

Selection bias is an important consideration because of possible over-representation of NSIP in this and other studies, due to the exclusion of IPF patients in whom typical HRCT appearances obviated biopsy. Furthermore, although histological evaluation provided diagnostic security and allowed a comparison between IPF and fibrotic NSIP, biopsied patient cohorts are known to be younger and to have less severe functional impairment [26]. However, serial FVC trends are known to have a greater prognostic value in less severe disease (as judged by lack of desaturation on a baseline walk test) [3]. Thus, marginal trends in FVC may be less prognostically useful in IPF patients with advanced disease.

The recent widespread introduction of N-acetylcysteine therapy as part of standard therapy for IPF and severe fibrotic NSIP had the potential to confound our results, based upon findings in the IFIGENIA study [7]. This consideration prompted us to limit the date of presentation to June 2005. In a small percentage of patients, N-acetylcysteine was introduced during follow-up in the last year of the follow-up period, to October 2006. However, it is unlikely that this had a major effect on our findings, as it is known

that mortality is not significantly influenced by anti-oxidant therapy during the first year of treatment [7].

It should also be stressed that the results of this study are more directly applicable to clinical practice than to therapeutic trials, which generally last for 12 months in IPF. Although six month follow-up was almost always possible in surviving patients in our cohort, follow-up at 12 months was highly variable (especially in the last five years of the study, with the advent of a "shared care" algorithm with local chest physicians). Thus, an evaluation of the prognostic significance of 12 month functional trend (as in an earlier study containing some patients in the current study [2], was no longer practicable in this extended population. Our findings need to be reproduced in another cohort, with follow-up extended to 12 months, to validate marginal change in FVC as a primary end-point in pharmaceutical studies.

Progression free survival provides an additional outcome variable but represents a blunt end-point when compared to mortality, as it depends upon the timing of routine monitoring and opportune lung function testing. By contrast, vital status is generally collated monthly. This factor is unlikely to have materially influenced our results in IPF patients as follow-up PFT were performed three to six monthly in almost all cases.

In conclusion, short-term marginal changes in FVC predict a poor outcome in patients with IPF. Our results have important implications for clinical decision-making and recruitment into clinical therapeutic trials.

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TABLE LEGEND

Table One – Demographics, baseline clinical data & selected pulmonary function indices compared between IPF and NSIP. IPF patients were slightly older with decreased survival, and more likely to be ever smokers and male, otherwise the two disease cohorts had comparable baseline lung function and treatment rates.

Table Two – Prevalence of serial decline at six months compared between IPF and NSIP. In IPF, a higher proportion of patients had either significant or marginal decline compared to those with NSIP ($p<0.001$).

Table Three – Prognostic value of marginal decline (5-10% change) in FVC when patients with significant decline (>10% change) are excluded, controlled for disease severity. In IPF, mortality is higher with both marginal and significant decline than in stable disease, when controlled for baseline disease severity ($p<0.005$) with no difference in mortality between patients with marginal FVC decline and patients with significant FVC decline (both $p<0.001$). Marginal decline in FVC did not predict mortality in NSIP.

Table Four – Proportional hazards comparative analysis of marginal FVC thresholds in IPF, with the exclusion of patients with a significant decline in FVC. The prognostic significance of thresholds of 4% and 5% did not differ. By contrast, a 3% threshold was always inferior to 4% and 5% thresholds.

Table Five – Prognostic value of marginal decline (5-10% change) and significant decline (>10% change) in FVC in IPF (n=84), based on the sensitivity and specificity of these thresholds for death within one year and death within two years. The prognostic advantage of marginal change lay in increased sensitivity, particularly for death within two years. Predictive values and likelihood ratios are also shown for comparison.

FIGURE LEGEND

Figure One – Four year survival in relationship to the magnitude of FVC serial change at 6 months in IPF (n=84). Declines of 5-10% (marginal) and >10% (significant) were both associated with a worse prognosis than stable disease ($p < 0.005$).

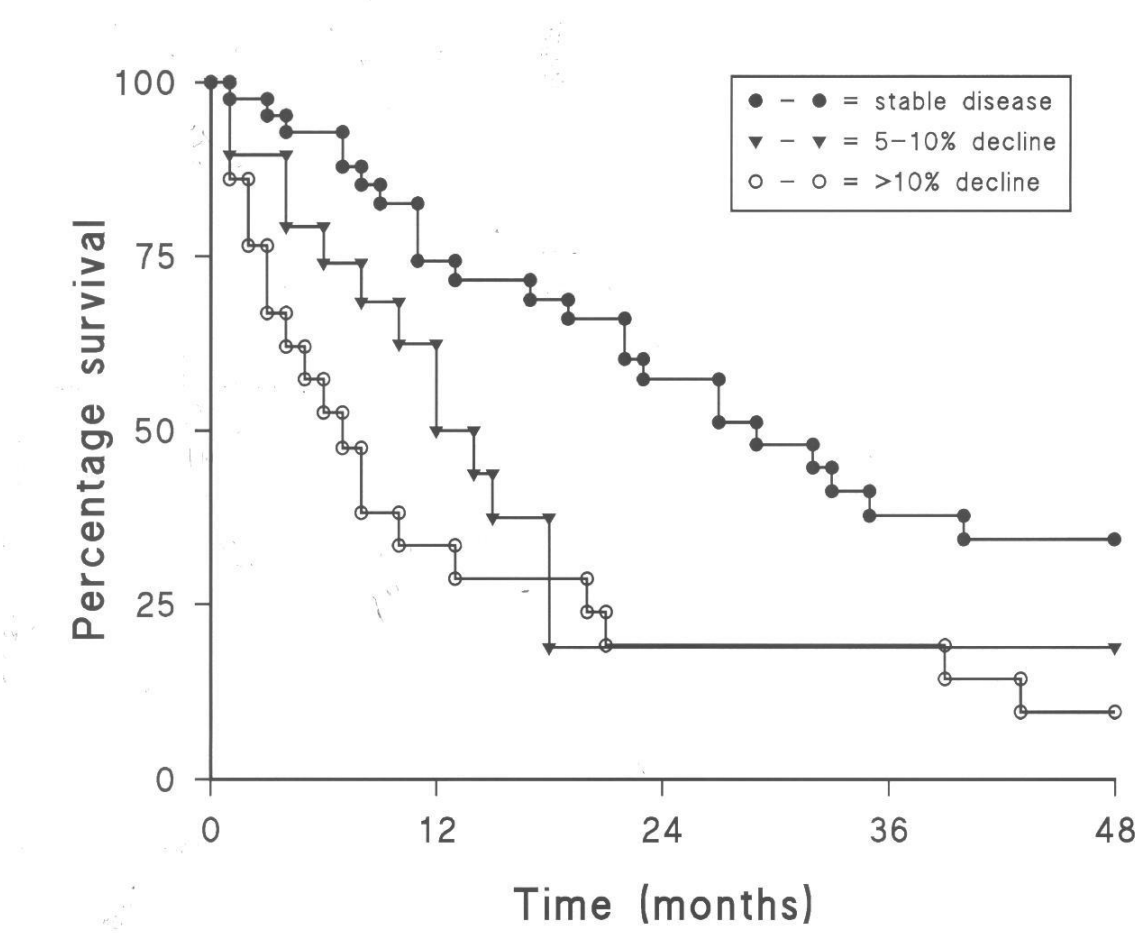

Figure Two – Four year survival in relationship to the magnitude of DL_{CO} serial change at 6 months in IPF (n=84). Survival did not differ between those with stable disease or a 7.5-15% (marginal) decline. Patients with a >15% (significant) decline had a worse prognosis than those with stable disease or a marginal decline ($p<0.0005$).

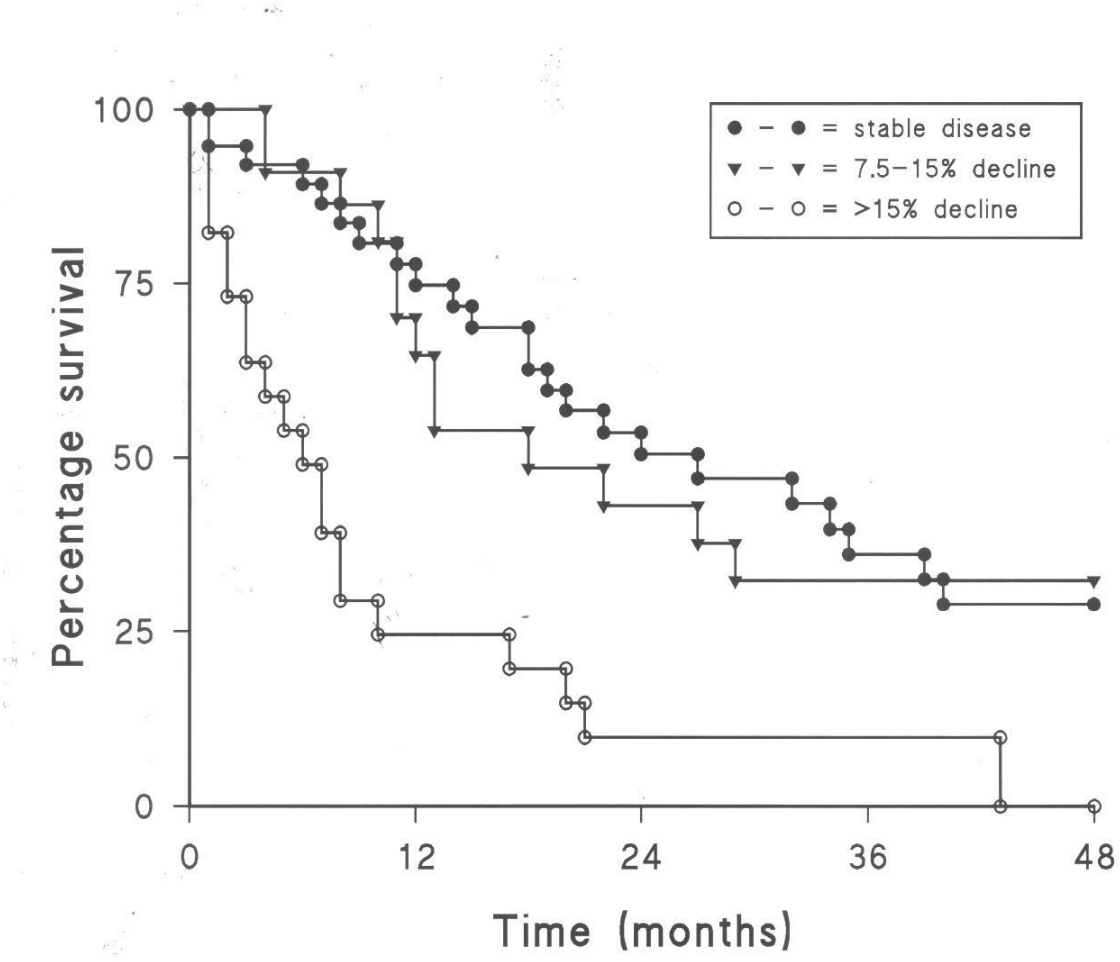

Figure Three – Two year progression free survival in relationship to the magnitude of FVC serial change at 6 months in IPF (n=84). A decline of 5-10% (marginal) or >10% (significant) is associated with worse prognosis than stable disease ($p < 0.005$). Patients with marginal decline had an intermediate progression free survival compared to those with stable disease or a significant decline in FVC.

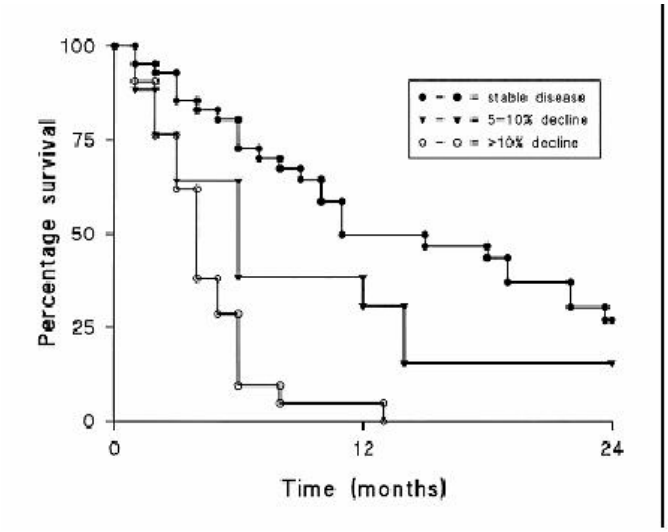

Table One

	IPF	NSIP

	(n = 84)	(n = 72)
Age*	57.4 +/- 8.50	50.9 +/- 9.9
Male/Female*	69/15	42/30
Smokers Ever/Never*	62/22	36/35
DL_{CO} % predicted	41.90 +/- 12.85	43.80 +/- 15.1
FVC % predicted	72.66 +/- 18.73	71.5 +/- 22.5
Treated	83 (99%)	70 (97%)
- Combination	57 (68%)	49 (68%)
- Prednisolone	26 (31%)	21 (29%)
No/Unknown treatment	1/0 (1%/0)	2/1 (3%/1%)
CPI	50.32 $\pm$ 11.3	48.3 $\pm$ 18.7
Deaths*	68 (84%)	32 (44%)
Median survival	23 months	90 months

Definition of abbreviations: DL_{CO} = diffusing capacity; FVC = forced vital capacity; CPI = composite physiologic index; NSIP = non-specific interstitial pneumonia; IPF = idiopathic pulmonary fibrosis.
* refers to statistically significant difference $p<0.05$.

Table Two

	IPF (n = 84)	NSIP (n = 72)	p value
$\underline{DL_{CO}}$			
Significant decline (>15%)	23 (27%)	13 (18%)	0.13
Marginal decline (7.5-15%)	23 (27%)	4 (6%)	<0.001
Marginal or significant decline (>7.5%)	46 (55%)	17 (24%)	<0.001
<u>FVC</u>			
Significant decline (>10%)	22 (26%)	13 (18%)	0.19
Marginal decline (5-10%)	19 (23%)	7 (10%)	0.06
Marginal or significant decline (>5%)	41 (49%)	20 (28%)	<0.01

Definition of abbreviations: DL_{CO} = diffusing capacity; FVC = forced vital capacity; NSIP = non-specific interstitial pneumonia; IPF = idiopathic pulmonary fibrosis.

Table Three

	IPF (n=84)	NSIP (n=72)

	HR	CI	p value	HR	CI	p value
5-10% decline FVC (univariate)	2.31	1.19-4.50	0.014	1.36	0.40-4.66	0.62
5-10% decline FVC (DL_{CO} controlled)	3.33	1.61-6.88	<0.001	1.46	0.42-5.00	0.55
5-10% decline FVC (CPI controlled)	3.60	1.70-7.62	<0.001	1.29	0.38-4.42	0.69

Definition of abbreviations: DL_{CO} = diffusing capacity; FVC = forced vital capacity; CPI = composite physiologic index; NSIP = non-specific interstitial pneumonia; IPF = idiopathic pulmonary fibrosis.
Significant ($p < 0.05$) relationships are shown, with hazard ratios, expressing the difference in risk of mortality between those with change and those without (with 95% confidence intervals).

Table Four

FVC Decline	**Proportional hazards analysis**

7% Threshold	HR = 1.76 (0.86, 3.60) p=0.12
6% Threshold	HR = 2.08 (1.05, 4.13) p=0.04
5% Threshold	HR = 2.31 (1.19, 4.50) p=0.01
4% Threshold	HR = 2.11 (1.11, 4.00) p=0.02
3% Threshold	HR = 1.43 (0.75, 2.68) p=0.27

Significant ($p < 0.05$) relationships are shown, with hazard ratios, expressing the change in risk of mortality between those with change and those without change (with 95% confidence intervals).

Table Five

FVC Decline	12 months	24 months

5% Threshold	Sensitivity 83% (15/18) [63-95%]	Sensitivity 65% (28/43) [51-78%]
	Specificity 61% (40/66) [49-72%]	Specificity 72% (28/39) [57-84%]
	PPV 37% (15/41) [23-52%]	PPV 72% (28/39) [57-84%]
	NPV 93% (40/43) [83-98%]	NPV 65% (28/43) [50-78%]
	LR 2.12 [1.47-3.04]	LR 2.31 [1.34-3.99]
10% Threshold	Sensitivity 67% (12/18) [45-85%]	Sensitivity 37% (16/43) [24-52%]
	Specificity 85% (56/66) [75-92%]	Specificity 85% (33/39) [71-94%]
	PPV 55% (12/22) [35-73%]	PPV 73% (16/22) [53-88%]
	NPV 90% (56/62) [81-96%]	NPV 55% (33/60) [43-67%]
	LR 4.4 [2.28-8.49]	LR 2.42 [1.05-5.56]

PPV = positive predictive value; NPV = negative predictive value; LR = Likelihood ratio; 95% Confidence Intervals are shown.