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Rate of Progression of Lung Function Impairment in Alpha-1-Antitrypsin Deficiency

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Abstract

The aim was to identify alpha-1-antitrypsin (A1AT) deficient patients who have rapidly progressive disease.

Methods: 101 PiZ patients had annual lung function measurements over a 3-year period and the results were related to factors that may influence decline.

Results: Mean annual decline of forced expiratory volume in 1 second (FEV1) was 49.9 ml. The greatest FEV1 decline was in the moderate severity group (FEV1 50-80 %) with mean annual decline of 90.1 ml, compared with 8.1 ml in the very severe group (FEV1 <30%). However, annual decline in KCO was greatest in the severe and very severe groups. When the whole group was divided into tertiles for FEV1 decline, the fast tertile compared with the slow tertile had more patients with bronchodilator reversibility (BDR) (mean 73% versus 41%, p=0.010), more males (mean 79% versus 56%, p=0.048) and lower body mass index (BMI) (mean 24.0 versus 26.1, p=0.042). Logistic regression analyses confirmed FEV1 decline was independently associated with BMI, BDR, exacerbation rate and high physical component SF36 scores. Conclusion: In PiZ A1ATD patients, FEV1 decline was greatest with moderate disease, unlike KCO decline that was greatest in severe disease. The FEV1 decline showed associations with BDR, BMI, gender and exacerbation rates.

Keywords

Chronic obstructive pulmonary disease, alpha-1-antitrypsin deficiency, lung function tests, disease progression

Introduction

Progression of emphysema in alpha-1-antitrypsin deficiency (A1ATD) is known to occur at an accelerated rate when compared with usual chronic obstructive pulmonary disease (COPD)(1;2)]. At present there is uncertainty about which patients have the greatest rate of progression and therefore may show the clearest signal to alpha-1-antitrypsin (A1AT) augmentation trials or response to future treatments. This reflects a lack of knowledge of the natural history of the disease and completion of effective clinical trials of treatment.

Logically, effective preventative therapy should be introduced early to prevent subsequent deterioration. However it is currently unknown whether all patients with A1ATD will deteriorate and at what rate. Index patients identified by presentation to health care services have worse lung function than matched non-index siblings(3). Lifelong non-smokers show less progression and lower mortality(1;4), but a significant number develop airflow obstruction in middle age(5). Nevertheless, many subjects remain unidentified, either because the diagnosis has not been considered or they remain clinically well. To identify all patients extensive screening would be necessary, with long term follow up, such as the Swedish cohort study(6).

The variation in progression rate in A1ATD patients has also hampered clinical therapy trials since large numbers of subjects need to be studied over a long

period of time to determine efficacy(7). However targeting only patients who are rapidly progressing to such trials would reduce the numbers needed and decrease the necessary duration of the study. Indirect data from the US National Institutes of Health (NIH) registry provides supporting evidence for this concept. The only patients demonstrating a possible benefit for augmentation therapy were those with a rapidly declining forced expiratory volume in 1 second (FEV1) in the moderately affected group(1). Furthermore this is supported by the observation that rapid decliners in the German sequential study showed a subsequent slowing of progression following augmentation(8).

The present study was designed to answer several questions. Firstly to assess the progression of airflow obstruction and a more specific measure of emphysema (the carbon monoxide transfer factor) in patients with a wide spectrum of physiological impairment; secondly to identify factors that are associated with the decline in lung function; and finally to determine factors that are associated with the most rapid decline in order to identify the most appropriate patients for clinical trials and those most likely to benefit from effective interventions.

Methods

The UK Antitrypsin Deficiency Assessment and Programme for Treatment (ADAPT) programme has been collecting data on A1ATD patients prospectively

since 1996, in order to gain understanding of the natural history of the condition and form a basis for future treatments. None had received A1AT augmentation therapy, since it is not yet licensed in the UK. At the time of analysis all patients who had been followed for at least 3 years were identified. Forty patients were excluded because they had less than 4 consecutive annual lung function measurements including baseline. Additionally 3 were excluded because they had lung transplants. These 43 excluded patients were of milder severity on average than those included in the analysis (mean baseline FEV1 percent predicted 70.5 in those excluded compared with 54.3 in those included). There were thus 101 patients on the registry with PiZ phenotype who had lung function recorded annually over a 3-year period. Using regression equations, the average decline in FEV1 and gas transfer corrected for lung volume (KCO) was calculated over the three years (4 measurements) for each patient. The patients were then divided into groups according to baseline FEV1 (% predicted), equivalent to American Thoracic Society (ATS)/ European Respiratory Society (ERS) severity groups for COPD(9). The average decline over 3 years for FEV1 and KCO was then determined for each group. Factors associated with the decline were identified from baseline characteristics by univariate analysis. All correlates were then entered into a linear regression analysis to identify independent factors that predicted overall decline. This compared FEV1 and KCO decline as continuous variables against the factors, adjusting for age, sex, cumulative smoking exposure and baseline lung function.

To identify factors characteristic of rapid decline the 101 patients as a whole were then separately divided into tertiles according to the speed of FEV1 decline. The fast decline tertile and the slow decline tertile were compared for differences, using univariate and multivariate analyses, in the following parameters, assessed at baseline: sex; body mass index (BMI); acute reversibility to bronchodilator (defined by American Thoracic Society criteria; >= 200ml change in FEV1 and 12% change from baseline FEV1 after 400 microgrammes of inhaled salbutamol(10)); smoking status; chronic bronchitis (Medical Research Council criteria(11)); age; health status scores, from the Short Form 36 (SF36) physical and mental component scores, and St. George's Respiratory Questionnaire (SGRQ) total score; exacerbation rates characterised as Type 1 and 2 as described by Anthonisen(12), derived from self-reported retrospective recall on annual questionnaire; baseline FEV1 (% predicted); baseline KCO (% predicted); extent of emphysema on CT scan (inspiratory and expiratory films, lower and upper zones) using the Voxel Index (-910 Hounsfield units) as described previously(13).

The 95 of the 101 patients who had complete KCO data were also divided into tertiles according to their rate of KCO decline, and univariate and multivariate analyses were performed comparing the fast and slow decline tertiles for the same parameters as for the decline in FEV1 analyses described above.

The lung function equipment used was MasterScreen PFT (Jaeger, Germany) and quality control of equipment and technician input was according to American Thoracic Society (ATS)/ European Respiratory Society (ERS) standards(14-16).

High resolution computerised tomography (HRCT) scans were performed using a GE Pro speed Scanner (General Electric Medical Systems, Milwaukee, USA) to obtain 1mm slices. The scanner was calibrated weekly for water and air. A full scan was performed at maximal inspiration (10mm intervals) and a limited scan on expiration (30mm intervals). Two slices were chosen for analysis: the level of the aortic arch (upper zone) and the level of the inferior pulmonary vein/ right atrial confluence (lower zone). The data were subjected to density mask analysis, which highlighted lung voxels with a density less than -910 Hounsfield Units (HU). The Voxel Index is the percentage of highlighted voxels with a density lower than this threshold, reflecting the proportion of emphysematous tissue.

The exacerbation data was obtained from annual questionnaires based on retrospective recall. The questions were: 1) "Have you had any episodes of increased sputum volume or purulence since the last visit? If yes…How many? Which months?"; 2) "Have you had any episodes of increased breathlessness since the last visit? If yes…How many? In which months?". Where the answer was yes to question 1) and 2), the number of occasions where the identified months matched, was the number of Antonisen Type 1 and Type 2 exacerbations during that year.

Ethical approval was granted by the local research and ethics committee and all patients gave informed consent for the investigations.

Data analysis

The annual declines in FEV1 and KCO for each patient were estimated from all of the data using simple linear regression (SPSS® version 12). Multiple linear regression was used to adjust the continuous variables FEV1 decline and KCO decline for age, gender, cumulative smoking status and baseline FEV1 or KCO and to investigate the effect of other variables on the adjusted values.

Separately, non-parametric univariate analyses of the fast versus slow FEV1 and KCO decline tertiles for the parameters of interest were performed using Mann Whitney U tests. Multivariate analyses of FEV1 and KCO decline were then performed using forward stepwise logistic regression analysis (SPSS® version 12), with the same factors that were entered into the univariate analysis, using fast or slow decline tertile as the dependent variable. The significant variables in the stepwise analyses were then included in further logistic regression analyses along with age, gender, cumulative smoking exposure and FEV1 to see if they remained significant following adjustment for these factors.

Results

For the patients as a whole, the mean annual decline in FEV1 was 49.9 +/- 7.4 ml per year. When divided into severity groups according to baseline FEV1 (% predicted), the fastest average decline in FEV1 was in the moderate severity group (FEV1 % predicted 50-80%) at 90.1 +/- 19.7 ml per year. The speed of decline was also faster than average in the severe group (FEV1 % predicted 50-80%) at 51.9 +/- 7.6 ml per year, but lower than average in the mild group (FEV1 % predicted >80%) at 31.6 +/- 19.3 ml per year and in the very severe group (FEV1 % predicted <30%) at 8.1 +/- 9.6 ml/ year. The results are summarised in Figure 1.

However, the results for KCO decline differed from those for FEV1. The average KCO decline for the whole group was 0.015 +/- 0.004 mmol/min/kPa/l per year. When divided into severity groups for baseline FEV1 % predicted (*Figure 2*) there was a faster decline in KCO in the severe (0.030 +/- 0.006 mmol/min/kPa/l per year) and very severe (0.025 +/- 0.008 mmol/min/kPa/l per year) groups than in the moderate (-0.004 +/- 0.007 mmol/min/kPa/l per year) and mild groups (0.0122 +/- 0.012 mmol/min/kPa/l per year).

Multiple linear regression of FEV1 decline as a continuous variable on the factors listed in Table 1, adjusting for age, gender, cumulative smoking exposure and

baseline FEV1, showed baseline KCO, upper zone inspiratory CT scan Voxel Index and BMI were significantly associated with fast decline. BMI was most strongly associated with FEV1 decline (p=0.008) and once this was entered into the model, none of the other possible explanatory variables was significant.

Table 1 shows the results of univariate analysis for parameters that may be associated with FEV1 decline (with p-values) for differences between the fast decline (n=33) and the slow decline (n=34) tertiles. In the fast decline group, there were more patients with BDR (73% versus 41%, p=0.010), more males (79% versus 56%, p=0.048), and lower BMI (mean 24.0 versus 26.1, p=0.042). Multivariate analyses comparing the fast decline and slow decline tertiles indicated that the features that were independently predictive of fast decline of FEV1 were BDR, low BMI, high exacerbation rate and a high SF36 component score (*Table 2*).

Multiple linear regression of KCO decline as a continuous variable on the factors listed in Table 1, adjusting for age, gender, cumulative smoking exposure and baseline KCO, showed baseline FEV1 and the four CT scan Voxel Indices were significantly associated with fast decline. Lower zone expiratory CT scan Voxel Index had the strongest association with KCO decline (p=0.002) and once this was entered into the model, none of the other possible explanatory variables was significant.

Table 3 shows the results of univariate analysis for parameters potentially associated with KCO decline, when comparing the fast and slow decline tertiles. FEV1 (mean 41.8% predicted versus 60.2%, p=0.002) and emphysema Voxel Index scores on lower zone expiratory scan (mean 47.4% versus 33.1%, p=0.010) and upper zone expiratory scan (mean 24.2% versus 16.6%, p=0.042) were significantly different between the 2 groups. When multivariate analyses were performed comparing the fast decline and slow decline tertiles (*Table 4*), the only parameter that was independently predictive of fast decline of KCO was FEV1.

Discussion

The UK database provides a unique opportunity to study multiple factors in a cohort of highly characterised A1ATD patients not receiving augmentation therapy. Those with consecutive annual lung function had an average decline in FEV1 determined by summary statistics over a 3-year period of 49.9 ml/year. There have been few such studies reported in the literature, although the patients in the placebo group (n=28) in the Dutch/Danish pilot study of A1AT augmentation therapy(7), had an average decline in FEV1 of 59.1 ml per year over 3 years. In a comparative study between Danish patients (n=97) not receiving A1AT augmentation and German patients receiving augmentation(17), the Danish group had an average decline in FEV1 of 75.0 ml per year. In a German study pre- and post- A1AT augmentation treatment(8), the pre-treatment

group (n=96) had a decline in FEV1 of 49.2 ml/ year. Finally, in a US A1AT registry study(1), the mean decline in FEV1 was 56 ml per year in those never receiving A1AT augmentation therapy. Thus with the exception of the Danish/ German comparative group(17), data from all these studies are comparable, despite the wide range of initial FEV1 in our patients.

The decline is dependent on several factors. Firstly it relates to the initial FEV1 and our data show that the greatest change occurs in those with initial moderate FEV1 (50 to 80 %predicted) impairment (90.1 ml/ year), which is comparable with results from the US registry of 81.2 ml/ year in those not receiving augmentation therapy(1). The lack of decline in the most severe group (average 8.1.ml/ year) probably reflects a survivor effect(12), since, by study design, data could only be obtained from patients who survived at least 3 years. Since mortality reflects FEV1(18-23) it is likely that any rapid decliners in this group will have died during the study period. Why this observation is at variance with data from the NIH report for the similar group (average decline was 46.5 ml/year in those with FEV1 <35% not receiving augmentation therapy) remains unknown, especially as the median follow up was longer (52 months) in the NIH study.

When FEV1 decline was compared as a continuous variable, correcting for various confounding factors, BMI was found to have the best association in this more general analysis. In order to identify a specific subset at risk for rapid decline comparison was made between the two extreme tertiles for decline. This

has implications for both selection of patients for clinical trials of potential interventions and early introduction of effective therapies. Many factors were found to be associated with more rapid decline in these analyses. The finding that FEV1 decline was greater in patients with BDR and in males is in agreement with data from the US registry data(1). Lower BMI has been linked with greater progression of disease and mortality in A1ATD(24) and usual COPD(25). In the logistic multivariate analysis, BDR, low BMI and exacerbation frequency were found to be independent predictors of decline in FEV1.

Exacerbation frequency is known to relate to a speedier decline in lung function in A1ATD(26) and usual COPD(27). However the relationship to better physical health status may at first seem counter-intuitive. The most severely restricted patients, however, would be those with the lowest FEV1 and the reduced FEV1 decline in this group probably explains the association. Nevertheless with all these confounding factors, differences in any may explain the greater rate of progression seen in the untreated group in the Danish/German comparative study, as well as possibly the range of initial impairment(17).

The data differed for KCO decline, which was greatest in patients with severe disease, as defined by baseline FEV1 (% predicted). This would suggest that rapid decline in gas transfer is a late phenomenon in disease progression. Unlike FEV1 decline, which largely reflects bronchial disease, KCO decline reflects alveolar destruction alone. The analyses confirmed that only factors associated

with disease severity (baseline FEV1, CT Voxel indices) were significantly associated with KCO decline. Recent studies have shown that emphysema distribution relates differentially to FEV1 and KCO(28;29). Emphysema in A1ATD tends to dominate in the lower zones and spread to the upper zones as disease progresses. Lower zone emphysema has been shown to affect FEV1 more than KCO and upper zone emphysema has the opposite effect. Therefore it could be expected that KCO decline would become more pronounced in more severe disease as emphysema progresses from the bases to involve the upper zones as found here.

These data provide information central to the identification of fast decliners. For FEV1 the decline is greatest in moderate to severe disease and in this group BDR, low BMI and increased exacerbation frequency independently predict the rate. Thus if FEV1 decline is the primary outcome, patients with these characteristics would be best recruited for the testing of interventional strategies and instigation of effective preventative therapy.

Although KCO is a more specific measure of emphysema, it progresses most rapidly in the most severe groups. At this point physiological impairment is well established and it is unlikely that gas transfer would be an effective marker for identifying rapid decliners early enough in the disease to be effective or to provide a robust group for long term studies to determine the efficacy of new treatments.

In the current study, CT scans were not available in all patients over the 3 years. However other studies have shown that this parameter alone shows progression independent of disease stage(30). This reinforces its use as a primary outcome measure, especially since it is the best indirect measure of pathological emphysema. If the efficacy of specific interventions is confirmed using CT scores as an outcome, it is also likely to become the measure of choice in determining rapid progression before physiological tests become adversely affected.

The current study had some limitations. The analysis was performed only on those patients on whom 4 consecutive annual pulmonary function test results were available, in order to obtain the most accurate regression data. Therefore patients were excluded who did not have consecutive lung function performed because of missed appointments, withdrawal from the programme, or death. Exclusion of this latter group in particular could modify the associations with declining lung function towards factors that influence survival (the “healthy survivor effect”). The results of the logistic regression analyses compared the fast and slow tertiles for lung function decline, with the aim of identifying differences between the two extreme groups, but when a separate linear regression analysis was undertaken assessing lung function decline as a continuous variable the results were slightly different. Most data was determined objectively, but the exacerbation data relied on subjective recall and because the patients were visiting the centre from all parts of the country, independent verification of

exacerbations and hospitalisations from health records was impossible. Nevertheless when diary card identification and primary care records have been assessed such recall has proven reasonably reliable(31), suggesting the associations found here are likely to be valid.

In summary, we have shown that in a group of PiZ phenotype A1ATD patients, FEV1 decline was greatest in those with moderately severe disease, and this showed associations with BDR, BMI, male gender and (in a multiple regression analysis) exacerbation rate. KCO decline, on the other hand, was greatest in severe disease, and was only associated with other measures of disease severity (FEV1 and CT densitometry). These findings have implications for the subgroups of patients to target with future clinical trials, and the stage at which effective therapy should be targeted.

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Figure legends

Figure 1: FEV1 decline according to 4 severity groups based on FEV1 (% predicted). The mean and standard error bars are shown for data at the start (BASE) and at the end (M36) of the 3-year follow up. Note the greatest decline in the moderate severity group. Key: y= the mean difference in FEV1 decline (shown with standard error) from baseline to 36 months. BASE= baseline FEV1. M36= month 36 FEV1.

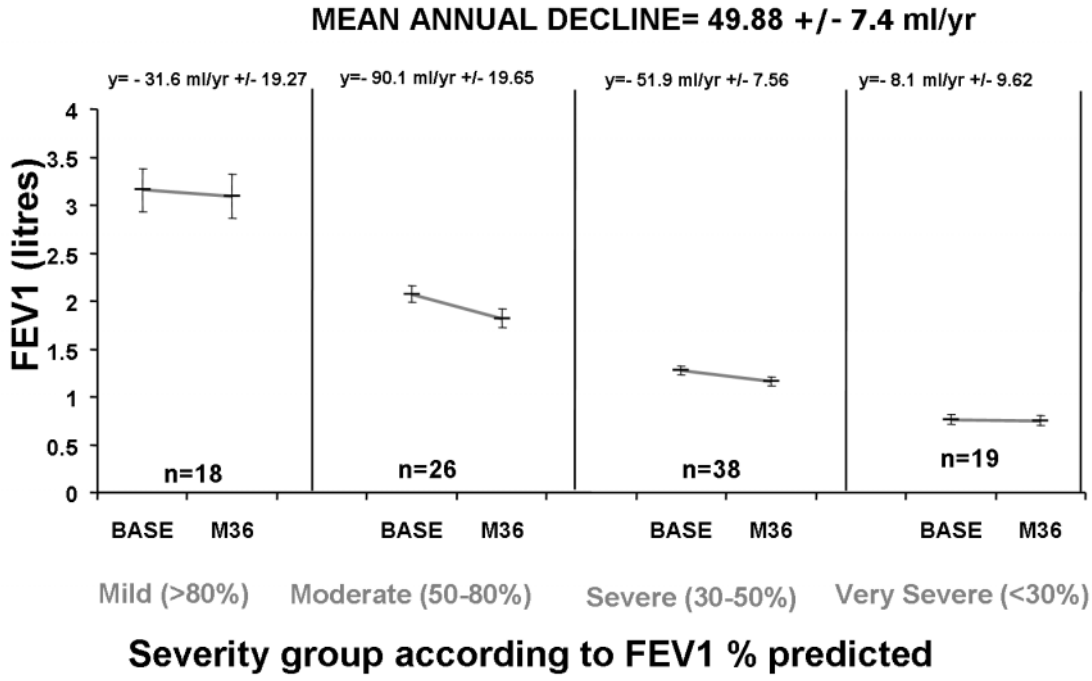
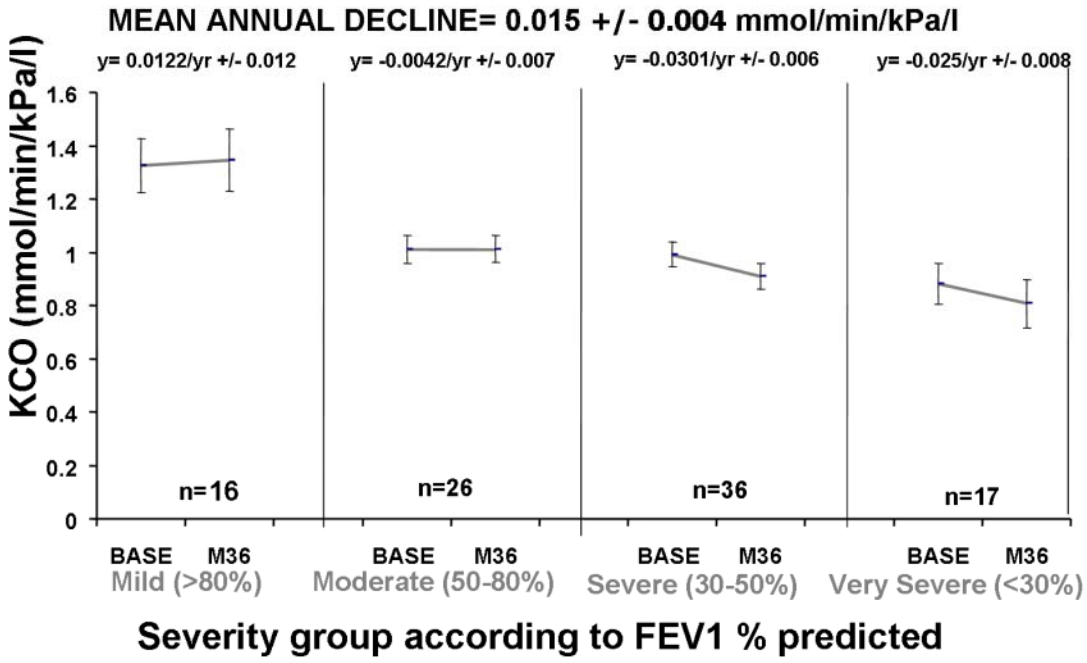


Figure 2: KCO decline according to 4 severity groups based on FEV1 % predicted. The mean and standard error bars are shown for data at the start (BASE) and at the end (M36) of the 3-year follow up. Note the greatest decline in severe and very severe groups. Key: y= the mean difference in KCO decline (shown with standard error of the difference) from baseline to 36 months. BASE= baseline KCO. M36= month 36 KCO.



Tables

Table 1: *Univariate analysis comparing the fast tertile for rate of decline in FEV1 (n=33), the middle tertile (n=34) and the slow tertile (n=34). The significance of differences between the fast and slow tertiles are shown (p) and those statistically significant are highlighted. Key: FEV1= forced expiratory volume in 1 second; SD= standard deviation; BMI= body mass index; SGRQ= St George's Respiratory Questionnaire; SF36= short form 36; ATS= American Thoracic Society; KCO= gas transfer corrected for alveolar volume; CT= computerized tomography.*

Parameter	**Fast tertile for FEV1 decline**		**Middle tertile For FEV1 decline**		**Slow tertile for FEV1 decline**		**Significance (fast versus slow tertile)**
	n	**Result**	**n**	**Result**	**n**	**Result**	**P value**
Gender	33	♂=26, ♀= 7	34	♂=22 ♀= 12	34	♂=19, ♀=15	**p=0.048**
Age (years)	33	Mean 51.2 (SD 8.62)	34	Mean 52.7 (SD 11.0)	34	Mean 49.1 (SD 8.57)	p=0.184
Smoking	33	Ever= 26, Never= 7	34	Ever= 28 , Never= 6	34	Ever= 29, Never= 5	p=0.222
Cumulative smoking history (pack years)	33	Mean 17.0 (SD 13.6)	34	Mean 19.8 (SD 14.7)	34	Mean 18.7 (SD 16.6)	p=0.801
Index case	33	Yes= 30, No= 3	34	Yes= 31, No= 3	34	Yes= 26, No= 8	p=0.113
BMI (kg/m^2)	33	Mean 24.0 (SD 2.63)	34	Mean 26.1 (SD 4.01)	34	Mean 26.1 (SD 4.33)	**p=0.042**
Chronic bronchitis	33	Yes= 13, No=20	34	Yes= 14, No=20	34	Yes=19, No=15	p=0.180
SGRQ total score	33	Mean 49.6 (SD 20.1)	34	Mean 56.2 (SD 18.5)	34	Mean 51.6 (SD 24.7)	p=0.498
SF36 physical component score	33	Mean 40.3 (SD 9.41)	34	Mean 33.9 (SD 10.5)	34	Mean 36.1 (SD 12.0)	p=0.063
SF36 mental score	33	Mean 48.4 (SD 13.0)	34	Mean 48.7 (SD 10.4)	34	Mean 49.5 (SD 11.0)	p=0.950
Bronchodilator reversibility	33	Yes= 24, No= 9	34	Yes= 24, No= 10	34	Yes= 14, No= 20	**p=0.010**
Baseline FEV1 (% predicted)	33	Mean 60.1 (SD 22.7)	34	Mean 47.9 (SD 24.9)	34	Mean 55.0 (SD 35.8)	p=0.053
Baseline KCO (% predicted)	33	Mean 64.0 (SD 21.9)	33	Mean 68.9 (SD 18.5)	34	Mean 71.6 (SD 28.3)	p=0.205
Upper inspiratory CT scan Voxel Index (%)	33	Mean 37.3 (SD 17.7)	34	Mean 31.8 (SD 15.3)	33	Mean 29.9 (SD 19.1)	p=0.070
Upper expiratory CT scan Voxel Index (%)	32	Mean 23.2 (SD 13.9)	33	Mean 20.1 (SD 15.5)	33	Mean 20.6 (SD 19.8)	p=0.238
Lower inspiratory CT scan Voxel Index (%)	33	Mean 48.3 (SD 19.7)	34	Mean 52.2 (SD 15.4)	33	Mean 43.6 (SD 21.4)	p=0.509
Lower expiratory CT scan Voxel Index (%)	32	Mean 37.1 (SD 18.3)	33	Mean 43.0 (SD 18.0)	33	Mean 36.6 (SD 22.1)	p=0.906
Exacerbation rate (per year)	33	Mean 1.61 (SD 1.20)		Mean 1.48 (SD 1.07)	34	Mean 1.22 (SD 0.71)	p=0.267

Table 2: *Results of logistic regression analyses with fast/ slow tertile for rate of decline in FEV1 as the dependent variable. All variables listed in Table 1 were available for inclusion in the stepwise model; variables listed were forced into the adjusted model. Odds ratio relate to odds of being in the fast tertile. 95% confidence intervals (CI) for odds ratio are shown in parentheses. Key: FEV1= forced expiratory volume in 1 second; BMI= body mass index; SF36= short form 36; ATS= American Thoracic Society.*

Parameter	**From stepwise logistic regression**		**From logistic regression adjusted for gender, age, smoking and FEV1**	
	Odds ratio (95% CI)	**P value**	**Odds ratio (95% CI)**	**P value**
SF36 physical component score	1.102 (1.030-1.180)	**0.005**	1.080 (1.004-1.161)	**0.039**
Exacerbation rate	2.760 (1.245-6.119)	**0.012**	2.725 (1.184-6.271)	**0.018**
Bronchodilator reversibility (ATS criteria)	4.316 (1.300-14.334)	**0.017**	3.997 (1.083-14.748)	**0.038**
BMI (kg/m^2)	0.818 (0.680-0.984)	**0.033**	0.775 (0.620-0.968)	**0.025**
Gender (female)	-	-	0.445 (0.108-1.839)	0.264
Age (years)	-	-	1.005 (0.925-1.091)	0.913
Smoking (pack years)	-	-	1.002 (0.958-1.047)	0.935
FEV1 (% predicted)	-	-	1.016 (0.990-1.044)	0.232

Table 3: *Univariate analysis comparing the fast tertile for rate of KCO decline (n=32), the middle tertile (n=31) and the slow tertile (n=32).The significance of differences between the fast and slow tertiles are shown (p) and those statistically significant are highlighted. Key: FEV1= forced expiratory volume in 1 second; SD= standard deviation; BMI= body mass index; SGRQ= St George's Respiratory Questionnaire; SF36= short form 36; ATS= American Thoracic Society; KCO= gas transfer corrected for alveolar volume; CT= computerized tomography.*

Parameter	**Fast tertile for KCO decline**		**Medium tertile for KCO decline**		**Slow tertile for KCO decline**		**Significance**
	n	**Result**	**n**	**Result**	**n**	**Result**	**P value**
Gender	32	♂= 21, ♀=11	31	♂= 21, ♀=11	32	♂= 20, ♀=12	p=0.796
Age (years)	32	Mean 50.3 (SD 7.43)	31	Mean 51.7 (SD 7.91)	32	Mean 51.2 (SD 11.2)	p=0.667
Smoking	32	Ever= 28, Never= 4	31	Ever= 26, Never= 5	32	Ever= 24 , Never= 8	p=0.887
Cumulative smoking history (pack years)	32	Mean 22.3 (SD 15.9)	31	Mean 15.2 (SD 10.3)	32	Mean 18.8 (SD 17.6)	p=0.293
Index case	32	Yes= 29, No= 3	31	Yes= 27, No= 4	32	Yes= 26 , No= 6	p=0.285
BMI (kg/m^2)	32	Mean 25.1 (SD 3.65)	31	Mean 24.6 (SD 3.28)	32	Mean 26.1 (SD 4.26)	p=0.468
Chronic bronchitis	32	Yes= 15, No= 17	31	Yes= 15, No= 16	32	Yes= 12, No= 20	p=0.451
SGRQ total score	31	Mean 56.6 (SD 17.8)	31	Mean 47.6 (SD 21.2)	31	Mean 54.2 (SD 22.3)	p=0.938
SF36 physical component score	32	Mean 36.3 (SD 9.46)	31	Mean 48.7 (SD 9.36)	32	Mean 34.9 (SD 12.4)	p=0.493
SF36 mental component score	32	Mean 48.0 (SD 11.6)	31	Mean 50.4 (SD 12.4)	32	Mean 48.5 (SD 9.71)	p=0.936
Bronchodilator reversibility (ATS criteria)	32	Yes= 25, No= 7	31	Yes= 15, No= 16	32	Yes= 20, No= 12	p=0.175
Baseline FEV1 (% predicted)	32	Mean 41.8 (SD 16.4)	31	Mean 60.6 (SD 32.3)	32	Mean 60.2 (SD 29.7)	**p=0.009**
Baseline KCO (% predicted)	32	Mean 68.1 (SD 20.9)	31	Mean 67.9 (SD 28.0)	32	Mean 68.6 (SD 22.1)	p=0.952
Upper inspiratory CT scan Voxel Index	32	Mean 34.1 (SD 16.1)	31	Mean 37.4 (SD 17.0)	32	Mean 27.8 (SD 18.7)	p=0.087
Upper expiratory CT scan Voxel Index	32	Mean 24.2 (SD 15.9)	31	Mean 23.5 (SD 17.8)	32	Mean 16.6 (SD 15.3)	**p=0.042**
Lower inspiratory CT scan Voxel Index	32	Mean 55.0 (SD 13.4)	31	Mean 47.3 (SD 18.0)	32	Mean 42.8 (SD 23.6)	p=0.067

Lower expiratory CT scan Voxel Index	32	Mean 47.4 (SD 13.9)	31	Mean 47.4 (SD 13.9)	32	Mean 36.1 (SD 19.6)	**p=0.010**
Exacerbation rate (per year)	32	Mean 1.42 (SD 1.52)		Mean 1.56 SD (1.05)	32	Mean 1.38 (SD 1.37)	p=0.673

Table 4: *Results of logistic regression analyses with fast/ slow tertile for rate of decline in KCO as the dependent variable. All variables in Table 3 were available for inclusion in the stepwise model; variables listed were forced into the adjusted model. 95% confidence intervals (CI) for odds ratio are shown in parentheses. Key: FEV1= forced expiratory volume in 1 second.*

Parameter	**From stepwise logistic regression**		**From logistic regression adjusted for gender, age and smoking**	
	Odds ratio (95% CI)	**P value**	**Odds ratio (95% CI)**	**P value**
FEV1 (% predicted)	0.964 (0.938-0.991)	**0.009**	0.964 (0.938-0.991)	**0.009**
Gender (female)	-	-	0.910 (0.269-3.075)	0.879
Age (years)	-	-	0.977 (0.916-1.043)	0.490
Smoking (pack years)	-	-	0.999 (0.967-1.033)	0.965