Original Research

Proposal and Validation of the Minimum Clinically Important Difference in Emphysema Progression

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Running Head: Proposal of MCID Lung Density in AATD

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Abbreviations: AATD; alpha-1 antitrypsin deficiency, RCT; randomised controlled trial, CT; computerised tomography, COPD; chronic obstructive pulmonary disease, FEV_1;forced expiratory volume in one second, MCID; minimum clinically important difference, SD; standard deviation, MDD; minimal detectable difference, CI; confidence interval, SEM; standard error of the mean, PD15;15th percentile lung density, K_{CO}; carbon monoxide transfer co-efficient, TLC; total lung capacity, SGRQ; St George's respiratory questionnaire, PRO; patient reported outcome

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Abstract

Background: The severity of emphysema may be measured by lung density on CT scanning, and in alpha-1 antitrypsin deficiency (AATD) this measure has been used as the primary outcome in trials of disease modifying therapy, namely augmentation. However, the minimum clinically important difference (MCID) in lung density change is not known; this study aimed to derive and validate MCIDs for density values in AATD.

Methods: The distribution method and anchoring density against FEV_1 was used to derive mean and 95% confidence intervals for the MCID. Data from systematic reviews of CT density measurement and therapy for AATD obtained both absolute and annual change in lung density. Using the range of potential MCID generated by these methods, a value was chosen for validation against mortality, lung function and health status in the Birmingham (UK) AATD cohort, using regression to adjust for confounders.

Results: Anchor and distribution methods generated a probable MCID of -1.87 g/L/year (range -1.53 to -2.20). The greatest differences between groups were found at the -2.2g/L/year with a greater FEV_1 decline in individuals with greater lung loss. Absolute lung density change had a probable MCID of -2.04g/L (range -1.83 to -2.30), and there was a difference in lung function ($p<0.001$) and mortality; where individuals whose absolute lung loss of more than -2.04g/L had a greater risk of death ($p<0.05$).

Interpretation: From initial evidence, we have shown absolute lung density change as a potential outcome for emphysema modifying therapies in AATD than annual density change, with an MCID of -2.04g/L.

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INTRODUCTION

Alpha-1 antitrypsin deficiency (AATD) is the only widely recognised genetic risk factor for emphysema[1]. Enhancing AAT levels using plasma derived protein (augmentation therapy) has therefore been the standard of care in some countries for many years[2]. Meta-analysis of RCT data[4], and a single adequately powered RCT[5], have suggested a consistent benefit on emphysema progression, as defined by quantitative CT lung densitometry. However, these data remain controversial with drug regulators and clinicians due to the debate on the clinical impact of densitometry changes as the primary outcome measure.

Quantitation of emphysema based on lung density has become a widely used technique in research over the last 20 years. A systematic review has shown that lung density relates to conventional measures of disease severity and outcomes in non-deficient COPD[6] and AATD, describing lung density measured by CT being the best predictor of subsequent survival[7]. It is a repeatable[8-10], specific and a highly sensitive measure of emphysema progression. These attributes make it a suitable outcome for drug trials targeting the pathophysiology of emphysema. However, unlike many other measures used in COPD trials, such as FEV_1 or quality of life, there is not an established minimal clinically important difference (MCID). An accepted MCID could provide better clarity in understanding the impact of quantitative CT imaging of emphysema progression, as well as facilitating power calculations for experimental trial design and its interpretation.

An MCID is defined as "the smallest change in an outcome that a patient would identify as important"[11]. It represents a move away from simply being a statistically significant difference in one outcome and instead towards a threshold beyond which patients would notice a benefit. There are two recognised methods for proposing an MCID, namely the "anchor" and the "distribution" methods. The anchor method uses an established MCID from a recognised clinical parameter and plots the change of the known 'anchor' against the change in the

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parameter being explored. For example, if lung density is correlated with FEV_1 in the same patient cohort, then the density difference equivalent to the MCID of FEV_1 (100mls) can be determined by interpolation. The value obtained would be an appropriate MCID for CT densitometry[12]. The distribution method has multiple variations but measures the standard deviation (SD) to determine a threshold which exceeds the margin of measurement error[11]. For this reason, the distribution method may also be more correctly regarded as the minimal detectable difference (MDD).

This study was designed to identify a range of potential MCID values for absolute and annual lung density decline in AATD using the anchor method and distribution method. Using AATD cohort data, the MCID values were validated against lung function, health status and mortality.

METHODS

Determination of MCID using anchor method

Only one published paper contained lung density data anchored against FEV_1[14]. This was achieved by correlating lung density with FEV_1 change. However, the data was presented as a pooled group of placebo and augmentation treated patients, whose disease progression was different. This meant that the effect of augmentation had to be considered in the anchoring process. The placebo and treatment arms from the pooled data were anchored to the change in CT density and the change in FEV_1on both axes, generating a linear regression plot (Figure 1). This slope between time bound metrics; Δdensity and ΔFEV1 was reported as approximately 8.5. By then solving simultaneous equations, the intercept of the placebo and treatment arms would be 6.8 and 10.2 respectively. By inputting the new slope and using two known values of x and y into the linear regression equation y;a+bx it was possible to calculate the intercept, and thus the MCID and its 95% confidence intervals (CI).

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Determination of MDD using distribution method

Using our prior systematic review studies in AATD[4], the mean and SD of CT lung density (as measured by the PD15 g/L^{-1}) at baseline and with subsequent annual change were selected. Two statistical methods were used to determine the MDD based on the data obtained at baseline and for the lung density decline/year: standard error of the mean (SEM) and 0.5*SD. Given this is a baseline change, the proposed MDD will be an absolute value rather than annual change. Similarly, where we have used the annual change in SD, this MDD represents a proposed value for annual lung density decline.

As CT lung density is known to be the most sensitive measure of emphysema progression[13], rather than moderate or large effects, we selected the adjustment for small effects only and calculated 95% CI for the estimates of MDD. The potential MCID derived by anchoring[14] was plotted on a graph alongside the MDD values generated by the distribution method to illustrate the degree of agreement between techniques (figure 2).

Validation by comparing characteristics and survival of patients by MCID or MDD

Annual Lung Density Decline

AATD patients were selected from a cohort in Birmingham, UK who had taken part in either an observational study or in the placebo arm of an RCT[7,14]. Only patients which had ≥2 CT scans performed using a smooth reconstruction algorithm (B30f), slice thickness 5mm and an increment of 2.5mm were selected. CT images were analysed by PULMO software to derive the 15th percentile density (PD15) as the lung density. The density decline was calculated by comparing the first and last CT scans. This group has been reported previously[7]. After obtaining the range of proposed MCID values obtained from the decline distributions (range shown in figure 2), Comparative analyses were conducted by comparing patients with lung

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density decline above or below the proposed MCID. Rate of death and disease progression as determined by FEV_1, gas transfer or health status decline (SGRQ) were compared between groups. Exploratory analyses were also conducted using the full range of plausible MCID and their 95% CI, as determined by the methods above. Data normality was explored prior to comparison of groups, and appropriate parametric or non-parametric tests selected; statistical analysis was carried out using SPSS® 29.0 and statistical significance was assumed at $p<0.05$. Multivariable regressions were then carried out, adjusting for age and baseline density, as in our prior work[7]. Two tailed tests were used throughout, since the RAPID study showed some patients, whose density increased during follow up, though this was less common than decline.

Absolute Lung Density Change

All patients in a separate, multicentre, British study of physiology and lung density were included for this analysis[15]. We examined cross-sectional data only for absolute lung density decline; here we used the mean density, and then compared patients with baseline density above the median v median minus the proposed MDD (or more), this being -2.04g/L (range shown in figure 1) for lung function and quality of life at baseline. Univariate statistics were used for all comparisons.

RESULTS

Anchor Method

Published AATD data provided enough information to correlate FEV_1 and CT lung density change over time[14] and by solving equations for anchoring, this generated an MCID of -2.03g/L/year (range -1.87 to -2.20).

Distribution Method

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Three studies reported the baseline and annual change in CT lung density in placebo arms (Table 1).

Using the baseline lung density SD and the two methods of calculating MCID, the generated values (95% CI) are as follows: SEM; -2.04g/L and 0.5*SD;10.2g/L. When assessing the annual density decline, the values were: SEM -0.34g/L/year and 0.5*SD 1.74g/L/year.

The proposed MCID and ranges are shown in Figure 2.

Validation against longitudinal outcomes

There was cross-sectional data available for 147 AATD patients, and longitudinal data for 77 AATD patients, as reported previously [7, 15]. Table 2 shows the baseline characteristics of these patients, stratified by absolute and annual decline in CT lung density for cross-sectional and longitudinal cohorts, respectively.

Comparative Analyses

The cross-sectional dataset compared groups with patients with above median lung density (34.77g/L) with patients with a median minus the MDD of -2.04, this being 32.73g/L. In comparative analyses of the longitudinal cohort, the lowest value of the proposed MCID range of the annual CT lung density decline, -2.2g/L/year, demonstrated the greatest differences between groups in lung function measures. Comparative analyses were carried out all values of MCID, but these did not show significant differences. See supplement for comparisons of data at the middle MCID threshold.

Table 2 shows comparisons of outcomes with patients either side of the proposed absolute and annual change of lung density MCID thresholds, comparing baseline characteristics, mortality rate and subsequent decline in lung function and health status. This demonstrates that patients with an absolute lung density worse than the proposed MCID have significantly poorer lung

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function parameters but comparatively similar health status. Those with lung density decline in excess of the proposed MCID, ie the fast decliners, exhibited a statistical significantly lower baseline CT lung density and greater FEV_1 decline.

Survival Analyses

The longitudinal cohort data and was used for multivariable Cox regression analyses. The hazard ratios (HR) and 95% CI for death were compared in patients whose decline were below the tested MCID with patients whose decline were above the tested MCID. Baseline co-variables were included and adjusted for in the multivariate analysis; age, lung density, FEV_1pp (FEV_1 percentage predicted) and SGRQ. The follow up period was on average 11.8 years.

Table 3 shows the HR for death in patients with lower density decline than the listed value, relative to those with a higher density decline. This was statistically significant for absolute decline MCID values only. No significant differences were shown in the risk of death when comparing fast decliners vs slow decliners divided by the annual MCID.

DISCUSSION

Our study demonstrated a plausible MCID for absolute lung density decline of 2.04g/L, on the basis that this value lies within a range that is detectable (MDD; distribution method) in independent groups. Our study is strengthened using a systematic literature review as well as validating in highly characterised AATD cohorts. These results will be important for powering trial design in emphysema, specifically AATD.

Conceptually we felt it was important to generate MCID based not only on the distribution of measures in a population at baseline, but also based on lung density change over time. The measures at baseline reflects a person's past disease progression, in that they must have deteriorated from a healthy state to a lower density, however this does not necessarily reflect

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subsequent progression, particularly in cases with precipitating factors such as smoking. We have shown this previously in the Birmingham cohort, in whom decline in lung function differs according to smoking status[17]. Consequently, the distribution of density change may differ from the distribution of baseline density, such that detectable differences in each will also differ. Furthermore, a change in absolute lung density is different from the rate of density decline when it comes to designing clinical trials and interpreting the effects of treatment. Augmentation therapy appears to alter the rate of decline over time[5] and powering on an absolute lung density difference equivalent to MCID could give different results and durations compared to lung density change per year. As more targeted therapies for emphysema are developed, trials may well involve focused populations equally difficult to recruit as those in AATD studies, thus efficient designs might aim for a shorter duration on treatment – to do this an MCID in g/L/year is more desirable than an overall lung density change.

An alternative method to ensure that an MCID is valid would be to test the MCID for relationship to other outcomes important to patients, or generally accepted as clinically relevant. For this reason, we also tested relationship between absolute and annual change MCID estimates against FEV_1, K_{CO} and SGRQ decline. The FEV_1 decline did relate to annual lung density change, but there was no significant relationship to K_{CO} and SGRQ, which likely reflects a combination of sensitivity and small cohort size. The greatest difference between groups was identified when comparing the cohort at the MCID of 2.2g/L/year decline - the upper limit of MCID annual decline range generated from the anchor method. This potentially suggests this patient cohort represents the rapid end of AATD progression. The K_{CO} was generally greater in the cross-sectional group compared with the longitudinal group and interestingly, in the cross-sectional dataset, a greater K_{CO} was found in the group with a lower lung density. This suggests possibly another factor that may be affecting the K_{Co} other than density such as the disparity in the cohort of patients and/or the equipment used. When

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assessing mortality, the mid-range and 95% CI of our proposed absolute lung density MCID all related significantly to death, with greater lung loss conferring to a higher likelihood of death, although annual density change alone did not relate to mortality.

A true MCID should reflect important issues for the patient, so ideally, we should also have anchored against health status in published literature, although this was not possible (no correlations between SGRQ and density published in RCTs). Whilst we would have been able to do this in this AATD cohort, we felt it was not appropriate to generate an estimate based on anchoring to SGRQ as this data is only from one (probably unique) population. Hence we limited our anchoring strategy to FEV_1. Various studies in COPD and AATD have related FEV_1 and SGRQ, and whilst correlations exist, they are not always strong; a systematic review quoted an r value between FEV_1 and SGRQ of -0.46, though the relationship seemed to strengthen where an increase in FEV_1 was associated with improvement in SGRQ[18]. It is also debatable whether SGRQ is the most appropriate patient-reported outcome (PRO) to use in an AATD population for anchoring as it was generated for use initially in non-deficient COPD and a PRO developed in an AATD population (which is generally younger) might differ. Having a disease-specific PRO was recognized as a patient priority by the European Respiratory Society working party for AATD[20].

We recognise the small cohort size and the low cases of mortality may generate a skewed picture and therefore limits the lung densitometry MCID as a sound validation tool. Further work using a larger sample size and including patients with a range of AATD progression would provide stronger validation. An additional limitation is that the underlying cohorts used to derive the MCIDs do not contain complete data on potentially relevant factor such as smoking status, smoking history, exacerbation history, comorbidities, or socio-economic status. Lack of these data make generalization of our MCID to other cohorts unclear. Data on

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the type of CT scanner and study site, which may also have influenced the results, were not available.

Since our analyses have encompassed both MCID (anchor method) and MDD (distribution method) is also important also bear in mind why MDD was developed. As MDD identifies a difference that surpasses the instrumental noise, essentially there is greater confidence that the change is not affected by random variability. In most cases this was so that trials could be designed around MDD for a measure that would actively improve after a therapeutic intervention (eg an increase in FEV_1 in asthma following bronchodilator therapy). Whether the distribution method is appropriate for baseline measure that improve with therapy rather than dynamic and time dependant parameters, such as emphysema progression is debatable, and thus supports the approach of using a time bound MCID (ie our annual change MCID rather than an absolute value in g/L). This will be more relevant for therapies which reduce progression as opposed to reversing a degenerative process rather than for regenerative processes for emphysema in future.

Since finding a radiographic MDD is of great interest (and has potential to serve as a surrogate endpoint for clinical interventions), examining a meaningful absolute MDD could also be explored in cohorts with longitudinal data from clinical trials, looking at absolute decline as the primary predictor, though we were unable to execute this in our cohort.

INTERPRETATION

In conclusion, initial evidence suggests an MCID in absolute CT lung density decline of -2.04g/L, and a possible MCID in annual CT lung density decline of -1.87g/L/year in AATD. This demonstrates promise for the use of radiographical MDD and encourages further work to validate our proposal exploring cohort data with absolute and annual lung density decline.

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Declaration of Interests

EH, DC and DK declare no conflicts of interest. AT reports financial support was provided by Grifols Inc. AT reports a relationship with CSL Behring that includes: consulting or advisory, funding grants, and speaking and lecture fees; honoraria or grant outside this work include GSK, AZ, Chiesi. RS reports financial support from CSL Behring for investigator funding. PE reports honoraria and consulting fees for GSK, Chiesi, AstraZeneca and Takeda. All authors declare no conflicts of interest in relation to the present study.

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Tables

Table 1: Published baseline and annual change in CT lung density in placebo arms of RCTs

	No. of patients	Baseline lung density mean (SD) [g/L]	Annual lung density loss mean (SD) [g/L/year]	Reference
	28	73.00 (25.29)	-2·57 (-2.18)	(16)
	39	45·48 (16.95)	-1·39 (-5.50)	(14)
	87	48·90 (15.50)	-2·19 (-2.33)	(5)
Total	154	52·42 (20.4)	-2·06 (3.4)	

SD;standard deviation

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Table 2. Clinical parameters for patients with lung density decline faster or slower than MCID

	Absolute			Annual		
	Lung Density < 32.73 g/L N;69 unless stated otherwise	Lung Density ≥34.77g/L N;73 unless stated otherwise	*P*	Fast decliners (Lung density < -2.2g/L/year) (N;37 unless stated otherwise)	Slow decliners (Lung density ≥-2.2g/L/year) (N;40 unless stated otherwise)	*P*
Age	60.76 (8.98)	57.54 (10.2)	0.03[a]	57.6 (7.53)	52.6 (2.82)	0.48
Male sex	*26 (37.7%)*	*34 (46.6%)*	0.28	*20 (54.1%)*	*24 (60%)*	0.59
Smoking status[b] (%)						
Current	4 (7.4)	2 (3.4)	0.62	3 (12.0)	1 (2.3)	0.24
Former	37 (68.5)	41 (69.5)		15 (60.0)	29 (72.5)	
Never	13 (24.1)	16 (27.1)		7 (28.0)	10 (25.0)	
Pack year history[b]	12.9 (11.8)	13.0 (16.4)	0.98	18.8 (20.1)	18.1(15.3)	0.87
COPD[b]	53 (100.0)	55 (93.2)	0.16	22 (88.0)	40 (100.0)	0.09
Bronchiectasis[b] (%)	14 (26.9)	19 (33.3)	0.60	4 (16.0%)	4 (10.0%)	0.66
Asthma (%)	2 (3.8)	4 (7.1)	0.74	8 (32.0)	6 (15.0)	0.14
Annual exacerbation frequency[b]	1.33 (1.21)	1.48 (1.32)	0.55	1.50 (1.59)	1.39 (1.69)	0.80
FEV_1	1.35 (0.54)	1.87 (0.84)	<0.01[a]	1.77 (0.93)	1.43 (0.72)	0.06
FEV_1 %	44.76 (18.0)	64.10 (22.1)	<0.01[a]	52.61 (14.1)	52.65 (29.9)	0.17
K_{CO}[b]	0.76 (0.22)	1.09 (0.647)	<0.01[a]	1.94 (2.70)	1.05 (0.31)	0.13
K_{CO} %[b]	51.0 (14.7)	66.2 (15.1)	<0.01[a]	25.07 (8.58)	21.8 (6.87)	0.17
CT Density (g/L)	22.6 (7.48)	51.5 (14.4)	<0.01[a]	69.0 (33.2)	47.9 (21.0)	<0.001[a]
SGRQ[b]	48.3 (18.1)	40.9 (19.0)	0.02[a]	42.2 (14.8)	40.2 (15.2)	0.29
Death[c]	*15 (27.8%)*	*9 (37.5%)*	0.1	*12 (32.4%)*	*15 (37.5%)*	0.64
FEV_1 lung decline (mL/year)				-49(64)	-14 (36)	0.03[a]
K_{CO} decline				-0.82 (0.77)	-0.314 (0.51)	0.12
SGRQ decline[d]				1.85 (2.12)	0.44 (2.21)	0.20

N;sample size, FEV_1;forced expiratory volume in one second, K_{co}; carbon monoxide transfer coefficient, TLC ;total lung capacity, SGRQ;St George's respiratory questionnaire

Data is shown as mean (standard deviation) or *N (%)* [a];p<0.05. Values in bold represent those <0.12 used for multivariate regression analysis. Decline in lung function is shown as % predicted/year unless otherwise stated, and health status as total SGRQ and health status change in total SGRQ/year.

[b]*Missing data. (see supplement)*

[c]*Incomplete death data of cross-sectional cohort outside of Birmingham with approximately 15 and 14 participants.*

[d]*Incomplete SGRQ decline data for 16 and 24 participants respectively.*

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Table 3. Risk of death in multivariable Cox regression across the 95% CI for MCID in the longitudinal cohort

MCID	HR	95% CI	p value
Absolute lung density decline (g/L)			
-2.30	4.55[a]	1.30-16.67	0.02
-2.04	4	1.16-1.41	0.03
-1.83	4	1.16-1.41	0.03
Annual lung density decline (g/L/year)			
-2.20	1.52	0.60-3.85	0.38
-1.87	2.18	0.89-5.26	0.07
-1.53	1.62	0.67 - 3.85	0.28

MCID;minimum clinically important difference, HR;hazard ratio, CI;confidence interval
HR compares lung density decline below the MCID in reference to density decline above the MCID.
[a]*For example; patients with an absolute lung density decline of 2.3g/L or more had a 4.5 times greater risk of death compared to those with an absolute density decline less than 2.3g/L when adjusted for baseline co-variables.*

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Figures

Figure 1. Demonstration of the anchor method

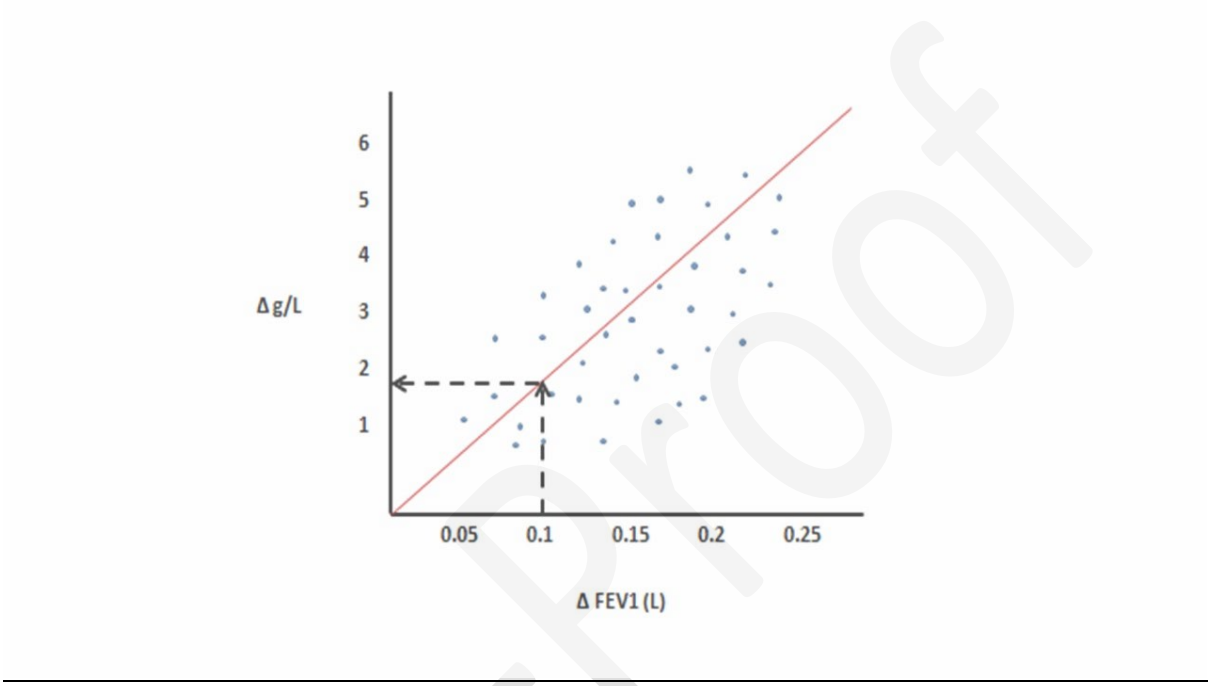

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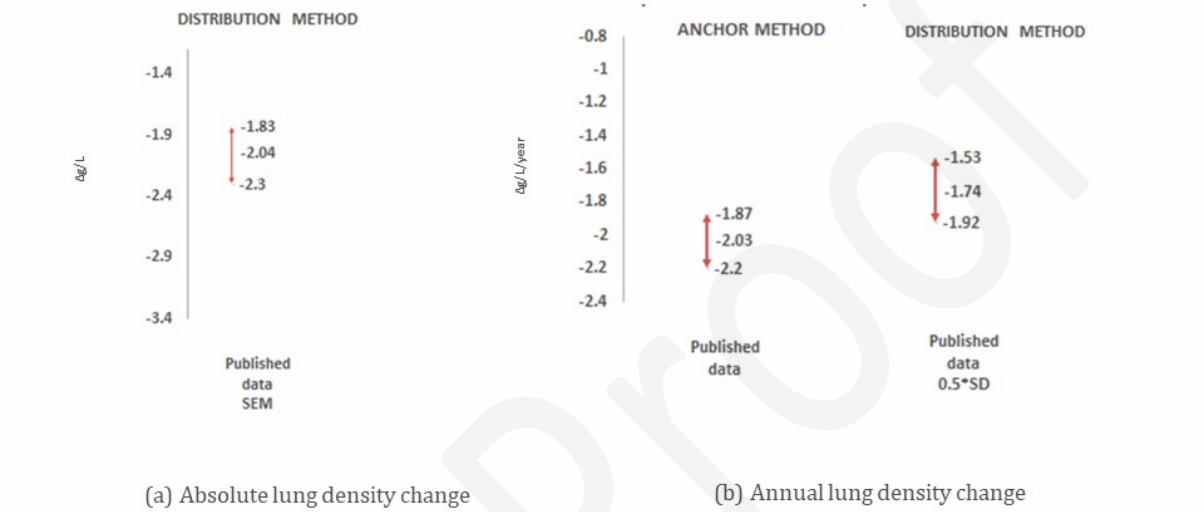
Figure 2. Summary of proposed MCIDs for absolute and annual CT lung density change



(a) Absolute lung density change

(b) Annual lung density change

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Online Supplement

STUDY PARTICIPANTS

Cross-sectional data were obtained from an NIHR study from namely Southampton, Leicester, Nottingham, Royal Free, Brompton and Cambridge hospitals from 2009 to 2015[1].

Longitudinal data were obtained from AATD patients in the Birmingham cohort. Patients were selected if they had ≥2 CT scans performed as part of an observational study[1], or in the placebo arm of an RCT[2] from years 1997 to 2013 and followed up for a median period of 9.19 years (2.5 - 11.9).

STATISTICAL ANALYSIS

SOFTWARE

Analysis was performed using IBM® SPSS® Statistics 29.0.0.0

COMPARATIVE ANALYSES

Baseline and decline clinical parameters were compared between groups above and below the range of proposed MCID values for annual CT density decline in the longitudinal data and the CT baseline density in the cross-sectional data.

This was conducted by exploring data normality for each outcome followed by the appropriate tests were selected; Mann-Whitney *U* tests and Independent T tests for continuous outcomes and Chi-squared and Fisher's exact tests for binary outcomes were ran.

SURVIVAL ANALYSES

Only the longitudinal data from the Birmingham cohort were used for the survival analyses. Multivariable cox regression analyses were conducted adjusting for age, CT Density, FEV_1pp and SGRQ. Assumptions were explored in each group and the co-variates prior to the regression analyses. No trends were identified in analyses of proportional hazards, trends of co-variates against time and non-linearity of each co-variate.

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Supplementary Results

HANDLING MISSING DATA

Missing cases were excluded from analyses. In the cross-sectional data, approximately 3% of cases were missing in the lung parameters as shown in e-Table 1. There was loss to follow up of patients from outside the Birmingham therefore approximately 20% of patients in both groups of death data was not collected.

e-Table 1. Summary of missing patient data in the cross-sectional cohort comparing groups below and above the MCID of Absolute CT density change at 2.04g/L

	Absolute CT density change <-32.73 g/L		Absolute CT density change ≥34.77g/L	
	n	Missing data n (%)	n	Missing data n (%)
Age	69	0	73	0
Male sex	69	0	73	0
FEV_1	67	2 (2.9)	73	0
FEV_1 %	67	2 (2.9)	73	0
K_{CO}	67	2 (2.9)	71	2 (2.7)
K_{CO} %	67	2 (2.9)	71	2 (2.7)
CT Density (g/L)	69	0	73	0
SGRQ	61	8 (11.6)	66	3 (4.1)
Death	54	15(21.7)	59	14 (19.2)

N=sample size, FEV_1=forced expiratory volume in one second, K_{co}= carbon monoxide transfer co-efficient, SGRQ=St George's respiratory questionnaire

In the longitudinal data, there were approximately 10% of cases missing per group, summarised in e-e-Table 2. In clinical parameters of the longitudinal cohort, the number of missing cases were similar between groups bar baseline SGRQ and decline in SGRQ.

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e-Table 2. Summary of missing patient data in the cross-sectional cohort comparing at the MCID of Absolute CT density change at 2.2g/L/year

Parameter	Annual CT density change <-2.2g/L/year		Annual CT density change ≥-2.2g/L/year	
	N	Missing data n (%)	N	Missing data n (%)
Age	37	0	40	0
Male sex	37	0	40	0
FEV_1	37	0	40	0
FEV_1 %	37	0	40	0
K_{CO}	34	3 (8.1)	33	7 (17.5)
K_{CO} %	34	3 (8.1)	33	7 (17.5)
CT Density (g/L)	37	0	40	0
SGRQ	23	14 (37.8)	35	5 (12.5)
Death	37	0	40	0
FEV_1 decline	33	4 (10.8)	31	9 (22.5)
FEV_1 decline (mL/year)	33	4 (10.8)	31	9 (22.5)
K_{CO} decline	30	7 (18.9)	36	4 (10)
SGRQ decline	12	25 (67.6)	24	16 (40)

N=sample size, FEV_1=forced expiratory volume in one second, K_{co}= carbon monoxide transfer co-efficient, SGRQ=St George's respiratory questionnaire

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LONGITUDINAL COHORT: CLINICAL PARAMETERS OF THE WITH CT DENSITY DECLINE FASTER OR SLOWER THAN MCID THRESHOLD (1.87G/L/YEAR)

e-Table 3 compares the groups at the middle MCID threshold of 1.87g/l. There were no significant differences between the two groups.

e-Table 3. Clinical parameters for patients with CT density decline faster or slower than MCID value of -1.87g/L/year

Clinical Parameter	FAST decliners (Decline<-1.87g/L/year) N=46 unless stated otherwise	SLOW decliners (Decline ≥ -1.87g/L/year) N= 31 unless stated otherwise	P value
Age	51.6 (11.67)	54.4 (9.12)	0.269
Male sex	*24 (52.2%)*	*20 (64.5%)*	0.283
FEV_1	1.68 (0.91)	1.46 (0.73)	0.345
FEV_1 %	52.74 (25.49)	43.47 (22.61)	0.85
K_{CO}[a]	1.23 (1.28)	0.97 (0.31)	0.51
K_{CO} %[a]	24.06 (8.45)	22.40 (6.83)	0.78
CT Density (g/L)	65.75 (5.17)	46.24 (21.63)	0.07
SGRQ[b]	39.82 (20.6)	48.56 (13.74)	0.06
Death	*16 (34.8%)*	*11 (35.5%)*	0.95
FEV_1 decline[a]	-0.66 (1.88)	-0.33 (1.38)	0.73
FEV_1 decline (mL/year)[a]	-0.398 (0.06)	-0.281 (0.04)	0.45
K_{CO} decline[a]	-0.72 (0.78)	-0.56 (0.44)	0.33
SGRQ decline [c]	0.69 (3.95)	0.52 (2.05)	0.22

N=sample size, FEV_1=forced expiratory volume in one second, K_{CO}= carbon monoxide transfer co-efficient, SGRQ=St George's respiratory questionnaire

Data is shown as mean (SD) or *N (%)* Decline in lung function is shown as % predicted/year unless otherwise stated, and health status as SGRQ and health status change as SGRQ/year.

[a] *Missing data of 1-10 subjects per group*

[b] *Nb the SGRQ data – there is 14 out of 46 (30.4%) and 5 out of 31 (16.1%) participant data missing*

[c] *Health status decline 29 out of 46 (56.6%) and 12 out of 31 (38.7%) are missing*

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SURVIVAL DATA

Cox regression analyses calculated hazard ratios comparing density decline above the MCID in reference to density decline below the MCID adjusted for with baseline characteristics as listed in e-Table 4.

e-Table 4. Risk of death in multivariable Cox regression across the 95% CI for MCID in the longitudinal cohort

	HR	95.0% CI of HR		P value
		Lower	Upper	
Absolute CT Density Decline >= 2.04g/L (n=58)	Ref.			
Absolute CT Density Decline ≤2.04g/L (n=19)	**0.248**	**0.071**	**0.862**	**0.028**
Baseline Age	1.055	0.999	1.113	0.054
Baseline CT Density	0.983	0.944	1.024	0.417
Baseline FEV_1pp	0.998	0.955	1.044	0.94
Baseline SGRQ	**1.052**	**1.017**	**1.088**	**0.003**

n=sample size, HR=hazard ratio, CI = confidence interval, FEV_1pp=forced expiratory volume in one second percentage predicted, SGRQ=St George's respiratory questionnaire.

Variables in bold represent p-value <0.05

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