Online Supplement

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

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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.

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.

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

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*

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

e-References

1. Crossley D, Stockley J, Bolton CE, et al. Relationship of CT densitometry to lung physiological parameters and health status in alpha-1 antitrypsin deficiency: initial report of a centralised database of the NIHR rare diseases translational research collaborative. BMJ Open. 2020;10(6):e036045-e036045. doi:10.1136/bmjopen-2019-036045
2. Dirksen A, Piitulainen E, Parr DG, et al. Exploring the role of CT densitometry: a randomised study of augmentation therapy in 1-antitrypsin deficiency. European Respiratory Journal. 2009;33(6):1345-1353. doi:10.1183/09031936.00159408