Lung density associates with survival in Alpha 1 antitrypsin deficient patients

Green, Clara; Parr, D.g.; Edgar, Ross; Stockley, R.a.; Turner, Alice

DOI:
10.1016/j.rmed.2016.01.007

Document Version
Peer reviewed version

Citation for published version (Harvard):
Green, C, Parr, DG, Edgar, R, Stockley, RA & Turner, A 2016, 'Lung density associates with survival in Alpha 1 antitrypsin deficient patients', *Respiratory Medicine*, vol. 112, pp. 81-87.
https://doi.org/10.1016/j.rmed.2016.01.007

Accepted Manuscript

Lung density associates with survival in Alpha 1 antitrypsin deficient patients

C.E. Green, D.G. Parr, R.G. Edgar, R.A. Stockley, A.M. Turner

PII: S0954-6111(16)30004-X

DOI: 10.1016/j.rmed.2016.01.007

Reference: YRMED 4841

To appear in: *Respiratory Medicine*

Received Date: 30 October 2015

Revised Date: 14 January 2016

Accepted Date: 16 January 2016

Please cite this article as: Green C, Parr D, Edgar R, Stockley R, Turner A, Lung density associates with survival in Alpha 1 antitrypsin deficient patients, *Respiratory Medicine* (2016), doi: 10.1016/j.rmed.2016.01.007.

LUNG DENSITY ASSOCIATES WITH SURVIVAL IN ALPHA 1 ANTITRYPSIN DEFICIENT PATIENTS

CE Green[1], DG Parr[2], RG Edgar[3], RA Stockley[3], AM Turner[1]

1. Centre for Translational Inflammation Research, University of Birmingham, Birmingham, B152WB, United Kingdom (UK)
2. University Hospitals Coventry and Warwickshire, Clifford Bridge Road, Coventry, UK
3. University Hospital Birmingham, Mindelsohn Way, Edgbaston, Birmingham, B15 2GW, UK

Corresponding Author: C E Green, address as above; email clara.green@nhs.net

Key words: Chronic obstructive pulmonary disease, Alpha 1 antitrypsin deficiency, Quality of life, Survival

Word count: 2851

Abstract word count: 200

Conflict of interest statement: AMT's institution has received grants from the Alpha 1 Foundation, which is partially funded by manufacturers of A1AT augmentation therapy, and has a future grant from Grifols Biotherapeutics. AMT and RAS head the UK A1ATD registry, which has received grants from both Grifols Biotherapeutics and CSL Behring. DGP has had previous research funding from Grifols Biotherapeutics, and has consulted for CSL Behring. CEG and RGE have no conflicts to declare.

Funding: AMT is currently funded by the Alpha 1 Foundation and Linde REAL Fund. CEG is funded by the West Midlands Chest Fund. The UK registry has received unconditional funds from Grifols Biotherapeutics and CSL Behring.

ABSTRACT

Introduction

CT density correlates with quality of life (QOL) scores and impaired upper zone lung density associates with higher mortality in alpha one antitrypsin deficiency (A1ATD). We hypothesised that decline in CT densitometry would relate to survival or deterioration in QOL in A1ATD.

Methods

All augmentation naïve PiZZ patients in the UK A1ATD registry with ≥two successive quantitative CT scans were selected. Patients were divided into groups based on CT density decline and the relationship to survival and change in QOL compared by univariate analyses and multivariate Cox regression. Analyses were performed for whole lung, upper zone and lower zone density separately. Exploratory analyses of FEV1 subgroups were conducted.

Results

110 patients were identified; 77 had whole lung and lung zone density recorded on two CT scans, 33 patients had upper zone data only on four scans. Decline in lower zone density associated with survival, even after adjustment for baseline lung density (p=0·048), however upper zone density and whole lung density decline did not. This difference appeared to be driven by those with FEV1 >30% predicted.

Conclusion

Rate of change in lung densitometry could predict survival in A1ATD.

INTRODUCTION

Alpha-1-Antitrypsin Deficiency (A1ATD) is a genetically determined anti-proteinase deficiency predisposing to emphysema[1]. Patients classically have rapidly progressive emphysema and thus reduced life expectancy[2]. Factors predicting mortality in untreated A1ATD include FEV1, gas transfer(Kco) and lung density[2]. Rapid FEV1 decline occurs with higher baseline FEV1 and frequent exacerbations, whereas Kco decline is greatest in patients with severe airflow obstruction[3, 4].

Observational studies have suggested that emphysema progression in A1ATD may be slowed by augmentation therapy[5], which is recommended for use in non-smoking patients with FEV1 35-60% predicted in the USA/Europe[6] and 25-80% predicted in Canada[7], in the presence of emphysema on CT scan. However, an influence on FEV1 decline is difficult to prove because it is a poor surrogate of emphysema, thus more patients are needed to detect change in randomised controlled trials (RCTs), with consequent cost and logistic implications. Trials of augmentation have therefore been powered to detect decline in CT densitometry which allows for a more reasonable sample size[8-10], and a properly powered study has recently confirmed its beneficial effect on this outcome measure[11]. However CT density is not yet used routinely in clinical practice to assess A1ATD patients.

We hypothesised that the rate of decline in CT density would relate to subsequent survival in patients who had never received augmentation therapy (augmentation naive) A1ATD patients. We chose to analyze density decline in patient groups (no decline versus decline) rather than using a continuous outcome as we felt this would be more meaningful for clinical decision making, such as selection for augmentation therapy.

MATERIALS AND METHODS

Patients

The UK A1ATD registry assessment and follow up procedures are described elsewhere; all patients gave informed consent and studies were approved by the local ethics committee[4]. In brief it was established in 1996, and is still running; patients continue follow up annually in the stable state until death or withdrawal. This study therefore represents a retrospective analysis of prospectively collected data. All augmentation naive patients with ≥two quantitative CT scans prior to 2010 were selected and subsequent deaths and lung transplants noted. Patients with whole lung, as well as upper and lower zone density measurements recorded were included. Follow up time was defined as time from determination of decline (e.g. second CT scan date) to date of analysis (censored at 31/12/2012).

CT scan analysis

All scans were done in the stable state, for research purposes, a median of two years apart (range 0·9-3·3) between 2002-2005, the protocol being described in our previous work, and measuring density at total lung capacity (TLC)[12]. Whole lung density was measured as the 15th percentile lung density (PD15), calculated from the frequency histogram of lung voxels at -910HU and defined as the density threshold of the lowest 15% of voxels, as described in our previous work[9, 13]. Density is calculated as g/l by adding 1000 to the PD15. Total decline in lung density and time between scans determined the annual rate of decline per patient. In the 77 patients who had two scans regression analysis across time points to calculate decline was not possible. In the 33

patients who had four scans we used the first and last scans only to calculate decline in order to ensure that methods were identical for both groups.

Statistical analysis

All analyses were undertaken in SPSS® (version 20; IBM, USA). Firstly, we examined the relationship between decline in CT density and lung physiology by comparing the proportion of patients in different CT decline categories to patients with/without a significant decline in lung function (defined as faster than normal aging, i.e. a deteriorating % predicted). Next, univariate analyses compared patients with declining density to those not declining, and those alive without transplantation to those who died, using t-tests (normally distributed data), Mann-Whitney-U-tests (non-normally distributed data) or Chi square tests (frequency variables). Multivariate analysis was then performed using Cox regression. Variables with univariate $p<0.15$ were considered for inclusion in multivariate analysis, up to a maximum of one covariate/ten deaths. [14] All analyses are reported one-tailed since there was a clear one way hypothesis (i.e. lung density decline would associate with reduced survival). Finally the primary test cohort in whom lower zone data was available, were sub-stratified by FEV1 <30%, 30-50% and >50% predicted, prior to analyses as before.

RESULTS

110 patients were identified; 77 had whole, upper and lower zone lung density recorded on 2 CT scans from our current scanner using the same software; one patient had received a lung transplant and was excluded for the main analysis. Of the remainder, 9 had their scans as part of the placebo arm of EXACTLE[10] and the others as part of observational study protocols or clinical care. A further 33 patients had upper

zone data from a previously used scanner and were analysed separately; one patient from the previous dataset was also scanned this way, thus n=34 for this replication dataset. Five of these patients had also received lung transplants and were excluded from analysis. (Figure1) None were current smokers; mean pack year exposure was 17·1 (SEM 1·7). Table one shows patient characteristics.

CT data available	**Whole, upper & lower zone lung density group**				**Upper zone lung density only group**			
Status *N(%)*	**All** *76*	**Alive** *49 (64.5)*	**Dead** *27 (35.5)*	**p value**	**All** *29*	**Alive** *12 (41.4)*	**Dead** *17 (58.6)*	**p value**
Male patients	*44 (57.9)*	*28 (63.6)*	*16 (36.4)*	*0.858*	*22 (75.9)*	*10 (83.3)*	*12 (70.6)*	*0.333*
Age (years)	52.1 (14.8)	50.8 (18.2)	56.0 (10.8)	**0.003**	52.5 (8.6)	52.3 (10.3)	52.5 (6.8)	0.195
Median follow up (years)	7.2 (1.6)	8.3 (0.9)	5.7 (4.4)	**<0.001**	9.5 (6.4)	13.5 (0.5)	7.8 (3.2)	**<0.001**
FEV1 (% predicted)	45.3 (29.6)	50.1 (39.6)	36.9 (24.5)	**0.011**	33.6 (35.9)	57.8 (38.3)	24.2 (14.1)	**0.001**
FEV1/FVC	34.0 (23.0)	35.0 (29.5)	33.0 (14.3)	0.051	38.6 (30.6)	55.7 (38.4)	30.7 (20.2)	**0.003**
DLCO (% predicted)	64.9 (38.4)	70.7 (36.6)	53.9 (45.3)	**0.029**	86.7 (26.1)	90.6 (12.1)	69.3 (30.2)	**0.038**
KCO (% predicted)	60.5 (28.3)	62.6 (28.8)	59.5 (26.8)	0.113	71.2 (23.6)	78.9 (18.1)	67.2 (33.3)	0.075
Chronic bronchitis	*31 (40.8)*	*15 (30.6)*	*16 (59.3)*	***0.015***	*14 (48.3)*	*6 (50.0)*	*8 (47.1)*	*0.438*
Baseline density (g/l)	46.2 (28.7)	55.4 (54.9)	39.8 (18.2)	**0.002**	-	-	-	-
Change in density/year	-2.13 (4.08)	-2.89 (6.07)	-2.08 (2.76)	0.501	-	-	-	-
Density declining	*65 (85.8)*	*42 (85.7)*	*23 (85.2)*	*0.293*	-	-	-	-
UZ density	30.33 (26.49)	30.65 (25.94)	26.53 (28.86)	0.981	57.50 (35.45)	65.4 (31.35)	55.65 (35.67)	0.135
LZ density	49.29 (27.58)	48.91 (31.33)	49.31 (32.10)	0.671	-	-	-	-
UZ density decline/year	-1.72 (3.03)	-1.57 (3.14)	-2.06 (3.97)	0.051	-1.74 (2.90)	-2.03 (3.89)	-1.52 (2.66)	0.069
LZ density decline/year	-1.45 (5.28)	-0.94 (4.37)	-3.41 (5.26)	**0.025**	-	-	-	-
UZ density declining	*54 (77.1)*	*33 (71.7)*	*21(87.5)*	*0.115*	*17 (50.0)*	*6 (35.3)*	*11(64.7)*	*0.364*
LZ density	*52 (74.3)*	*31 (67.4)*	*21 (87.5)*	*0.058*	-	-	-	-

declining								
SGRQ	44.6 (31.2)	39.1 (24.4)	54.6 (22.2)	**0.001**	61.8 (31.1)	49.5 (40.3)	66.8 (20.1)	**0.010**

Table 1: Clinical characteristics

The table shows characteristics of the cohort, stratified by survivor status, and the univariate test statistics comparing survivors with those who died. Frequency data is shown as n (%), and is in italics. Scale variables are shown in normal type as median (IQR). Significant differences between survivors and those that died are shown by a bold type p value. UZ = upper zone, LZ=lower zone. Density decline/year measured as change in whole lung density; UZ and LZ density decline defined as a deterioration in density in the upper or lower third of the lung respectively (all at -910HU). Chronic bronchitis was defined using the MRC definition[15].

Relationship of CT density decline to other clinical features

Whole lung CT density decline occurred in 57.2% of patients whose FEV1 did not decline any faster than normal aging (i.e. remained at the same % predicted), compared to 42.8 of those with declining FEV1. More marked differences occurred when considering density by lung zone (Figure 2a). Most patients with no decline in K_{CO} or DL_{CO} also exhibited no decline in CT density, a pattern that was maintained across zones (Figure 2b & 2c). Consequently, decline in KCO and DLCO had a higher sensitivity than FEV1 decline to predict CT density decline (see table 2).

Density decline in upper and lower zone correlated reasonably well (σ=0·62, p<0·0001), however 31% of patients who exhibited no deterioration in their upper zone had a decline in their lower zone density and 13% of patients whose lower zone was stable had a decline in upper zone density.

Patients with no decline in the lower zone exhibited no significant difference in age, FEV1, DL_{CO}, pack years smoked, degree of bronchodilator reversibility, prevalence of chronic bronchitis[15] or emphysema from those whose lower zone was declining (all p>0·17). Those with no decline in the upper zone were slightly younger (47·3 v 53·1

years, p=0·03) and had better baseline lung density in both upper and lower zones (p=0·022 and 0·015 respectively), but exhibited no other significant physiological or demographic differences (all p>0·36) from those whose upper zone was deteriorating.

Decline in lung function (faster than normal ageing)	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
FEV1	44	91	96	23
KCO	76	50	89	29
DLCO	84	25	88	20

Table 2: The ability of lung function decline to predict CT density decline
The table shows the sensitivity, specificity and predictive values for FEV1, DLCO and KCO decline to predict CT density decline

Survival

In the whole lung density cohort 27 patients died during follow up. Table 1 shows univariate comparisons of survivors compared to those who died. Upper and lower zone density decline had p<0·15 hence were appropriate to take forward to Cox regression (unlike whole lung density). Only one co-variate could be included due to low numbers of deaths; we therefore chose baseline density as this was the most strongly associated difference between survivors and those who died. Cox regression demonstrated that baseline density (p=0·029) and lower zone density decline (p=0·048) were associated with subsequent death, whilst patients whose upper zone density was declining showed a similar trend, albeit non-significant (p=0·072). Kaplan-Meier plots are shown in figure 2. We also assessed a composite outcome of 'death or transplant', however since this only added one case to the group the result did not change appreciably.

Similar analyses were performed using the upper zone density measurement group, excluding 5 transplanted patients. Table one shows demographics and univariate analyses. There was no association between decline in upper zone densitometry and survival hence progression to multivariate analysis was inappropriate. Addition of the 5 transplanted subjects and assessment of the composite measure 'death or transplant' did not change the results.

Impact of starting lung function

Since there was a difference in lung function between survivors and those who died, addition of FEV1 as a co-variate would not have been meaningful due to high correlation with baseline density ($r=0.66$, $p<0.0001$). However, we sub stratified the group by FEV1 and repeated the survival analysis for three sub-groups: FEV1 < 30%, 30-50% and $\geq$50% predicted. The analysis was undertaken primarily using lower zone density decline, as this was significant in the initial multivariate model. We also repeated the analysis using whole lung density decline, because whole lung density has been the outcome measure used in augmentation trials, and augmentation is currently recommended based in part on FEV1. There were relatively few deaths per subgroup, hence to maximise power and minimize risk of type I error[16] we restricted the number of variables in the model; CT density decline alone was included as there were <20 deaths/subgroup. In patients with FEV1 <30%, neither lower zone CT density ($p=0{\cdot}255$) nor whole lung density ($p=0{\cdot}286$) decline associated with survival. In patients with FEV1 30-50% lower zone decline in densitometry showed an apparent trend toward poor survival, at least visually, though this was not statistically significant for lower or whole lung density decline (Figure 4a & 4c). In patients with FEV1 >50%

lower zone CT density decline related to death (p=0·024; Figure 4b) but whole lung density did not (p=0·198; Figure 4d).

We recognize that there are conflicting views regarding power and covariates in regression analyses[17], hence an analysis containing all potential covariates allowable in a more lenient method is shown in the supplement.

DISCUSSION

We have demonstrated that change in lower zone lung CT densitometry relates to survival in A1ATD, and that measurement of FEV1 and gas transfer alone will not identify all patients who have declining lung density.

Our main aim was to determine whether change in CT density relates to survival. CT density has been the primary outcome measure for RCTs of augmentation therapy in A1ATD, as it is more sensitive to change than other outcomes[10]. However densitometry was considered an insufficiently validated outcome with reference to 'hard' outcomes like survival and QOL in a key systematic review of augmentation[18]. Survival and QOL have obvious relevance to cost-effectiveness models incorporating quality adjusted life years (QALYs). Of these, mortality was the most important input factor in a recent comparison of economic modeling methods in a lifetime model of usual COPD[19], and was our focus.

We divided our patients into two groups for each measure of CT density: no decline and decline. Arguably this could reduce power to show associations between density decline rate and outcome, however we chose this method because a key reason underlying our

study was the desire to find a threshold that would aid decision making. In most areas of clinical practice a specific threshold is used to define deviation from normality, and in the absence of a known normal value for CT density decline in health, no decline seemed a reasonable threshold to choose. An alternative approach could have been analysis of decline greater than the average compared to less than the average. The disadvantage of this is that the two groups potentially become similar to one another, whereas our approach effectively selects the more unusual patient (no decline) as a comparator. This ought to have greater power to detect differences because it uses an extreme phenotype. Mortality was lower in patients with no decline in their lower zone, whether using our threshold or when using it as a quantitative variable (supplement). Augmentation therapy typically results in a slowing of CT density change approaching 1g/l/year[9-11] in whole lung density, but the effect varies according to the region scanned, being most marked in the lower zone[20]. The magnitude of the difference in whole lung density decline between survivors and those who died was less than the difference in density that augmentation typically provides, suggesting that augmentation might improve survival, though this has not been confirmed in trials to date. This is not surprising as augmentation trials have only been up to three years in duration, and it is apparent from our Kaplan-Meier plots that deaths were generally occurring beyond this time. Analysis of matched treated v untreated cohorts with long follow up durations may be a way to confirm this in future. However our results suggest that lower zone density change is a better surrogate outcome for long term mortality than the whole lung density used in augmentation RCTs.

We also found that upper zone density decline is less relevant to mortality in A1ATD than our previous cross-sectional results suggested[2]. Contrary to intuitive thinking

about A1ATD lung disease, which is recognized mainly in the lower zone, and which we might surmise then progresses to the upper zone, we have previously published a model demonstrating that upper zone change may be an early phenomenon[21]. We have also observed that FEV1 relates more to lower zone disease, whilst gas transfer reflects upper zone disease better [12], and that FEV1 decline typically occurs most early in disease, with gas transfer decline being more rapid in those with lower FEV1[4]. The densitometry data presented here suggests that upper and lower zone disease may progress independently in some patients, at least over the period of time we observed, perhaps accounting for these apparent inconsistencies. Repeating the analysis in an independent cohort would be necessary to clarify this further.

Subgroup analyses based on FEV1 showed an apparent separation of curves on Kaplan Meier plots suggesting that there may be an effect on mortality in the patients with a presentation FEV1>30% predicted. However, this was not statistically significant presumably due to inadequate power, as the number of deaths per group was low. We took a conservative statistical approach, consistent with classical teaching to include no more than one variable per ten events[22], aimed at maximizing power and minimizing bias, although arguments can be presented for taking a broader statistical approach[16]. However, our results are consistent with past trials and observational work, suggesting that this group consists of those most likely to show an augmentation effect[10, 23]. Gas transfer declines most rapidly when FEV1 is <30%[4], suggesting that emphysema is still progressing at this point. This is supported by previous studies which demonstrated that lung density declines at a similar rate in patients with FEV1 < and > 30%.[16] hence it would be logical to expect an augmentation effect on density decline, indicative of reduced progression, to associate with better survival even at this level.

This was, however, not the case in our lower zone analyses, perhaps because this region links more to FEV1 than gas transfer in A1ATD[12], or because all patients at this poor level of lung function have a high risk of death, regardless of whether densitometry is still declining.

Finally, we considered whether lung function decline was a good enough surrogate for CT density decline to use in clinical practice. Around half of patients who exhibited no significant decline in FEV1 (i.e. normal aging) had whole lung CT density decline. Thus use of serial spirometry to select patients most likely to benefit from augmentation would miss many at risk individuals. Serial gas transfer would be a more reliable marker of the emphysema process detected by density change, but would still miss around 20% of patients with a declining CT scan. (Figure 2b,c) Importantly, we have also shown that some patients do not decline at all, at least over the period we monitored density, but none of the standard measures taken in clinical practice differentiated them clearly from decliners. This suggests that serial CT densitometry, would be the most reliable way to identify progressing high risk A1ATD patients for more aggressive treatment (i.e. augmentation) and lower risk A1ATD patients who could safely be monitored. However such decisions would not be simple and it is likely that CT density would add to the other lung function features, exacerbation history and symptom burden, rather than being viewed as the sole factor to determine treatment prescription. The relatively good sensitivity of DLCO decline to predict CT decline, albeit with poor specificity, together with the opposite pattern for FEV1 sensitivity and specificity highlights this. However, if we were to move to routine use of densitometry hospitals/clinics would either need to buy software and train staff, or commission services from external providers of CT studies and analysis to ensure consistency and

accuracy. Access to different technology may also make standardization across different countries difficult to achieve although this has been possible in clinical trials.

The main strength of our study is its' ability to link the primary outcome used in clinical trials of augmentation (lung densitometry) to a key clinical long term effect, namely survival. The main limitation is the number of patients with serial densitometry carried out sufficiently long ago to allow meaningful survival analysis. However, the size of our primary cohort (n=76) is close in size to the placebo group of the RAPID trial[11] of augmentation, and equal to the number enrolled in EXACTLE[10] (the two most recent RCTs of augmentation therapy for A1ATD) and thus is comparable in the field. The larger sub-group used a protocol which is equivalent to that used in augmentation trials, so we believe our findings are robust and generalisable. Finally, we did not have prospectively collected exacerbation diary data on all patients (exacerbation history was gained by recall at each stable state visit), thus we could not adequately account for exacerbations in our analyses. However, over the time between scans it is unlikely that exacerbations would have a large impact on CT density decline.

CONCLUSION

We have shown that change in CT densitometry is a valid surrogate outcome measure for survival in A1ATD. There is potential for clinical usage to bring A1ATD management closer to a personalized, risk-based approach.

CONTRIBUTION STATEMENT

CEG conducted data analysis and drafted the manuscript, DGP analysed CT scans and advised on data analysis, RAS established the ADAPT programme and advised on data

analysis, RGE assisted with data collection, AMT assisted with data collection, revised the manuscript and acts as guarantor. All authors reviewed the manuscript prior to submission.

ACKNOWLEDGEMENTS

We would like to thank Dr M Sevenoaks for access to some of the CT scan data and staff at CSL Behring for their input to discussions of relevance of these findings to clinical trial outcomes

FIGURE LEGENDS

Figure 1: Flow diagram demonstrating the selection of patients for further analysis

Figure 2: Relationship between decline in CT density and decline in lung function

a) FEV1
b) K_{CO}
c) DL_{CO}

Each chart shows patients whose % predicted was not changing (normal aging) and those with decline greater than normal aging (a falling % predicted), split into CT density decline groups. Many patients with an FEV1 that suggested only normal aging had CT density decline (p=0.043). Gas transfer measurement was better at detecting density decline, and there was no difference in the distribution of density and KCO decline (p=0.120) or DLCO decline (0.514).

Figure 3: Kaplan-Meier plots showing the impact of decline in density in upper and lower zone on survival

In each plot the dashed line indicates declining CT density, and the solid line no decline. Censored cases are marked by solid symbols (circles in the no decline group, squares in declining patients). Statistics were computed using log rank tests.

a) Lower zone p=0.048
b) Upper zone p=0.072

Figure 3: Kaplan-Meier plots stratified by starting FEV1 showing the impact of decline in lower and whole lung density on survival

The dashed lines represent declining density, and solid symbols censored cases, as before.

a) Lower zone, FEV1 30-50% predicted p=0.292
b) Lower zone, FEV1 >50% predicted p=0.024
c) Whole lung, FEV1 30-50% predicted p=0.171

d) Whole lung, FEV1 >50% predicted p=0.198

REFERENCES

1. Stockley, R.A. and A.M. Turner, *alpha-1-Antitrypsin deficiency: clinical variability, assessment, and treatment.* Trends Mol Med, 2014. **20**(2): p. 105-15.
2. Dawkins, P., et al., *Mortality in alpha-1-antitrypsin deficiency in the United Kingdom.* Respir Med, 2009. **103**(10): p. 1540-7.
3. Dawkins, P.A., et al., *Rate of progression of lung function impairment in alpha1-antitrypsin deficiency.* Eur Respir J, 2009. **33**(6): p. 1338-44.
4. Pillai, A.P., A.M. Turner, and R.A. Stockley, *Relationship of the 2011 Global Initiative for Chronic Obstructive Lung Disease strategy to clinically relevant outcomes in individuals with alpha1-antitrypsin deficiency.* Ann Am Thorac Soc, 2014. **11**(6): p. 859-64.
5. *Survival and FEV1 decline in individuals with severe deficiency of alpha1-antitrypsin. The Alpha-1-Antitrypsin Deficiency Registry Study Group.* Am J Respir Crit Care Med, 1998. **158**(1): p. 49-59.
6. *American Thoracic Society/European Respiratory Society statement: standards for the diagnosis and management of individuals with alpha-1 antitrypsin deficiency.* Am J Respir Crit Care Med, 2003. **168**(7): p. 818-900.
7. Marciniuk, D.D., et al., *Alpha-1 antitrypsin deficiency targeted testing and augmentation therapy: a Canadian Thoracic Society clinical practice guideline.* Can Respir J, 2012. **19**(2): p. 109-16.
8. Dirksen, A., et al., *A randomized clinical trial of alpha(1)-antitrypsin augmentation therapy.* Am J Respir Crit Care Med, 1999. **160**(5 Pt 1): p. 1468-72.
9. Stockley, R.A., et al., *Therapeutic efficacy of alpha-1 antitrypsin augmentation therapy on the loss of lung tissue: an integrated analysis of 2 randomised clinical trials using computed tomography densitometry.* Respir Res, 2010. **11**: p. 136.
10. Dirksen, A., et al., *Exploring the role of CT densitometry: a randomised study of augmentation therapy in alpha1-antitrypsin deficiency.* Eur Respir J, 2009. **33**(6): p. 1345-53.
11. Chapman, K.R., et al., *Intravenous augmentation treatment and lung density in severe alpha1 antitrypsin deficiency (RAPID): a randomised, double-blind, placebo-controlled trial.* Lancet, 2015.
12. Parr, D.G., et al., *Pattern of emphysema distribution in alpha1-antitrypsin deficiency influences lung function impairment.* Am J Respir Crit Care Med, 2004. **170**(11): p. 1172-8.
13. Parr, D.G., et al., *Validation of computed tomographic lung densitometry for monitoring emphysema in alpha1-antitrypsin deficiency.* Thorax, 2006. **61**(6): p. 485-490.
14. Bursac, Z., et al., *Purposeful selection of variables in logistic regression.* Source Code Biol Med, 2008. **3**: p. 17.
15. *Definition and classification of chronic bronchitis for clinical and epidemiological purposes. A report to the Medical Research Council by their Committee on the Aetiology of Chronic Bronchitis.* Lancet, 1965. **1**(7389): p. 775-9.
16. Vittinghoff, E. and C.E. McCulloch, *Relaxing the rule of ten events per variable in logistic and Cox regression.* Am J Epidemiol, 2007. **165**(6): p. 710-8.
17. Harrell, F.E., Jr., K.L. Lee, and D.B. Mark, *Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors.* Stat Med, 1996. **15**(4): p. 361-87.
18. Gotzsche, P.C. and H.K. Johansen, *Intravenous alpha-1 antitrypsin augmentation therapy for treating patients with alpha-1 antitrypsin deficiency and lung disease.* Cochrane Database Syst Rev, 2010(7): p. CD007851.

19. Hoogendoorn, M., et al., *Cost-effectiveness models for chronic obstructive pulmonary disease: cross-model comparison of hypothetical treatment scenarios.* Value Health, 2014. **17**(5): p. 525-36.
20. Parr, D.G., et al., *Detection of emphysema progression in alpha 1-antitrypsin deficiency using CT densitometry; methodological advances.* Respir Res, 2008. **9**: p. 21.
21. Holme, J., J.A. Stockley, and R.A. Stockley, *Age related development of respiratory abnormalities in non-index alpha-1 antitrypsin deficient studies.* Respir Med, 2013. **107**(3): p. 387-93.
22. Peduzzi, P., et al., *Importance of events per independent variable in proportional hazards regression analysis. II. Accuracy and precision of regression estimates.* J Clin Epidemiol, 1995. **48**(12): p. 1503-10.
23. Seersholm, N., et al., *Does alpha1-antitrypsin augmentation therapy slow the annual decline in FEV1 in patients with severe hereditary alpha1-antitrypsin deficiency? Wissenschaftliche Arbeitsgemeinschaft zur Therapie von Lungenerkrankungen (WATL) alpha1-AT study group.* Eur Respir J, 1997. **10**(10): p. 2260-3.

FIGURE LEGENDS

Figure 1: Flow diagram demonstrating the selection of patients for further analysis

Figure 2: Relationship between decline in CT density and decline in lung function

a) FEV1
b) K_{CO}
c) DL_{CO}

Each chart shows patients whose % predicted was not changing (normal aging) and those with decline greater than normal aging (a falling % predicted), split into CT density decline groups. Many patients with an FEV1 that suggested only normal aging had CT density decline (p=0.043). Gas transfer measurement was better at detecting density decline, and there was no difference in the distribution of density and KCO decline (p=0.120) or DLCO decline (0.514).

Figure 3: Kaplan-Meier plots showing the impact of decline in density in upper and lower zone on survival

In each plot the dashed line indicates declining CT density, and the solid line no decline. Censored cases are marked by solid symbols (circles in the no decline group, squares in declining patients). Statistics were computed using log rank tests.

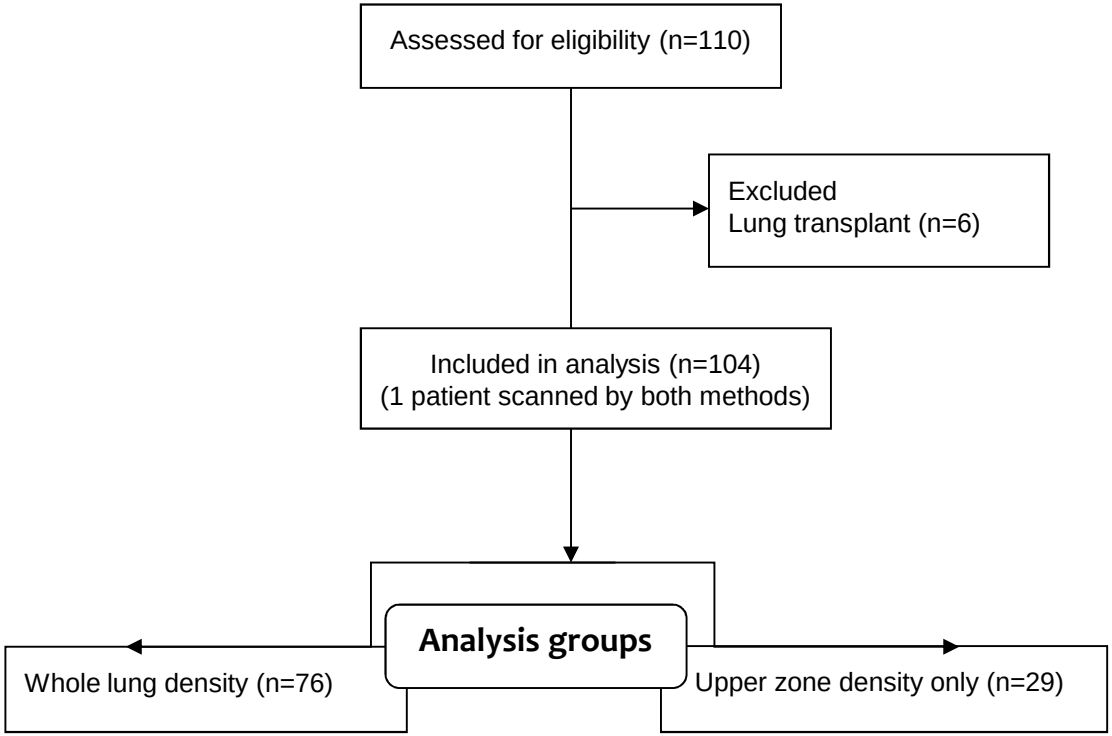
a) Lower zone p=0.048
b) Upper zone p=0.072

Figure 4: Kaplan-Meier plots stratified by starting FEV1 showing the impact of decline in lower and whole lung density on survival

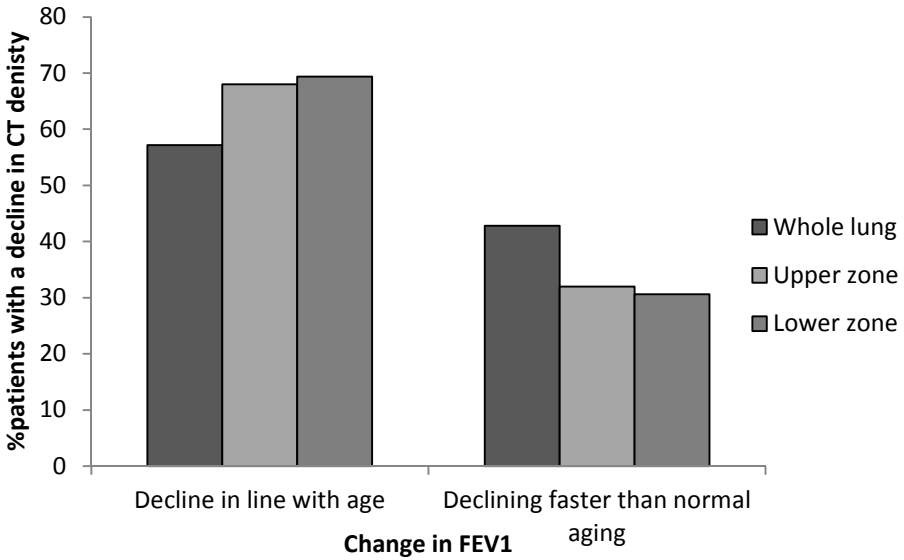
The dashed lines represent declining density, and solid symbols censored cases, as before.

a) Lower zone, FEV1 30-50% predicted p=0.292
b) Lower zone, FEV1 >50% predicted p=0.024
c) Whole lung, FEV1 30-50% predicted p=0.171

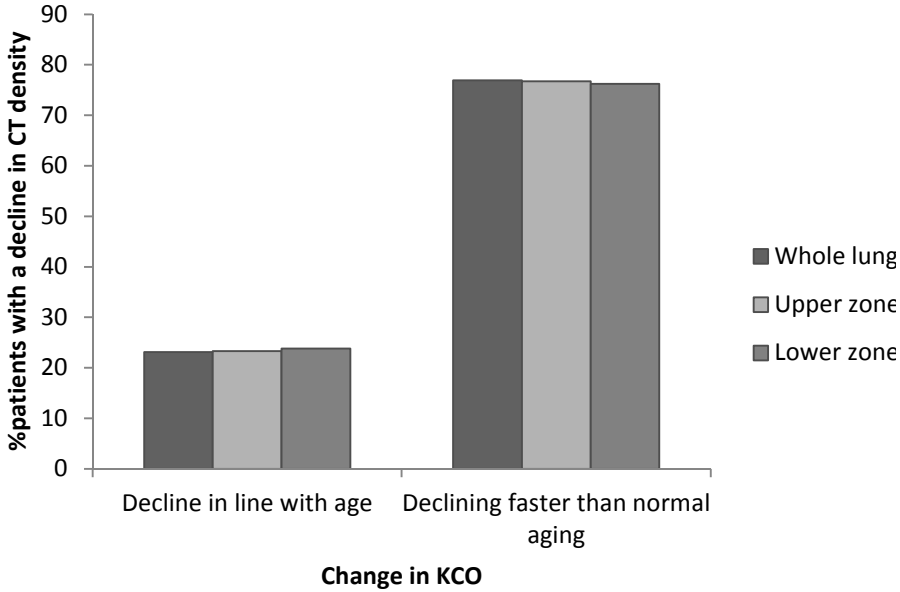
d) Whole lung, FEV1 >50% predicted p=0.198



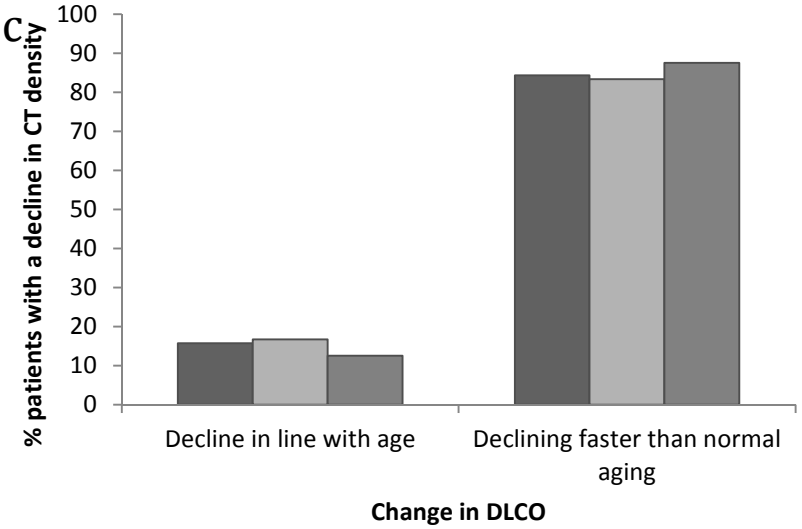
a


%patients with a decline in CT denisty
80
70
60
50
40
30
20
10
0
Decline in line with age
Declining faster than normal aging
Change in FEV1
Whole lung
Upper zone
Lower zone

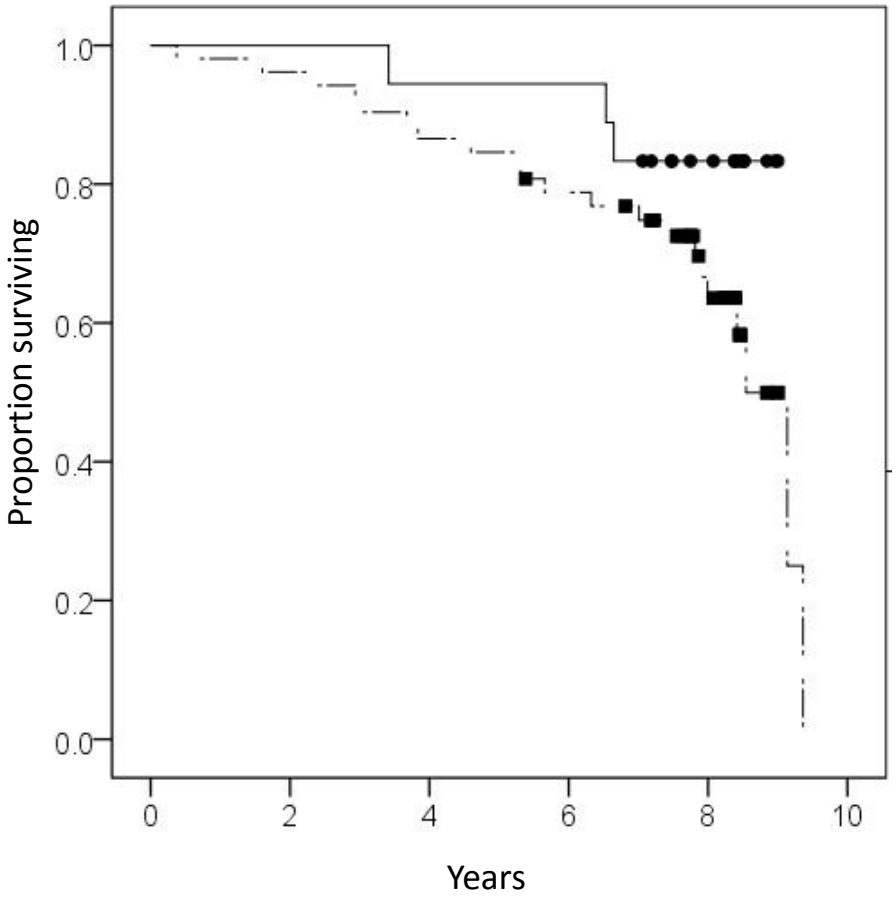
b


%patients with a decline in CT density
90
80
70
60
50
40
30
20
10
0
Decline in line with age
Declining faster than normal aging
Change in KCO
Whole lung
Upper zone
Lower zone

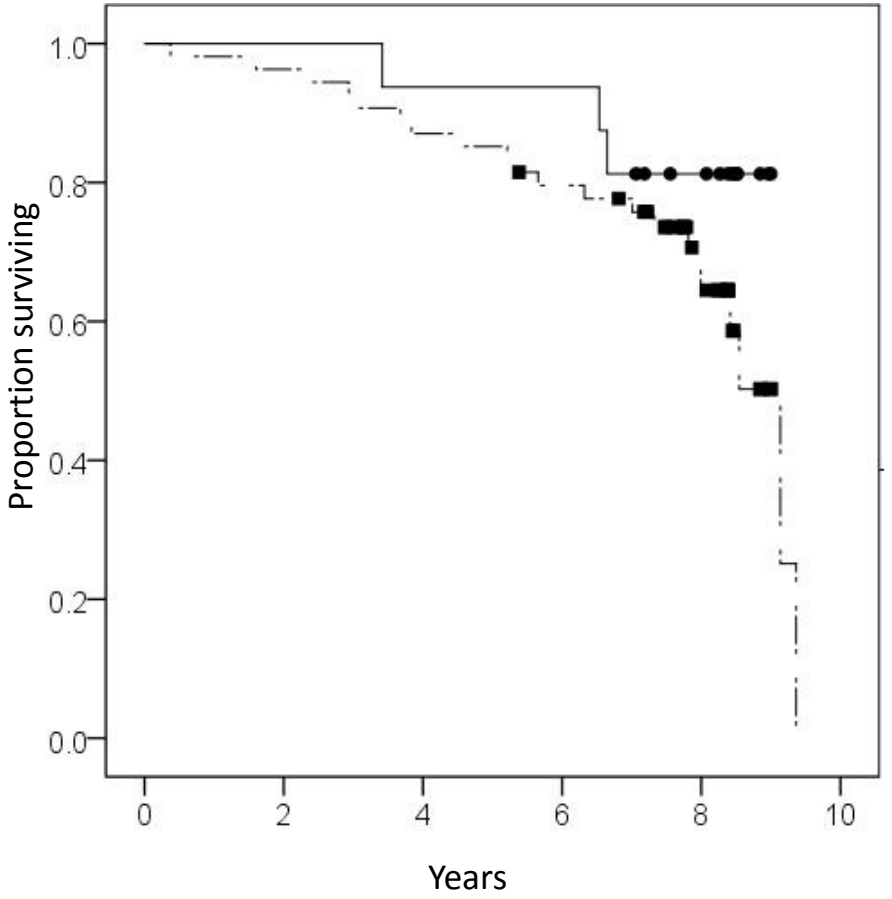
c


% patients with a decline in CT density
100
90
80
70
60
50
40
30
20
10
0
Decline in line with age
Declining faster than normal aging
Change in DLCO

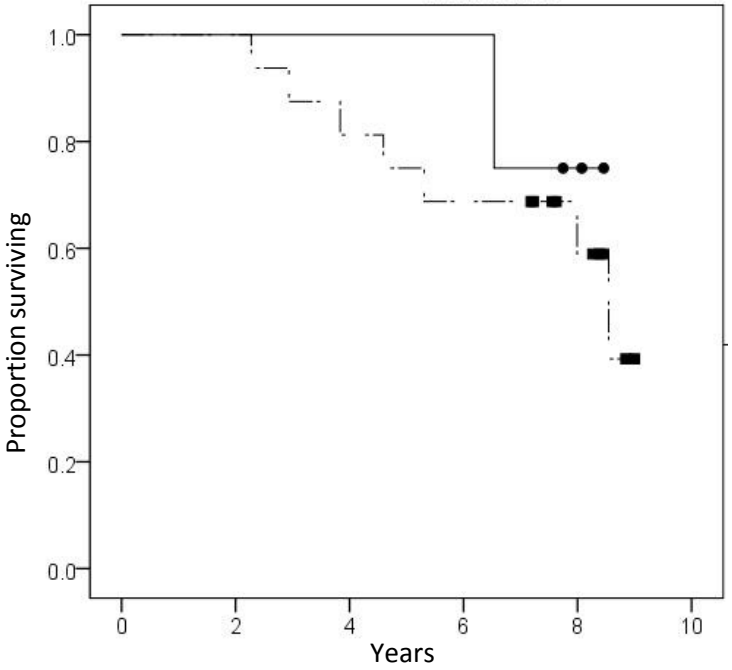
a


Proportion surviving
1.0
0.8
0.6
0.4
0.2
0.0
0
2
4
6
8
10
Years

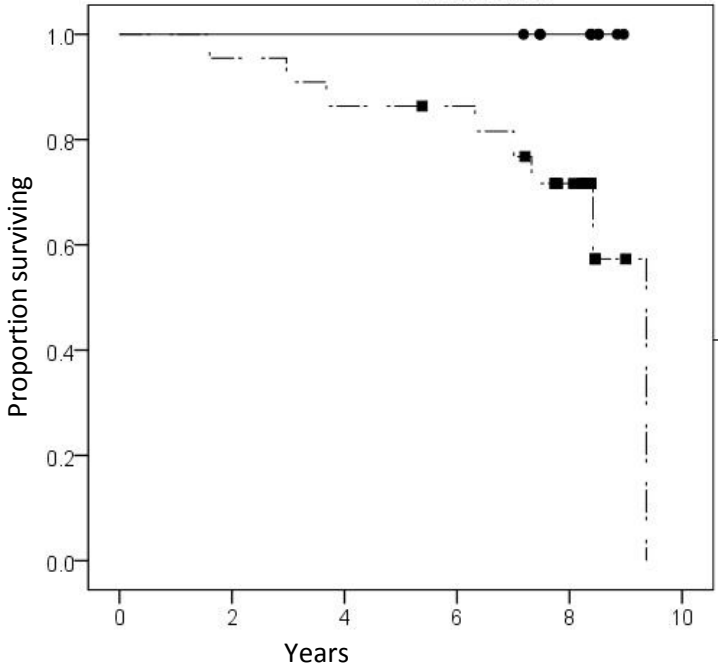
b


Proportion surviving
1.0
0.8
0.6
0.4
0.2
0.0
0
2
4
6
8
10
Years

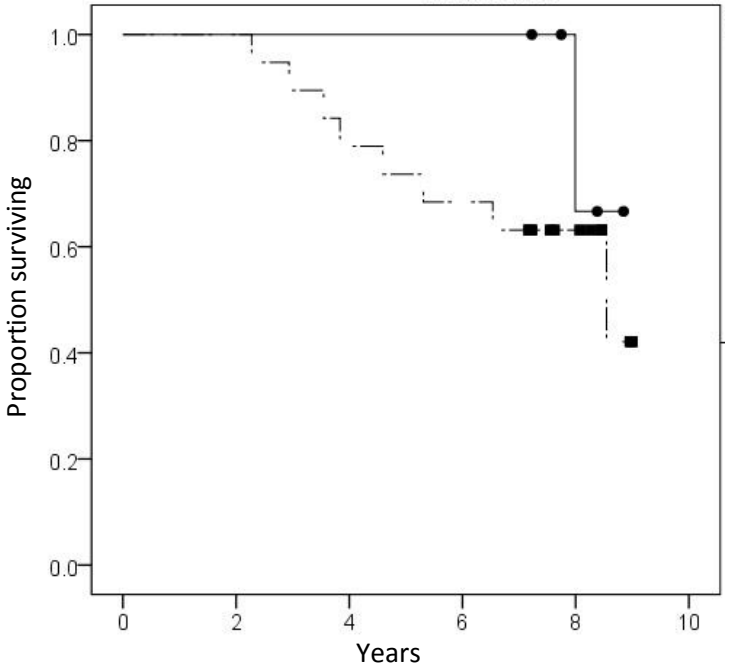
a



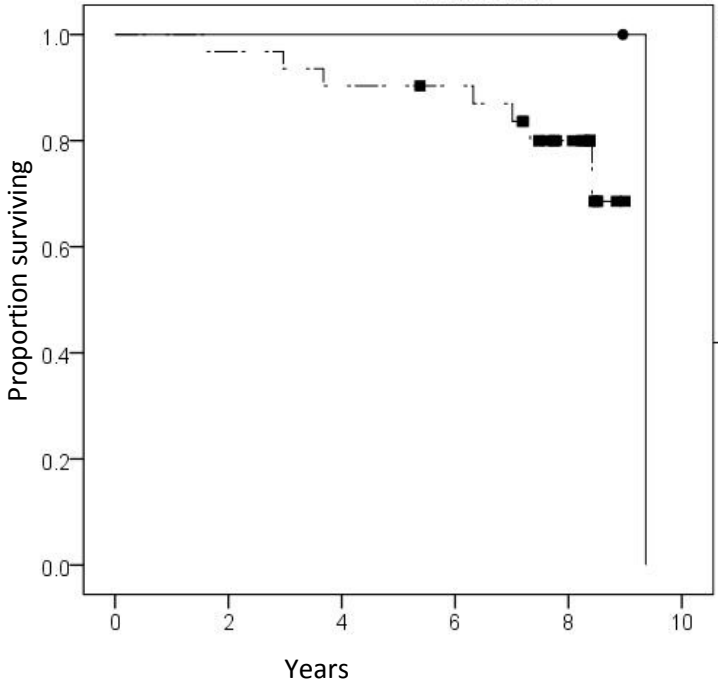
b



c



d



- Lower zone lung density associates with survival in alpha 1 antitrypsin deficient patients.
- Decline in upper zone density and whole lung density does not associate with survival.
- This difference appears to be driven by patients with FEV1>30% predicted.