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Lung density associates with survival in alpha 1 antitrypsin deficient patients

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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 ($p = 0{\cdot}048$), 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.

1. 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.

2. Materials and methods

2.1. Patients

The UK A1ATD registry assessment and follow up procedures are described elsewhere; all patients gave informed consent and

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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).

2.2. 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 and 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]. CT density analysis was performed using Pulmo-CMS software (Medis Specials, Leiden, The Netherlands). 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.

2.3. 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 ageing, 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.

3. 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. (Fig. 1) None were current smokers; mean pack year exposure was 17·1 (SEM 1·7). Table 1 shows patient characteristics.

3.1. 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 ageing (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 (Fig. 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 (Fig. 2b and c). 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 ($\sigma = 0{\cdot}62$, $p < 0{\cdot}0001$), 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 $p > 0{\cdot}17$). Those with no decline in the upper zone were slightly younger (47·3 v 53·1 years, $p = 0{\cdot}03$) and had better baseline lung density in both upper and lower zones ($p = 0{\cdot}022$ and $0{\cdot}015$ respectively), but exhibited no other significant physiological or demographic differences (all $p > 0{\cdot}36$) from those whose upper zone was deteriorating.

3.2. 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 $p < 0{\cdot}15$ 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 ($p = 0{\cdot}029$) and lower zone density decline ($p = 0{\cdot}048$) were associated with subsequent death, whilst patients whose upper zone density was declining showed a similar trend, albeit non-significant ($p = 0{\cdot}072$). Kaplan–Meier plots are shown in Fig. 3. 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 1 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.

3.3. 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 ≥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