

PREVALENCE AND IMPACT OF CO-MORBIDITY IN COPD DUE TO ALPHA 1 ANTITRYPSIN DEFICIENCY

Authors

A Pillai¹, A Pye¹, RA Stockley² & AM Turner^{1,3}

1. Centre for Translational Inflammation Research, University of Birmingham, Birmingham, B15 2WB, United Kingdom (UK)

2. University Hospital Birmingham, Mindelsohn Way, Edgbaston, Birmingham, B15 2GW, UK

3. Heart of England NHS Foundation Trust, Birmingham, B9 5SS, UK

*Corresponding Author:

AM Turner, address as above;
Email:a.m.turner@bham.ac.uk

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ABSTRACT

Background

Alpha 1 antitrypsin deficiency (AATD) is a rare genetic cause of chronic obstructive pulmonary disease (COPD). There are a number of conditions which are recognized to be common as co-morbidities in COPD unrelated to AATD, and a co-morbidity specific prognostic score exists (COTE index). In this manuscript we sought to describe the COPD related, and unrelated, co-morbidities seen in AATD and assess their impact on outcome. The relevant literature is also reviewed.

Methods

All PiZZ AATD patients who have COPD from the UK AATD registry were selected, and graded for severity of COPD using the GOLD criteria. Medical notes were reviewed to ascertain co-morbidity, and used to calculate the COTE score. Each co-morbid condition was tested for association with GOLD stage and subsequent death. Multivariate analyses, adjusting for smoking, age and GOLD stage, were used to ascertain independent relationships to death. COTE score was compared between GOLD groups and between survivors and those that died. Selected co-morbid diseases were also assessed using multivariate analyses for their relation to lung function decline.

Results

The most common co-morbid disease in AATD was bronchiectasis (31.1% of patients). Some common COPD related conditions were seen, such as osteoporosis (11.9%). Liver disease was observed in 5.5% of patients. In univariate analyses the presence of osteoporosis, depression or gastro-oesophageal reflux (GORD) associated with GOLD stage, being more common in group D patients (all $p < 0.05$). No co-morbid disease was associated with death after adjustment for co-variables. COTE scores were generally low and did not differ between survivors and those that died.

Conclusion

Co-morbid disease is common in AATD, but differs from usual COPD, and has little impact on mortality and lung function decline. The COTE index is not valid for use in AATD.

INTRODUCTION

COPD is associated with an increased incidence of cardiovascular, psychiatric and musculoskeletal morbidity, which may place a significant burden on the individual and the healthcare system. A universally accepted definition of co-morbidity is lacking. Traditionally the term has been used to include a disease coexisting with the primary disease under consideration, such that osteoporosis, ischaemic heart disease and bronchiectasis, all of which occur commonly in COPD, would be recognised co-morbidities. Assessing co-morbidities actively in usual COPD has been recommended by a number of guidelines, as well as the GOLD strategy document (1), as management of these may improve outcome (2). Some of the co-morbidities have been shown to adversely affect survival (3, 4), hence supporting a process of active assessment and treatment of these conditions. A disease specific co-morbidity index (COTE index) has been proposed (3) as a means to assess the mortality risk in patients with COPD.

Several mechanisms have been proposed to explain the co-morbidities seen including an overflow of pulmonary inflammation into the systemic circulation to affect other organs, shared genetic predispositions between COPD and other diseases (5, 6) and common environmental exposures, the most notable being cigarette smoking. However, no correlation between the type and intensity of inflammation in the lung and systemic circulation has been found (7), perhaps refuting the overspill hypothesis although this has been questioned (8). The view that pulmonary manifestations of COPD are a form of expression of a 'systemic' inflammatory state with involvement of multiple organs (9) is consistent with shared genetic predisposition and/or shared pathogenesis,

of whatever cause.

Alpha 1 antitrypsin deficiency is the only widely recognized genetic risk factor for COPD, and is estimated to affect 3 million people worldwide (10). Individuals with AATD typically develop lung disease at a younger age and with lower exposure to tobacco smoke than other COPD patients. Typical clinical features, which have been reviewed in detail elsewhere (11), include lower zone emphysema, liver fibrosis/cirrhosis and enhanced pulmonary inflammation. Clinically significant disease may run in families in both AATD and COPD, with similar genetic and environmental modifiers now being recognized to underlie this association (12-17). Consequently it is likely that AATD patients who have COPD may exhibit a similar pattern of co-morbidity to 'usual' COPD unrelated to AATD, and also a similarly poor prognosis if co-morbidity is present. The aim of the current study was to describe the prevalence of co-morbid disease in PiZZ AATD, and compare key longitudinal outcomes between patients with and without co-morbid disease.

METHODS

Subjects

Data in this manuscript pertains to patients from the UK Antitrypsin Deficiency Assessment and Programme for Treatment (ADAPT), which is a longitudinal research registry of patients with AATD in the UK, approved by the local Ethics Committee (approval number 3359a) and all patients gave written informed consent. The details of patient assessment, questionnaires completed and the tests performed at each annual visit as part of ADAPT have been previously described (18). Briefly, patients attend a single centre and undergo annual assessment of clinical health, lung function,

health status and exacerbations, using a range of validated questionnaires, nursing and medical review. Reversibility to bronchodilator is tested at baseline, and at subsequent reviews all lung function is assessed post-bronchodilator.

The registry database was reviewed to retrieve data on all PiZZ patients with a physiological diagnosis of COPD (FEV1 <80 % predicted and FEV1/FVC <0.7) and at least 3 years follow up data, as described elsewhere (18). Compliance with annual follow up is good (18), hence reflective of the entire UK AATD population. All patients were categorized into the four COPD groups described in the GOLD strategy based on their initial mMRC scores and exacerbation history. The combined risk, defined as the highest group assigned by the various possible methods described in the GOLD outcome strategy (1), was used to assign groups.

Co-morbidity and longitudinal outcomes

All co-morbid diseases were recorded; those previously associated with COPD, and those that formed part of the COTE index were sought actively in the medical records. The most relevant conditions, based on frequency or prior association in usual COPD, were selected for comparison with mortality. Other outcomes of relevance such as lung function decline were also tested for association with co-morbid disease where appropriate. The COTE index was calculated in all patients, and its validity with regard to mortality assessed by comparing COTE score between survivors and those who died. Mortality and lung function decline data were already available, as described previously (18).

Statistical analysis

Statistical analysis was performed using a statistical software package (SPSS, version 20 for Windows and Graph Pad software 2012). Univariate and multivariate analyses

were performed to compare frequency of co-morbid disease using GOLD combined risk groups, and to compare mortality between individuals with and without the 12 co-morbidities used by Divo *et al* for the COTE index(3), to determine whether they would indicate increased risk of death in patients with AATD. The t test was used to compare categories for parametric data, and the Mann-Whitney U test was used for nonparametric data. Chi Square analysis was used to determine differences in patient distribution between groups and ANOVA to compare means between three or more groups.

Two tailed tests were used in all univariate and multivariate analyses to determine differences between groups, with $p < 0.05$ taken to be statistically significant.

Regression was used to assess mortality in multi-variate analyses. Significant variables in the stepwise analyses were included together with age, sex and smoking status in order to determine whether they remained significant following adjustment for these factors. Linear regression analysis was used to identify independent factors that predicted overall lung function decline. This compared forced expiratory volume in 1 second (FEV1) and gas transfer (KCO) decline between those with a specified co-morbidity to those in whom it was absent, adjusting for age, sex and smoking status as before.

RESULTS

Prevalence of co-morbidity

Characteristics of the patient cohort have been described in our previous work (18). Table 1 summarizes the co-morbidities found in our patients with AATD and the relationship to GOLD stage. 76.1% of subjects studied had at least one co-morbidity; there were similarities in the frequently occurring co-morbidities in our cohort of PiZZ patients with AATD to

those reported in COPD - hypertension, hyperlipidaemia, GORD, depression and osteoporosis along with coronary artery

disease and diabetes. Liver cirrhosis was diagnosed in 28 (5.58%) patients overall and 50% of these (n = 14) were in group D.

Co-morbidity	Whole group n (%)	GOLD stage n (%)				p
		A	B	C	D	
Bronchiectasis	156 (31.1)	25 (16.0)	17 (10.9)	30 (19.2)	84 (53.8)	
Hypertension	118 (23.5)	25 (21.2)	15 (12.7)	18 (15.3)	60 (46.7)	
GORD	90 (17.9)	20 (22.2)	17 (18.9)	11 (12.2)	42 (46.7)	0.02
Depression	73 (14.5)	8 (11.0)	11 (15.1)	4 (5.5)	50 (68.5)	0.01
Hypercholesterolaemia	59 (11.8)	9 (15.3)	10 (16.9)	10 (16.9)	30 (50.8)	
Osteoporosis	56 (11.2)	2 (3.6)	6 (10.7)	8 (14.3)	40 (71.4)	0.03
Thromboembolic disease	34 (6.8)	9 (26.5)	4 (11.8)	1 (2.9)	20 (58.8)	
Liver cirrhosis	28 (5.6)	5 (17.9)	6 (21.4)	3 (10.7)	14 (50.0)	
Coronary artery disease	27 (5.4)	3 (11.1)	2 (7.4)	3 (11.1)	19 (70.4)	
Diverticular disease	23 (4.6)	4 (17.4)	3 (13.0)	4 (17.4)	12 (52.2)	
Diabetes	21 (4.2)	2 (9.5)	5 (23.8)	1 (4.8)	13 (61.9)	
Hypothyroidism	19 (3.8)	4 (21.1)	6 (31.6)	1 (5.3)	8 (42.1)	
Atrial fibrillation	14 (2.8)	4 (28.6)	1 (7.1)	0	9 (64.3)	
Pulmonary fibrosis	9 (1.8)	2 (22.2)	2 (22.2)	0	5 (55.6)	
Colitis	8 (1.6)	1 (12.5)	1 (12.5)	2 (25.0)	4 (50.0)	

Table 1: Co-morbidities seen in AATD, sub-stratified by GOLD group

The table shows co-morbidities ranked by prevalence in the whole cohort, with the % representing the proportion of the cohort with a given co-morbidity. The number (n) and % of cases of each co-morbid disease seen in each GOLD stage is then shown, together with a p value for the distribution of co-morbid disease between GOLD stages. Those that differed significantly are shown in the table with their p value, all others were not statistically significant ($p > 0.12$). It is notable that since there were more patients in group D, for most co-morbid diseases more cases numerically appear to be in this group.

Relationship of co-morbidity to mortality

Table 2 shows the mortality distribution of those with co morbidities according to the GOLD groups. Importantly 48.15% of

those with coronary artery disease died (n = 13), this being the highest proportion of deaths for any co-morbidity, and 11 of the deaths were patients in group D. Of those with hypertension, 26 (22%) died during the period of observation with the majority (n = 18) also being in group D; this is consistent with ischaemic heart disease being a common cause of death, and hypertension as a well-known risk factor. 35 patients with bronchiectasis died (22.44%), of whom 26 were in the high symptom high risk group D. Among those with a clinical diagnosis of liver cirrhosis, 11 (39.29%) died and again, the majority (9/11) were in group D. The co-morbidities were rarely mentioned in the death certificate.

Co-morbidity	Whole group n (%)	GOLD stage n			
		A	B	C	D
Bronchiectasis	35 (22.4)	0	4	5	26
Hypertension	26 (22.0)	1	3	4	18
GORD	8 (8.9)	1	1	0	6
Depression	21 (28.8)	2	2	1	16
Hypercholesterolaemia	11 (18.6)	0	1	3	7
Osteoporosis	11 (19.6)	0	2	0	9
Thromboembolic disease	13 (38.2)	1	0	0	12
Liver cirrhosis	11 (39.3)	0	1	1	9
Coronary artery disease	13 (48.2)	0	0	2	11
Diverticular disease	3 (13.0)	1	0	2	0
Diabetes	1 (4.8)	0	0	0	1
Hypothyroidism	6 (31.6)	0	0	0	6
Atrial fibrillation	5 (35.7)	0	0	0	5
Pulmonary fibrosis	1 (11.1)	0	0	0	1
Colitis	2 (25.0)	0	0	1	1

Table 2: Relationship between co-comorbidity and subsequent death

The table shows the number and % of patients with each co-morbidity who died. The number of deaths is also shown by GOLD stage. GOLD stage is known to relate to mortality, hence statistical significance of the distribution of death by GOLD stage has not been shown, as the multivariate analysis is more meaningful.

To determine if co-morbidity was associated with mortality after adjustment for GOLD group (combined risk), age and smoking status, logistic regression was performed with these co-variables plus the most prevalent co-

morbidities in turn. Addition of smoking status in the step wise regression analysis was not significant ($p > 0.05$). Odds Ratios were generated after adjustment in the regression for co-variables, and are shown in table 3 for the 6 most prevalent co-morbidities. Each appeared to confer a small increased risk of death, generally about 5% greater than that without the co-morbidity. However, with the addition of age ($p=0.0001$) and GOLD group ($p=0.0001$) both of which were significantly associated with death, the relationship of all co-morbidities to death was lost.

Co-morbidity	HR for death (95% CI)
Bronchiectasis	1.052 (1.023-1.079)
Hypertension	1.051 (1.024-1.081)
GORD	1.052 (1.024-1.081)
Depression	1.050 (1.022-1.078)
Hypercholesterolaemia	1.051 (1.024-1.080)
Osteoporosis	1.053 (1.025-1.082)

Table 3: Risk of death associated with co-morbid disease

The table shows the risk of death (hazard ratio) after adjustment for smoking status.

Co-morbid disease, GOLD stage and COTE

110 patients had one or more co morbidities from those that constitute the COTE index (21.91%). The COTE scores ranged from 1 to 8 in Group D, 1 to 6 in Groups B and C and 1 to 7 in Group A, with the mean COTE index being lower for Groups B and D (2.47 and 2.53 respectively) than for Groups A and C (3.13 and 3.00 respectively albeit with no statistically significant difference ($p=0.28$ between groups A and B and 0.41 between groups C and D). Among the 118 patients who died, 29 scored on the COTE index (24.6%); 89 had none of the requisite co morbidities. No predilection for a higher COTE index was observed among those who died.

Using regression analysis, after adjusting for age, smoking and GOLD groups, the COTE index was not higher in non-

survivors compared to survivors ($p = 0.31$).

Co-morbid disease and decline in lung function

In order for a co-morbid disease to plausibly associate with lung function decline, we reasoned that it would need to influence either exacerbation frequency or pathogenesis of underlying lung disease. Of the most frequently observed co-morbidities the most important ones we felt met these criteria were bronchiectasis and osteoporosis, because of their association with severe exacerbations, exacerbation rate or emphysema (19, 20). In univariate analyses, there was no significant difference in either FEV1 or KCO decline between those with and without the two co-morbidities. Multivariate analyses demonstrated no impact of the co-morbidity after adjustment for combined risk group and index status; results are summarized in table 4.

Co-morbidity	FEV1 decline		KCO decline	
	B (95% CI)	p	B (95% CI)	p
Bronchiectasis	0.02 (-0.31 – 0.42)	0.75	-0.01 (-0.44 – 0.38)	0.87
Osteoporosis	-0.01 (-0.62 – 0.48)	0.80	0.01 (-0.57 – 0.70)	0.84

Table 4: Risk of lung function decline associated with co-morbidity in multivariate analyses

DISCUSSION

We have shown that co-morbidity in AATD shares many similarities with usual COPD, in that the diseases seen are similar, however the impact of these appears less, in that they do not independently relate to mortality or lung function decline. Consistent with this the COTE index appears to be a less useful prognostic indicator than in 'usual' COPD.

Classical thinking regarding co-morbidity in AATD

Our study has reported a low (5.5%) prevalence of liver disease, although this is classically associated with AATD. Patients with AATD have long been recognized to have an increased risk of liver cirrhosis (21), which may be apparent in early life (22). In some cases liver disease is present only transiently, being diagnosed after investigation for prolonged neonatal jaundice, whilst in

others disease may progress to fibrosis, later followed by clinically apparent cirrhosis, and require childhood transplantation (23). In adults liver disease has been reported in several cohorts or case series, with prevalence varying depending on the feature used to diagnose its' presence; clinical signs or symptoms suggestive of liver disease were reported in 63% of patients in one small case series, whereas biopsy defined fibrosis/cirrhosis was seen in just 17.5% of the same group (24). Alternatively biochemical abnormalities of liver function (e.g. ALT) in the largest cohort reported to date was 7.7%, though ALT was deemed insufficiently sensitive to be used as the sole test for liver disease (25). However, in this cohort, liver disease was largely self-reported by the patient and since it was a registry it may reflect ascertainment bias.

In a further case series of patients followed from birth, where ascertainment bias should not be a factor, the rate of ALT abnormality at age 34 was zero (26). Our data also suggests that the prevalence of liver disease is low in adults with PiZZ AATD, at 5.5%, and is similar to the American cohort in which ALT was studied (7.7%) (25). we acknowledge that if more detailed tests (such as fibroscan or ultrasound) had been conducted on all patients then the prevalence data would likely be greater. There have also been suggestions that measurement of GGT may be a more sensitive indicator of liver disease (26), but this may be confounded by possible relation of this marker to lung disease (27). Alternatively, use of a panel of markers pertinent to liver fibrosis may add value (28) and clearly requires further study.

The factors associated with liver disease or liver function abnormalities in AATD are not well described, but include male

sex (21), oral contraceptive pill usage (29) and BMI (30). A number of studies have also shown that heterozygosity for the Z allele (e.g. PiMZ) confers an increased risk of fibrosis or cirrhosis compared to the general population, with some suggestion that alcohol acts as a cofactor in conferring this risk (31, 32). The wide variability of clinical presentation of liver disease in AATD patients suggests that intrinsic patient factors, such as genetics, interact with environmental factors, like alcohol or medication use, to determine the overall risk of liver disease. Further research into the risk factors determining progressive liver disease in children and adults will be important to optimize monitoring and management of such patients in future.

A number of other diseases have been associated with AATD, such as panniculitis(33), vasculitis (34)and fibromyalgia(35). However in our cohort we observed low prevalence of such conditions, and little impact on outcome from such. We have also reported previously that an increase in inflammatory bowel disease is observed in AATD patients (36), but in this larger cohort restricted to those with COPD this was not a clinically important problem for most.

‘Usual’ COPD co-morbidities seen in AATD patients and the relation to mortality risk

Co-morbidity in COPD influences mortality (3) and health related quality of life (HRQoL) (37) as well as sharing aspects of pathogenesis (38). Indeed co-morbidity is so important that a prognostic score derived from COPD co-morbidities (COTE) improves the ability of the COPD specific BODE index to predict death (4). However our data in AATD suggests that whilst the pattern of co-morbidity has

many aspects that are similar to 'usual' COPD, there are differences in the impact. This may be because the prevalence of the 12 co-morbidities described by Divo *et al* in 'usual' COPD(3), from which the COTE score was derived, were not so frequent in our patients with AATD.

Our data showed that bronchiectasis was the most prevalent co-morbidity in AATD, and it may be of clinical importance. In patients with moderate to severe COPD, bronchiectasis contributes to risk of death (20) and has been found to enhance the frequency and severity of exacerbations. Bronchiectasis was present in 31.1% patients with AATD which is similar to that published in 'usual' COPD UK cohorts where it has varied from to 29% in primary care in the UK (39) to 50% in the secondary care East London cohort (40). In other studies, however, the prevalence in 'usual' COPD has varied from as little as 4% in a multinational ECLIPSE cohort (41) to 57.2% in one study from Spain (20) which may reflect both acquisition bias and/or the criteria used to diagnose bronchiectasis. The distribution of bronchiectasis in AATD did not vary with GOLD grouping and did not relate to mortality in our cohort. Indeed the vast majority of the observed conditions showed no relationship to GOLD group. The exceptions were GORD, depression and osteoporosis, which were more common in GOLD group D.

Gastro-oesophageal reflux (GORD) is common in advanced COPD, though often asymptomatic (42), and predicts exacerbation frequency (43). Increasing episodes of GOR have also been demonstrated to be associated with lower HRQoL in the general population (44). It is therefore perhaps not surprising that GORD appeared to be more frequent in our AATD patients whose GOLD

grouping was indicative of poor HRQoL and frequent exacerbations. However this did not associate with mortality in our cohort, and it remains unclear whether active management of GORD symptoms could aid prognosis or symptomatology in AATD.

A systematic review carried out in 2006 in patients with severe COPD showed a prevalence of 37-71% for depression (45). It is often undertreated, with symptoms diagnostic of disease and the number on treatment varying widely in some studies (46). It has previously been reported that 'usual' COPD increases the risk of developing depression, and that physiologic measures of stage of COPD do not markedly affect this risk (47, 48), such that the observation of more cases in GOLD group D contrasts with the usual COPD literature. The fact that the association with death seen in univariate analyses disappeared after adjustment for GOLD group implies that any association seen initially was spurious, and occurred due to the fact that depressed patients were generally more unwell. It is possible that AATD patients with severe disease are affected more psychologically than usual COPD patients as their disease progresses, due to their relatively younger age, and hence the greater contrast in their physical abilities compared to age matched peers.

Osteoporosis was more common in GOLD group D patients. This finding is consistent with the observation that bone mineral density (BMD) decreases with increasing severity of 'usual' COPD (49) and that severe COPD is one of the risk factors for presence of a low BMD, seen in 75% of GOLD stage 4 patients (50). This association is further supported by studies in 'usual' COPD showing a mechanistic link between the two diseases, whereby both exhibit loss of

extracellular matrix and elevated inflammatory mediators such as (tumor necrosis factor- α) (51-54). Osteoporosis can cause fragility fractures, both vertebral and non-vertebral, which could further impair mobility and increase morbidity leading to poorer HRQoL; this is consistent with our data that patients with osteoporosis generally had higher CAT scores, as demonstrated by the fact that osteoporotic patients tended to be in group D, where by definition the CAT is >10 . However an effect on mortality was not borne out by our data, as osteoporosis did not relate to death once covariates were accounted for in multivariate analyses. Our observations are therefore consistent with the cross sectional observation of an association between osteoporosis and emphysema severity in AATD.

In addition the utility of the COTE index was less than in 'usual' COPD as it did not predict death in our patients. However, the weightings in the COTE index were derived from data in 'usual' COPD, and we observed some co-morbidities that differed from 'usual' COPD, which likely accounts for the difference. We therefore chose to review the relationship of co-morbidities observed in our cohort to mortality by specific regression analyses rather than relying solely on COTE. Many of the co-morbidities associated with 'usual' COPD have a pathogenesis known to relate to smoking (e.g. IHD) or are known to relate to demographic factors (e.g. age, sex) in COPD(47, 55). For this reason our regression analyses assessing co-morbid disease in AATD adjusted for such covariates prior to entering GOLD stage, this was also a relevant covariate because COPD severity is a risk factor for death. It has recently been shown in a large cohort, including AATD patients, that the new GOLD groups do not perform any better in this regard than FEV1 alone;

hence we could have used either in our study (56). However, we felt it useful to retain consistency of approach by concentrating on GOLD groupings rather than FEV1 for this analysis. We did not show any relationship of our most commonly observed co-morbidities to death, suggesting that derivation of an AATD specific COTE is not necessary. In 'usual' COPD, the prevalence and the mortality attributed to different co-morbidities varies between studies (4, 37, 41). The direct risk of death conferred by hypertension and hyperlipidaemia in 'usual' COPD is not considered significant although the presence of liver cirrhosis does increase risk (3). AATD patients are younger, on average, than those with 'usual' COPD and thus it is likely that prevalence of co-morbidities and hence their impact on mortality would differ. Furthermore in our patients, smoking status was not a significant contributor to mortality ($p>0.05$), perhaps because exposure was typically lower than in 'usual' COPD.

Relationship of co-morbidity to other clinically relevant outcomes in AATD

The other clinical outcome we chose to assess in this group was decline in lung function. However, we reasoned that this had potential to be influenced only by a selected few of our most prevalent co-morbidities. For instance, there was no sound biological reason to think hypertension would influence decline in lung function. The two co-morbidities we felt would be most relevant to assess with regard to FEV1 and gas transfer decline were bronchiectasis and emphysema. Whilst GORD might also be expected to influence lung function decline, by means of predisposition to exacerbations, this co-morbidity was often not confirmed by objective tests in our cohort (unlike

bronchiectasis and osteoporosis, which were generally supported by HRCT and DEXA scan evidence respectively). Consequently we decided not to analyse GORD in this regard until additional data is collected (see strengths/limitations section).

Frequent exacerbations play an important role in the long term decline in lung function in patients with moderate to severe COPD, and our previous data indicated that GOLD groups who exhibited more frequent exacerbations differed in their lung function decline (57). The presence of bronchiectasis has also been found to be associated with increased risk of airway colonisation and hence airway inflammation, and more frequent and severe exacerbations in usual COPD (40, 58). We reasoned that bronchiectasis could also potentially contribute to decline in lung function. However the data showed that bronchiectasis patients did not differ in FEV1 or gas transfer decline from those without. This may reflect the enhanced exacerbation risk already contained within the GOLD grouping, and hence would be adjusted for by our addition of GOLD group to the list of covariates. In addition there may be other factors in bronchiectasis which are of greater importance with regard to lung function decline, such as *Pseudomonas* colonization (59) and other microbial insults (60). Data on stable state sputum culture was not available in all our patients and thus it was not possible to take into account sufficiently for our analyses.

Emphysema is a key sub-group within COPD, and a particularly important feature of AATD. Gas transfer and the extent of emphysema seen on HRCT scans have been shown to be sensitive to disease progression in patients with COPD related to AATD (61) and it has been established that a more rapid decline

in gas transfer occurs late in disease (57), at a time when osteoporosis was more common in our cohort. However whether the association with severe disease is from a shared pathogenesis, as described above, or whether it is due to confounders such as increasing steroid use for frequent exacerbations, remains unclear. If the association were driven by shared pathology we reasoned that gas transfer decline in particular might be more marked in osteoporotic patients. However, this was not borne out by the data, thus implying that osteoporosis does not drive or progress alongside physiological decline in AATD.

Strengths and limitations

This is the largest cohort described to date in AATD with regard to co-morbidity, and the first to assess impact of these on longitudinal outcomes. However a more comprehensive assessment of co-morbidity might be valuable for future studies. It is possible that they could be diagnosed and/or better evaluated earlier in the disease process by use of more disease specific questionnaires. These include the Medical Outcomes Study Short-Form 36-item (SF-36) to assess the general health status (62), Frequency scale for symptoms of GORD (FSSG) questionnaire (63) and evaluation of anxiety and depression using HADS (64) in patients with AATD. This would provide a more comprehensive clinical assessment and enable the identification of undiagnosed, untreated or more severe co-morbidities that may benefit from specific interventions. Had such data been available we could have conducted more detailed analysis of the impact of each co-morbid disease – for instance GORD could reasonably have been examined for its relation to lung function decline, but it would have been more relevant to look at this in patients with more severe GORD rather than all

sufferers, particularly where the condition had not been confirmed by objective tests. There are a number of other outcomes generally thought to be clinically important in COPD; especially HRQoL and exacerbations. Whilst HRQoL data does exist for the group, in the form of CAT and SGRQ score (65), these are COPD and respiratory disease specific scores respectively so we felt it less relevant to assess with regard to relationship to co-morbidity. We could not to assess exacerbation rate per se, as this is already part of the GOLD grouping definition and hence the COPD severity using current method of calculation of GOLD stage/group. We also reasoned that exacerbation type, rather than rate, would be the more relevant field to consider with regard to the effect of co-morbid disease on this outcome – for example we might expect bronchiectasis to be associated with infective rather than non-infective exacerbations. Data on exacerbation type was not available for all patients at the time of analysis, hence the effect of co-morbidity on this outcome was not possible to assess. Finally, we were also unable to fully adjust for treatment effects in our analyses, given that the range of treatments was broad and changed over the period of follow up for many patients. However since no COPD treatment has been shown conclusively to reduce

mortality or lung function decline we do not feel this will have affected the results.

Conclusion

Co-morbidity is present in AATD but differs from the pattern seen in ‘usual’ COPD perhaps due to the differing age and smoke exposure of patients. The COTE score is not valid for use in AATD as a prognostic indicator.

Contributions

AP (Pillai) collected data, analyzed data and drafted some sections of the manuscript. AP (Pye) collected data. RAS reviewed the manuscript and supervised AP (Pillai) for some analyses. AMT drafted the manuscript and acts as guarantor.

Conflicts of interest

AMT and RAS have received honoraria or fees for advisory boards from manufacturers of medications for COPD. AMT and RAS have had grant funding processed through their institutions from manufacturers of treatments or potential future treatments for AATD. AP and AP have no conflicts to declare

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