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Mortality in Bronchiectasis: a long-term study assessing the factors influencing survival.

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Abstract

Rationale and Objectives – There is little literature about the mortality associated with bronchiectasis. The aim of this study was to investigate factors affecting mortality in patients with bronchiectasis.

Methods – 91 patients had investigations of aetiology, pulmonary function tests, high resolution computed tomography (CT), sputum microbiology, and quality of life scores and were then followed over 13 years.

Results – 29·7% of the patients died. On multivariate analysis; age, St. George's Respiratory Questionnaire activity score, *Pseudomonas aeruginosa* infection, total lung capacity (TLC), residual volume/TLC, and the transfer factor coefficient were all independently associated with mortality.

Conclusions – In patients with moderate to severe bronchiectasis, the mortality is associated with a degree of restrictive and obstructive disease, poor gas transfer, and chronic pseudomonas infection. These features should guide future research into disease progression, and identify those patients needing intensive treatment.

Introduction

Bronchiectasis is a chronic respiratory condition characterised by the abnormal dilatation of bronchial lumen [1]. Damaged airways predispose the patient to recurrent bacterial infections, which in more severe cases become chronic. This leads to a host inflammatory response which causes tissue damage, leading to a vicious circle of host-mediated, bacteria stimulated disease progression [2]. However, why in the majority of patients such progression is slow, whereas in others it occurs much more quickly is poorly understood.

Investigation of bronchiectasis aims to identify possible aetiologies and predisposing factors which may be treatable [3]. Management then centres on physiotherapy and antibiotics are used promptly in infective exacerbations. There is a lack of good randomised controlled trials for evidence based management in bronchiectasis, and many of the management programmes are extrapolated from the treatment of other conditions such as pneumonia and cystic fibrosis [4].

A clearer picture of the natural history and mortality in bronchiectasis would be of great value, both in allowing more accurate prognostic information, and in determining the specific characteristics of the disease that confer an increased risk of progression and mortality. This information will form the basis of future studies assessing the impact of therapies in bronchiectasis. Neutrophilic inflammation is thought to be a key component of the pathogenesis of chronic obstructive pulmonary disease (COPD), a condition in

which infective exacerbations have been linked to disease progression [5,6] and in which bronchiectasis is quite commonly seen in severe cases on CT scan [7]. A better understanding of disease mechanisms in bronchiectasis might also inform COPD research.

In 1994, 111 patients with bronchiectasis were studied to validate the St. George's Respiratory Questionnaire (SGRQ) as a tool in assessing the health status of patients with bronchiectasis [8]. Fourteen years on, we have now reassessed these patients and carried out an analysis of the factors in the original assessment which predict mortality. The purpose of the study was to provide prognostic information at baseline.

Methods

In the original study in 1994, 120 sequential patients with clinically diagnosed bronchiectasis were approached to take part in this outpatient study in the Host Defence Unit of the Royal Brompton Hospital, a tertiary referral centre. Of these 111 agreed to the study. The exclusion factors were bronchiectasis not being the predominant pathology and cystic fibrosis, however there were no patients in these group [8]. Each patient provided signed consent and the protocols were approved by the Hospital Ethics Committee. Each patient had full host defence investigations, which have been described elsewhere [9], including sweat testing for cystic fibrosis, two sputum samples which were also tested for non-tuberculous mycobacteria and a high-resolution computed

tomography scan (CT). Comprehensive lung function tests with body plethysmography were performed on two separate occasions six months apart at entry to the study.

The outcome of these patients was determined as of March 2007, thirteen years after the initial recruitment. Patients not followed up in our institution were tracked via general practioners, other hospitals and the Office for National Statistics, and death certificates were obtained in all patients that died. The CT scans were reassessed and on this basis the patient number was reduced further to only include patients who also had bronchiectasis according to CT criteria.

CT images of 1-1.5 mm thickness at 10mm intervals were scored for bronchiectasis [10,11] by two blinded, independent radiologists. The scoring system used was modified from the Bhalla system [12] and has been shown to be associated with low inter-observer variation [13]. Bronchiectasis extent and bronchial wall thickness were scored in each lobe on a scale of 0 to 3 (3: most severe changes). Bronchial dilatation and mucus plugging were grade from 0 to 2. A mosaic attenuation pattern (reflecting small airways obliteration) and emphysema were scored to the nearest 5%. The average score of the two observers, as a percentage of the maximum score possible to account for patients with lobectomies, was used for analysis.

Statistical Analysis

Kaplan-Meier curves were used to illustrate survival data. Variables were examined against survival using Cox's proportional hazards model: in multivariate models, a

stepwise approach was used to discard variables not independently linked to mortality ($p>0.05$). Hazard ratios are given with confidence intervals for significant ($p<0{\cdot}05$) and marginal ($0{\cdot}05<p<0{\cdot}15$) trends.

Stepwise multiple linear regression was used to identify independent CT determinants of lung function impairment. Lung function indices shown to have an independent impact on mortality (TLC, RV/TLC, KCO) were used as the dependent variables in separate models. The validity of the parametric assumptions of linear regression were confirmed with testing for heteroscedasticity and RV/TLC was subjected to zero skewness logarithmic transformation on the basis of this test.

Statistical analyses were performed using STATA (version 4).

Results

Patient demographics and survival

There were 111 patients that consented for the original SGRQ study in 1994. Review of CTs found no bronchiectasis in 12 patients and they were not included in further analysis. These patients had a clinical presentation compatible with bronchiectasis, but they did not satisfy the CT criteria. The data set was incomplete in a further eight patients and they were also excluded, leaving 91 patients in the study (92% of the eligible patients) (Figure 1). Patient demographics are shown in Table 1.

Table 1

Patient number	91

Mortality (dead/alive)	27 (29.7%) / 64 (70.3%)
Sex (female/male)	53 (58.2%) / 38 (41.8%)
Smoker (current/former/never)	1 (1.1%) / 20 (22%) / 70 (76.9%)
PSA/Non-PSA	20 (22%) /71 (78%)
Age (1994)	51·7 (12·1)
Recruitment to RIP/01-03-07 (months)	126·9 (38·0)
Period between CT and LF (months)	13·0 (14·1)

CT criteria - percentage of the maximum score attainable

Bx extent	33·1 (21·0)
Dilatation severity	39·7 (24·8)
Wall thickness	20·6 (12·4)
Small airway plugging	9·8 (14·7)
Large airway plugging	12·5 (13·1)
Mosaicism	7·5 (10·2)
Emphysema	3·9 (8·0)

LF criteria

FEV_1 %predicted	65·8 (28·1)
FVC %predicted	88·7 (23·6)
FEV_1/FVC %predicted	83·1 (9.0)
RV %predicted	136·8 (44·1)
TLC %predicted	103.1 (16.6)
RV/TLC %predicted	126·9 (31·3)
TLCO, %predicted	76·2 (20·4)
KCO, %predicted	95·4 (22·1)

Health related quality of life questionnaire scores

Fatigue	4·7 (2·4)
MRC wheeze	2·2 (1·3)
MRC dyspnoea	2·2 (1.0)
SGRQ total	45·9 (18·1)
SGRQ symptoms	71·9 (18·8)
SGRQ activities	49·1 (24·5)
SGRQ impacts	35·7 (19.0)

Aetiology

Idiopathic	51 (56%)
Post infective	20 (22%)
ABPA	8 (8.8%)
PCD	5 (5.5%)
Young's syndrome	4 (4.4%)
Hypogammaglobulinaemia	3 (3.3%)

Table 1. General characteristics of study patients with bronchiectasis. Data presented as mean (standard deviation) or number (percentage). Computed Tomography (CT) criteria expressed as a percentage of the maximal possible score for each criteria. Lung function (LF) criteria expressed as percentage of predicted values. MRC dyspnoea scores range from 1-5, with a score of 1 representing greatest breathlessness on strenuous exercise. SGRQ scores range from 0-100, with a zero score indicating no impairment in quality of life. Data is presented from time of entry into the cohort. Abbreviations; *Pseudomonas aeruginosa* (PSA), patient deceased (RIP), lung function (LF), bronchiectasis (Bx), forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), total lung capacity (TLC), residual volume (RV), carbon monoxide transfer factor (TLCO), carbon monoxide transfer coefficient (KCO), medical research council (MRC), St. George's Respiratory Questionnaire (SGRQ), allergic bronchopulmonary aspergillosis (ABPA), primary ciliary dyskinesia (PCD).

Patients were followed up from recruitment in 1994, to March 2007. During the 13-year follow-up, 29·7% of the bronchiectasis patients died. Using life expectancy data from the Office for National Statistics, the expected death rate of a 52 year old (mean age in our study) is 14.7% for males and 8.9% females over a similar 13-year timepoint [14]. Accounting for the mortality in our study, the mean length of follow up was 126·9 months (+/- 38·0). All the 91 patients were successfully accounted for at the end of the study. The cause of death was bronchiectasis, respiratory infection or respiratory failure in 19/27 (70·4%) cases. Haemoptysis was the terminal event in one of these patients. Two patients each died of renal failure and colon cancer, and one patient died of heart failure, cerebrovascular accident, liver metastasis, and pulmonary embolism respectively. Post-mortems were performed in three patients and the cause of death classified as suppurative bronchitis, bronchiectasis and heart failure. Of those who died during the study, the median age was 60. A Kaplan-Meier survival plot is shown in figure 2.

The aetiology of the bronchiectasis was as defined at recruitment and was similar to previous studies [9,15]. Idiopathic aetiology accounted for more cases (56·0%) than a

recent study from our institution (34·6%) [9]. Nevertheless, the same broad trends were observed with idiopathic and post-infective causes of bronchiectasis the most common aetiologies. The majority of the patients in the study were never smokers (76·9%) and the proportion of emphysema on the HRCT scans was also low (mean score <4%). There was a range of scores (Table 1) suggesting this study population covered a spectrum of disease activity, however broadly the cohort described a population with moderate to severe bronchiectasis. Bronchiectasis affected a total of 304 out of a possible 535 lobes examined on CT scan (56·8%). Spirometry showed that airflow obstruction was the predominant finding in this group of bronchiectasis patients, with an average FEV_1 of 1·85 l/min (65·8 % predicted) and FVC of 3·05 l (88·7% predicted), which is in accordance to other studies [15-17].

Mortality Risk Factors

All the measured variables were included in a univariate analysis shown in Table 2.

Table 2

Parameters	**RR (95% CI)**	***p* value**
Sex	1·96 (0·92-4·20)	0·082
Age	1·06 (1·02-1·09)	**0·001**
Smoker	1·78 (0·87-3·63)	0·120
PSA/Non-PSA	2·33 (1·04-5·18)	**0·039**
CT criteria		
Bx extent	1·04 (1·02-1·05)	**<0·0005**
Dilatation severity	1·03 (1·01-1·04)	**<0·0005**
Wall thickness	1·07 (1·04-1·10)	**<0·0005**
Small airway plugging		0·506
Large airway plugging	1·04 (1·02-1·07)	**0·002**

Mosaicism	1·03 (1·00-1·06)	**0·049**
Emphysema	1·05 (1·02-1·08)	**0·001**
LF criteria		
FEV_1, %predicted	0·97 (0·95-0·98)	**<0·0005**
FVC, %predicted	0·98 (0·96-0·99)	**0·003**
FEV_1/FVC, %predicted		0·209
RV, %predicted		0·176
TLC, %predicted	0.98 (0.96-1·01)	0·192
RV/TLC, %predicted	1·01 (1·00-1·02)	**0·021**
TLCO, %predicted	0·95 (0·93-0·97)	**<0·0005**
KCO, % predicted	0·98 (0·97-0·99)	**0·007**
Health related quality of life questionnaire scores		
Fatigue	1·14 (0·97-1·35)	0·122
MRC wheeze	1·26 (0·92-1·71)	0·147
MRC dyspnoea	2·89 (1·84-4·54)	**<0·0005**
SGRQ total	1·04 (1·01-1·06)	**0·002**
SGRQ symptoms	1·02 (1·00-1·04)	0·121
SGRQ activities	1·04 (1·02-1·06)	**p<0·0005**
SGRQ impacts	1·02 (1·00-1·04)	**0·035**

Table 2. Univariate Cox proportional hazard analysis with relative rates (RR), 95% confidence intervals (CI) and probability (p) values. RR >1 describes a positive correlation between the parameter and mortality, whereas RR <1 suggests a negative correlation. Abbreviations; *Pseudomonas aeruginosa* (PSA), Computed Tomography (CT), bronchiectasis (Bx), Lung Function (LF), forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), total lung capacity (TLC), residual volume (RV), carbon monoxide transfer factor (TLCO), carbon monoxide transfer coefficient (KCO), medical research council (MRC), St. George's Respiratory Questionnaire (SGRQ).

A relative rate (RR) >1 describes a positive correlation between the parameter and mortality, whereas a RR <1 suggests a negative correlation. There are large ranges of lung function, CT, and health status variables that have a strong relationship to mortality in this analysis. There are particularly strong associations for bronchiectasis extent,

bronchiectasis severity and wall thickness on CT assesment; FEV_1 and TLCO on lung function measurement; and dyspnoea and activity score on health status assessment. The relative rates and confidence intervals for the CT and lung function criteria appear much lower than for example the existence of pseudomonas. This is a function of them being continuous as opposed to categorical variables. For lung function tests, a risk ratio reflects a change in risk per unit lung function. In other words, a risk ratio of 0.97 for FEV_1 means that for every 1% change in FEV_1 there is a 3% change in risk. A difference of 30% FEV1 consequently confers a relative rate of 2.71 (confidence intervals 1.65, 4.45).

Several of these variables will represent different ways of measuring the same effect. The multivariate analysis demonstrated the variables with independent effects on mortality. Complex CT scoring systems are not practical for routine clinical practice and would not be available in most centres, and as such these variables were excluded from the multivariate analysis. Increased age, male sex, *Pseudomonas aeruginosa* colonization, and higher SGRQ activity scores (describing lower activity levels), in addition to higher RV/TLC and lower TLC, and KCO lung function measurements were independent predictors of mortality (Table 3).

Table 3

Parameters	**RR (95% CI)**	***p* value**
Age	1·10 (1·06-1·15)	<0·0005
PSA	3·61 (1·35-9.62)	0·010
Sex	3.42 (1.34-8.77)	0.010
LF criteria		

RV/TLCpred	1·03 (1·01-1·04)	<0·0005
TLCpred	0·95 (0·93-0·98)	<0·0005
KCOpred	0·96 (0·94-0·98)	<0·0005
Health related quality of life questionnaire scores		
SGRQ activities	1·05 (1·02-1·08)	<0·0005

Table 3. Multivariate Cox proportional hazard stepwise analysis with relative rates (RR), 95% confidence intervals (CI) and probability (p) values. RR >1 describes a positive correlation between the parameter and mortality, whereas RR <1 suggests a negative correlation. Abbreviations; *Pseudomonas aeruginosa* (PSA), Lung Function (LF), total lung capacity % predicted (TLCpred), residual volume % predicted (RVpred), carbon monoxide transfer coefficient % predicted (KCOpred), St. George's Respiratory Questionnaire (SGRQ).

Although not used in the main multivariate model, the CT variables were assessed together in a separate multivariate analysis to find the most important CT factors which had strong independent effects on mortality. Increased wall thickness (RR, 95%CI; 1·06, 1·03-1·10)($p<0·005$) and emphysema (1·04, 1·00-1·07)($p=0·027$), despite the low prevalence of this latter feature, were the strongest predictors of mortality in bronchiectasis from the CT findings.

Seven patients had lobectomies and four of these died. The mean TLC in the lobectomy group was 4·63 litres (l) (SD; 0·91), which was 80·43% (10·97) predicted compared to 6·00 l (1·42), 105·04% (15·55) respectively in the other patients. However, the lung function parameters that predicted mortality in the survival analysis were unchanged when these seven patients were removed.

There is no difference in mortality rates among the different aetiologies of bronchiectasis. As the number in several of the groups was very small, we separated them into idiopathic and known causes (p=0·57 Cox proportional hazard) and have illustrated mortality differences using Kaplan-Meier curves (Figure 2).

Functional – Morphological Correlations

The lung function measures that independently predict survival in bronchiectasis are TLC, RV/TLC and KCO, as shown above. The morphological correlates of these were examined by separate linear regression models with these three lung function measures as the dependent variables and the CT variables as cofactors. Regression coefficients (RC) >0 describes a positive correlation between the parameter measurements, whereas RC <0 suggests a negative correlation. TLC was positively correlated to mosaicism on the CT scan, RV/TLC was positively correlated with wall thickness and mosaicism, and KCO was negatively correlated with emphysema (Table 4).

Table 4

a) TLCpred

Parameters	RC (95% CI)	*p* value
Mosaicism	0·41 (0·06-0·75)	0·02

b) RV/TLCpred (log)

Parameters	RC (95% CI)	*p* value
Wall thickness	0·02 (0·01-0·02)	<0·0005
Mosaicism	0·01 (0·01-0·02)	0·001

c) KCOpred

Parameters	RC (95% CI)	*p* value
Emphysema	-0·85 (-1·4 - -0·30)	0·003

Table 4. Independent relationships between Computed Tomography (CT) measurements and the lung function measurements shown to correlate with mortality. Data presented as regression coefficient (RC), 95% confidence intervals (CI) and probability (p) values. RC >0 describes a positive correlation between the parameter measurements, whereas RC <0 suggests a negative correlation. Abbreviations; total lung capacity % predicted (TLCpred), residual volume/TLC % predicted (RV/TLCpred), carbon monoxide transfer coefficient % predicted (KCOpred). RV/TLCpred has been log transformed (log 56.93) to correct for skewness.

Longitudinal Data

The purpose of this study was to construct prognostic indices from baseline data. We did not routinely repeat these tests during the course of the study. Nevertheless, the majority of patients did have several repeat lung function and sputum investigations during follow up. There was an average decrease in KCO per year of follow up of 0.03 (95% CI; 0.01-0.04). This was significantly greater in those who died 0.05 (0.005-0.09) compared to the surviving patients 0.02 (0.004-0.03) (p=0.02, Mann Whitney). The longitudinal changes in TLC (0.02/year (-0.02–0.06)) and RV/TLC (0.1%/year (-0.62-0.82)) were insignificant with no difference between the patients that survived or died. Repeat sputum cultures were also performed in 17 of the 20 patients with *P. aeruginosa*. Of these, *P. aeruginosa* was a consistent finding in 11/17 with intermittent cultures in 6/17.

Discussion

Prior to this study, the outcome in adult bronchiectasis had not been well described and there has been a lack of long-term prospective studies. This study is unique in having a very well defined bronchiectatic population, all of which had extensive measurements of disease at baseline. Furthermore, all patients were followed prospectively until death or the end of the study 13 years later. The extensive nature of the testing in this study and the length of follow-up, mean that it is ideally placed to comment on features of bronchiectasis patients that influence mortality.

The average age of death in patients with bronchiectasis was found to be less than 55 years in a study in the 1960s [18], and most patients succumbed to the disease before the age of 40 in a report of 400 bronchiectatics in 1940 [19]. Since this time however the condition, aetiologies, and treatment have altered with the advent of vaccination programmes and the increased use of antimicrobials for childhood infections and tuberculosis. More recent studies have reported a variation in mortality rates in bronchiectasis with the worst being a 4 year survival of 58% [16], a retrospective study showing a 75% survival at 8·8 years [20], and the best being an 81% survival at 14 years [17]. The survival rates during our study were broadly comparable to the latter two studies, being 91% at 4 years, 83·5% at 8·8 years and 68·3% at the end of 12·3 years (Figure 2). The primary cause of death in our patients was respiratory, suggesting that patients die from, not just with, bronchiectasis.

This study looked specifically at the factors associated with mortality rate in bronchiectasis over a 13-year period. There are few previous studies assessing this, but

a poor initial ventilatory capacity [17], male sex [20], and a secondary diagnosis such as asthma or COPD [20] have all been suggested as inferring a worse prognosis in bronchiectasis. A more recent report prospectively followed 98 patients with bronchiectasis over a 4-year period in Turkey. Risk factors for mortality in this study were only looked at in a univariate analysis, and included age, low BMI, hypoxia, hypercapnia, radiographic extent, MRC dyspnea scale and lack of vaccinations [16]. The results of our study have demonstrated that the factors with an independent impact on mortality are age, SGRQ activity score, *P. aeruginosa* colonization, and TLC, RV/TLC and KCO lung function measurements.

Amongst a larger number of variables examined against mortality, most were not independently predictive and were discarded using a stepwise methodology, to develop a final model that contained only six covariates. Failure to discard non-significant variables would have resulted in confounding by collinearity (as, for example, between pulmonary function measures of airflow obstruction), as well as a degree of model over-fitting. However, it should also be acknowledged that in multivariate analysis, the retention of one collinear variable (quantifying, for example, airflow obstruction), as opposed to another, is sometimes a very close call. The multivariate modeling strategy used is predominantly for enabling mechanistic conclusions as opposed to predicting individual patient outcomes. The results should be interpreted as identifying the broad determinants of mortality (which includes the severity of airflow obstruction), in the search for pathogenetic insights. The model is not advanced as a multivariate clinical

index for immediate use. Nevertheless, the stronger univariate relationships we report are of immediate clinical relevance.

Formal CT scoring, as performed in this study, is unrealistic in routine clinical practice [21] and was not included in final multivariate modeling. This approach was further validated by the finding that CT features did not reach statistical significance for an independent effect on mortality when reentered into the modeling equations. The CT variables are nevertheless very useful in order to appreciate the pathogenetic correlates of the functional indices. The CT scan correlates of the lung function parameters with an independent impact on mortality, TLC, RV/TLC, KCO were mosaicism, wall thickness and mosaicism, and emphysema respectively.

Of the variables shown to have an independent effect on mortality in bronchiectasis, *P. aeruginosa* has previously been shown to infect patients with more extensive disease and severe airflow obstruction [22]. Two studies have shown that infection leads to an increased progression of disease [23] with a more rapid decline in lung function parameters [24]. The cause and effect relationship is less clear, as this pathogen may instead be a marker of disease progression as opposed to the cause for progression [25]. The independent effect of infection with *P.aeruginosa* on mortality shown in this study, suggests that it is likely to impact on survival more than just being a marker of severity. Infection control measures, such as clinic segregation, to avoid patient exposure to the bacterium should be investigated. Furthermore, treatment regimes designed to eradicate *P.aeruginosa,* when it occurs for the first time, have shown some benefit in delaying the

decline of lung function in patients with cystic fibrosis [26, 27], and may similarly impact on the progression of bronchiectasis [4]. This should be investigated in randomised controlled studies.

Poor lung function measurements have previously been shown to be associated with mortality in bronchiectasis [17]. Our study has shown an increased mortality in patients with a high residual volume to total lung capacity. This suggests the importance of obstruction in the presence of restriction in this condition. In the multivariate model, RV/TLC was more important than the other variables that measured obstruction, suggesting that obstruction had the greatest effect on mortality in the presence of some restriction. The importance of a component of restrictive lung disease in bronchiectasis is also confirmed by the correlation between mortality and a lower total lung capacity in this study. This relationship was still present when those patients who had lobectomies were removed. The final lung function measurement with an independent effect on mortality in this study is KCO. This demonstrates a vascular or emphysematous component that impacts on mortality in bronchiectasis. The low prevalence of emphysema in CT scans suggests the former as the more likely. There appears to be separate and independent effects of the three individual components of functional impairment on lung function testing with obstruction, restriction, and impairment of gas transfer all separately implicated in mortality. These components are likely to represent separate pathogenic components of bronchiectasis which may be important in helping to understand the impact of disease, in addition to providing specific targets for future

treatments. To elucidate the potential morphological correlates of these lung function measures, they were correlated with CT findings.

The measure of obstruction, RV/TLC, was correlated to mosaicism and wall thickness on CT scan. The correlation of functional obstruction to wall thickness does not differentiate between secretions and ablative bronchiolitis as the cause, however the relationship with mosaicism favours the latter as a morphological explanation to the obstructive functional element in bronchiectasis. This is in agreement with a previous study correlating CT findings with FEV_1, which is another measure of airways obstruction [28]. The authors concluded that airways obstruction in bronchiectasis was primarily related to intrinsic disease of small and medium airways, and not to the large airway abnormalities, airway mucus plugging, or emphysema. Small airways disease is prominent in histological studies of bronchiectasis with obstructive and inflammatory bronchiolitis leading to the features of airways obstruction and decreased radiographic attenuation [29].

In contrast, CT features could not explain the restrictive element, with total lung capacity showing only a positive correlation with mosaicism. Possible pathological correlates of lung restriction in bronchiectasis include parenchymal scarring secondary to previous infections, pleural disease, peribronchial fibrosis, and atelectasis. Peribronchial fibrosis has been demonstrated in histological studies of bronchiectasis [30], and this together with atelectasis distal to the ablated airways may not be detectable on CT scanning [28].

The contribution of poor gas exchange to mortality may be secondary to emphysema or to a pulmonary vascular component. The transfer factor coefficient was positively correlated to emphysema and not mosaicism, suggesting emphysema as the morphological correlate of low transfer factor. However, CT measurements of the pulmonary vasculature are poor and the possible importance of pulmonary hypertension in bronchiectasis is further highlighted by an earlier study in which cor pulmonale was present in 37% of patients who died from bronchiectasis [17]. From a management point of view, the importance of assessing pulmonary artery pressures in bronchiectasis patients with low transfer factors should be emphasized, as these patients may be amenable to some of the newer anti hypertensive agents.

In addition to helping understand the pathogenesis of the condition and providing additional targets for treatment, knowledge of the lung function factors associated with mortality may provide useful correlates for mortality against which future treatments can be tested and it may be used in defining subgroups of patients into prognostic categories. The severity of bronchiectasis is presently defined by the extent and grade of large airway dilatation. These features are not associated with prognosis and hence a paradigm involving lung function may be more appropriate. The study was not designed to investigate the rate of change of parameters over time and hence routine repeat measurements were not performed. The longitudinal investigations we have described were taken at different times and for different indications. With these limitations, it demonstrated a decline in KCO over time predominantly in the patients that died and this may be helpful in providing a basis for assessing the stability of patients over time.

In summary, this study has suggested the importance of lung function measurements in addition to age, *P.aeruginosa* infection and health questionnaire activity scores in the prognosis in bronchiectasis. It is important to note that the conclusions are referable to a tertiary centre and are subject to the limitation of a predominantly retrospective analyis. Nevertheless, knowledge of the results from this study should change investigation protocols and define patients that need more intensive management plans such as antibiotics or anti-inflammatory agents. The results may also help to define useful subgroups for assessment of treatment regimes in much needed randomised controlled trial to help advance bronchiectasis treatment towards a stronger evidence base.

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Competing Interests

None of the authors had any competing interests to disclose.

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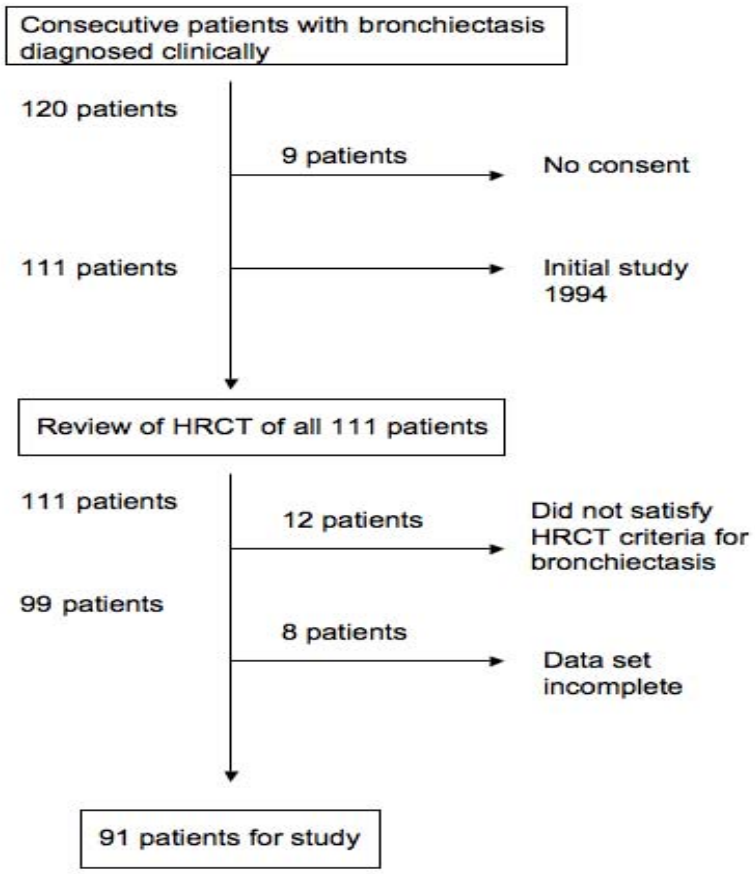
Figure Legends

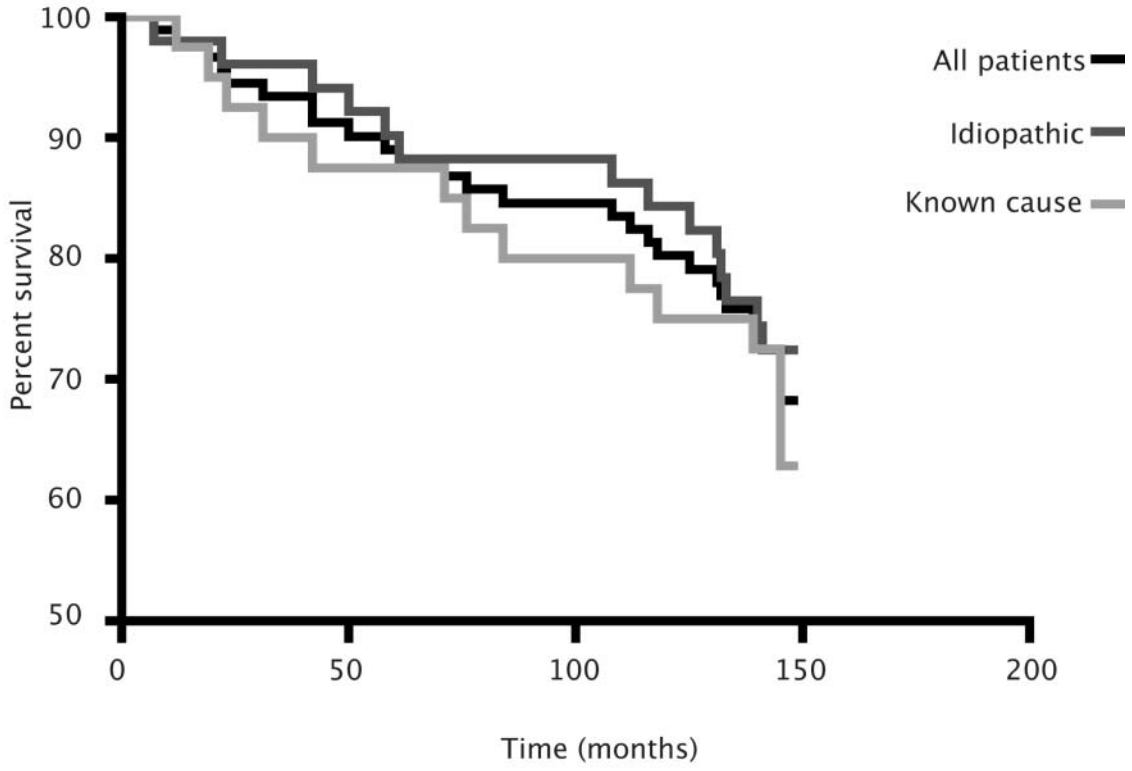
1. Flow diagram depicting patient selection.

Figure 1. Loebinger et al.



2. Kaplan-Meier plot illustrating the survival of the bronchiectasis patients, in addition to the idiopathic and known aetiology subgroups. There are no statistically significant differences between the plots (log rank test; p=0.85).

Figure 2. Loebinger et al



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