Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/rmed

Mortality in non-cystic fibrosis bronchiectasis: A prospective cohort analysis[☆]

P.C. Goeminne [a,*], T.S. Nawrot [b], D. Ruttens [a], S. Seys [c], L.J. Dupont [a]

[a] University Hospital of Gasthuisberg, Department of Respiratory Disease, Leuven, Belgium
[b] Center for Environmental Sciences Hasselt University, Hasselt, Belgium
[c] Laboratory of Clinical Immunology, Catholic University of Leuven, Leuven, Belgium

Summary

Introduction: There is limited data on mortality and associated morbidity in non-cystic fibrosis bronchiectasis (NCFB). Our aim was to analyze the overall mortality for all newly diagnosed patients from June 2006 onwards and to evaluate risk factors for mortality in this cohort.
Methods: 245 patients who had a new diagnosis of NCFB between June 2006 and October 2012 at the University Hospital of Leuven, Belgium, were included in the analysis. Death was analyzed until end of November 2013. All patients had chest HRCT scan confirming the presence of bronchiectatic lesions and had symptoms of chronic productive cough. Univariate and multivariate Cox proportional hazard survival regression analysis was used to estimate hazard ratios (HR) and their 95% confidence intervals (CI) of variables possibly predicting mortality.
Results: Overall mortality in NCFB patients who had a median follow-up of 5.18 years was 20.4%. Patients with NCFB and associated chronic obstructive pulmonary disease (COPD) had a mortality of 55% in that period. Univariate analysis showed higher mortality according to age, gender, smoking history, *Pseudomonas aeruginosa* status, spirometry, radiological extent, total number of sputum bacteria and underlying etiology. Multivariate analysis showed significant higher mortality with increasing age (HR = 1.045; *p* = 0.004), with increasing number of lobes affected (HR = 1.53; *p* = 0.009) and when patients had COPD associated NCFB (HR = 2.12; *p* = 0.038). The majority of the 50 deaths were respiratory related (*n* = 29; 58%).

Conclusion: NCFB patients with associated COPD disease had the highest mortality rates compared to the other NCFB patients. Additional risk factors for lower survival were increasing age and number of lobes affected.

Background

Bronchiectasis is defined as permanently dilated airways due to chronic bronchial inflammation caused by inappropriate clearance of various microorganisms and recurrent or chronic infection [1]. With the exception of cystic fibrosis (CF), there is a lack of research into bronchiectasis. Recently, De Soyza et al. proposed several research priorities in non-cystic fibrosis bronchiectasis (NCFB). They state that from an epidemiological point of view, more prospective data are needed on mortality and associated morbidity [2].

Several retrospective analyses have already been performed. In England and Wales, just under 1000 people die from bronchiectasis with the number increasing 3% per year [3]. In a hospital setting, mainly older age (>65 years), male gender, smoking history, mechanical ventilation, socioeconomic status (SES) and lower lung function show higher mortality [4—7]. In a cross-sectional retrospective analysis of patients known with a radiological diagnosis of bronchiectasis (including asymptomatic interstitial lung disease and thoracic tumor patients), we previously showed a 41-month death rate of 10.6% [8]. These data are in line with the long term prospective analysis by Loebinger et al. They found that over a 13-year period, 29.7% of the 91 patients died, and male gender, older age, lung function and *Pseudomonas aeruginosa* (PA) were correlated with higher mortality [9]. Another prospective analysis from Turkey showed an even poorer outcome with 4-year survival of only 58%. They suggest that the presence of hypoxemia, hypercapnia, dyspnea levels and radiographic extent lead to higher mortality [10].

Our primary aim was to analyze the overall mortality for all newly diagnosed patients from June 2006 onwards. We assessed the known risk factors such as age, gender, smoking history, number of lobes affected, type of bronchiectasis and PA and evaluated the impact on mortality of etiology, number of different bacteriological species in retrospective and prospective sputa, azithromycin and other long-term antibiotic use and presence/development of pulmonary hypertension (PH).

Materials and methods

Patient selection

Patients who had a new diagnosis of bronchiectasis between June 2006 and October 2012 at the University Hospital of Leuven, Belgium, were included in the analysis. Death was analyzed until end of November 2013. Patients with clinically significant and radiologically proven bronchiectasis were included in the analysis.

Bronchiectasis diagnosis

All patients had a chest high resolution computed tomography (HRCT) scan confirming the presence of bronchiectatic lesions and had symptoms of chronic productive cough. HRCT scans were evaluated by two experienced independent radiologists. Images obtained using 1 mm collimation at full inspiration were reviewed and bronchiectasis was deemed to be present if there was one or more of the following criteria: a bronchoarterial ratio greater than 1, lack of tapering of the bronchi and visualization of bronchi within 1 cm of costal or paravertebral pleura or abutting the mediastinal pleura [11]. Exclusion criteria were patients with a diagnosis of CF (CF transmembrane regulator sequences present on genotyping), an underlying tumoral problem causing the bronchiectatic lesions (post-radiation, secondary immunodeficiency due to chemotherapy or postinfectious due to tumoral obstruction) and patients with traction bronchiectasis caused by interstitial lung disease or sarcoidosis. Each patient with a diagnosis of NCFB was further evaluated for an underlying cause with serum protein electrophoresis, immunoglobulines (IgA, IgE, IgM, IgG, IgG_{1-3}), specific IgE to *Aspergillus fumigatus*, specific IgG to *A. fumigatus*, nasal NO measurement, sputum microbiology and ororhinolaryngological evaluation. Spirometry and plethysmography were performed to evaluate impact on lung function. Additional investigations were guided by clinical indication. Postinfectious NCFB was defined as NCFB where there is a clear medical history of a respiratory infection with a distinct isolated pathogen that meant the start of the chronic respiratory complaints or (when no such pathogen could be isolated), a history of recurrent childhood respiratory infections that meant the start of the chronic respiratory complaints. If patients with a primary diagnosis of idiopathic NCFB also had concomitant COPD, they were categorized in the COPD associated NCFB group. COPD was defined using the definition suggested by the Global Initiative for Chronic Obstructive Lung Disease (GOLD). More precisely, patients needed to have symptoms of shortness of breath, chronic cough or sputum production, and a history of exposure to smoke. Patients also needed persistent airflow limitation defined as the presence of a post-bronchodilator FEV_1/FVC ratio lower than 0.7 (www.goldcopd.org). The initial diagnosis of COPD was made by the general practitioner, the referring respiratory physician or by the outpatient clinic of COPD at the University Hospital of Leuven.

Data collection

The following patient data were collected at inclusion: age, gender, smoking habits (four categories: active, former, passive or never smoker), PA infection status according to the criteria defined by Lee et al. [12], total number of

different bacterial species in retrospective and prospective sputa, presence of PH (defined as a systolic pulmonary arterial pressure of ≥ 36 mmHg on echocardiography assuming normal right atrial pressure of 5 mmHg) [13], exacerbation rate (defined as the use of antibiotic treatment due to two or more of the following symptoms: increase in sputum volume, increase of sputum purulence, dyspnea, cough, hemoptysis or fever more than 38 °C), azithromycin use (a minimum dose of 250 mg three times a week during at least 3 consecutive months), other long-term antibiotic use (antibiotic treatment longer than 3 months), SES (based on education level and/or occupation of the head of household and divided by low, middle or high status), spirometry (according to the ATS/ERS guidelines [14,15]), number of lobes affected and type of bronchiectasis (based on the worst type present on HRCT: cylindrical, varicous or cystic). For all patients, sputum culture results, therapy use and death were assessed each six months. If death occurred, the patient file was reassessed to identify cause of death mentioned in the patient file.

Ethical committee

Approval was obtained from the local ethical committee of UZ Leuven, Belgium (B51060 − B32220084152) and was registered at ClinicalTrial.gov (NCT01792427).

Statistics

Data were expressed as mean with standard deviation (SD) or median with 25%−75% interquartile range (IQR) based on the distribution of the data. For percent survival and presentation of the figures on total mortality and etiology mortality subanalysis, a Kaplan−Meier analysis was performed with a log-rank test to compared different etiology subgroups and the curves presented using GraphPad Prism 5. For the univariate mortality analysis, Cox proportional hazard regression analysis was used to estimate hazard ratios (HR) and their 95% confidence intervals (CI) of several parameters possibly predicting NCFB mortality. For multivariate analysis of factors associated with mortality, a multivariate Cox regression analysis was performed. Variables that were significant in the univariate model were included in the multivariate analysis. Analysis was performed using SAS 9.3 and GraphPad Prism 5. P-values were considered to be significant if lower than 0.05 and two-tailed testing was performed.

Results

Patient characteristics

In total 245 patients with a median follow-up of 5.18 years (IQR 4.17−6.38) were included. Patient characteristics are shown in Table 1.

Univariate mortality analysis

Overall mortality in NCFB patients who had a median follow-up of 5.18 years was 20.4% (50 deaths, 195 survivors; Fig. 1).

Etiology subanalysis showed significant differences between the different causes (Fig. 2). Patients with bronchiectasis who had associated chronic obstructive pulmonary disease (COPD) had the worst outcome of all NCFB patients. During the median follow-up of 5.18 years, 55% of the COPD associated NCFB died. Over the median 5.18-year follow-up, 14% of the patients with idiopathic NCFB and 16% of the post-infectious NCFB died. In the miscellaneous group 12% died over the follow-up period. This group includes anatomic malformations, immunodeficiencies, rheumatic disease, primary ciliary dyskinesia (PCD), allergic bronchopulmonary aspergillosis (ABPA), α_1-antitrypsin deficiency, vasculitis and inflammatory bowel disease. For the larger subgroups in the miscellaneous group (rheumatic disease, ABPA and immunodeficiency), we found that 20% of the patients with rheumatic disease, 11% of the patients with an underlying immunodeficiency and 13% of the ABPA NCFB patients died over the median follow-up period of 5.18 years.

Subanalysis showed significantly different mortality curves in patients with different age, gender, smoking habits, chronic PA colonization (PACC) status (using the criteria defined by Lee et al.) [12], increased total number of different bacterial species in all collected sputa, spirometric values, radiological severity and extent of disease (Table 2). A trend was seen for SES, PH and long-term antibiotic use but no significance for exacerbation rate (Table 2). When we accounted for the duration of azithromycin use, results remained not significant ($p = 0.97$).

Multivariate analysis

Multivariate Cox regression analysis could identify three significant factors associated with higher mortality (Table 3). Age was associated with a higher mortality (HR = 1.045; 95% CI 1.01−1.08; $p = 0.004$) with a parameter estimate of 0.044. Increasing number of lobes affected were also significantly associated with mortality (HR = 1.53; 95% CI 1.11−2.09; $p = 0.009$) with a parameter estimate of 0.42. A third significant factor for higher mortality in the multivariate analysis was the presence of COPD associated NCFB (HR = 2.12; 95% CI 1.04-4.30; $p = 0.038$) as compared to other etiologies, even when omitting spirometric values from the analysis (as they might interact with COPD) (HR = 2.20; 95% CI 1.15−4.21; $p = 0.017$). Finally, a trend was seen when never smokers were compared to active smokers (HR = 2.55; 95% CI 0.96−6.79; $p = 0.06$).

Causes of death

The majority of deaths were respiratory related (58%; $n = 29$; respiratory failure, most frequently due to respiratory infection) or cardiovascular (16%; $n = 8$; acute myocardial infarction, rupturing aneurysm, arrhythmia, cardiac failure). For some patients (12%; $n = 6$) no clear cause of death was noted in the clinical records. Other causes were neurological (4%; $n = 2$; craniocerebral trauma and stroke), gastrointestinal (2%; $n = 1$; pancreatic tumor), nephrological (2%; $n = 1$; acute kidney failure), haematological (2%; $n = 1$; leukemia), euthanasia (2%; $n = 1$) and intoxication (2%; $n = 1$; alcohol).

Table 1 Patient characteristics: For socio-economic status ($n = 189$) and PH ($n = 117$) we did not have data from all patients. Data are expressed as median with IQR or mean with standard deviation. All antibiotic treatment was given for at least 3 months. Colistimethate was inhaled. The bacteria isolated in sputa mentioned in the table are the most relevant bacteria with a prevalence of more than 5%. The postinfectious causes were tuberculosis ($n = 23$), childhood recurrent infections without a clear pathogen ($n = 18$), *Mycobacterium avium* complex ($n = 3$), invasive aspergillosis ($n = 2$), HIV ($n = 1$), childhood measles pneumonia ($n = 1$) and severe childhood diphtheria ($n = 1$). The 'miscellanous' group includes α_1-antitrypsin deficiency ($n = 2$), vasculitis ($n = 3$), inflammatory bowel disease ($n = 5$), anatomic malformations ($n = 3$), PCD ($n = 8$), rheumatic disease ($n = 25$), immunodeficient ($n = 18$) and ABPA ($n = 15$). ABPA = Allergic Broncho-Pulmonary Aspergillosis; COPD = chronic obstructive pulmonary disease; F = Female; FEV_1 = Forced Expiratory Volume in one second; FVC = Forced Vital Capacity; IQR = Interquartile range; M = Male; NCFB = Non-cystic fibrosis bronchiectasis; PCD = Primary Ciliary Diskinesia; PH = Pulmonary Hypertension; TMP/SMX = trimethoprim/sulfamethoxazole. *Pseudomonas aeruginosa* status was categorized according to the criteria by Lee *et al*. [12].

Gender M/F	49%/51%
Median age (years)	68 (IQR 56—78)
Total $n°$ of different bacterial species in retrospective sputa	1 (IQR 0—2)
Number of exacerbations	1 (IQR 0—3)/year
Smoking history	Never smokers 48.9%
	Former smokers 30.3%
	Passive smokers 3.2%
	Active smokers 17.6%
Socio-economic status ($n = 189$)	Low 52.9%
	Middle 42.3%
	High 4.8%
PH in echocardiography ($n = 117$)	45.3%
Etiology	Idiopathic 32%
	Postinfectious 20%
	Miscellanous 31%
	COPD associated NCFB 17%
Pseudomonas aeruginosa status	Never 78.8%
	Free 9.4%
	Intermittent 3.6%
	Chronic 8.2%
$n°$ of lobes affected	One lobe 17.1%
	Two lobes 25.3%
	Three lobes 24.9%
	Four lobes 16.8%
	Five lobes 15.9%
Type of bronchiectatic lesion	Cilyndrical 62%
	Varicous 30%
	Cystic 8%
FEV_1%	70% ± 27%
FVC%	87% ± 25%
Bacteria isolated in sputa	
- *Haemophilus influenzae*	18.8%
- *Streptococcus pneumonia*	14.6%
- *Staphylococcus aureus*	13.5%
- *Aspergillus spp.*	11.4%
- *Moraxella catarrhalis*	7.8%
- *Stenotrophomonas maltophilia*	6.9%
Long-term antibiotic use	
- Azithromycin use	38%
- Other	clarithromycin ($n = 10$), itraconazole ($n = 7$), voriconazole ($n = 2$), colistimethate ($n = 6$), rifampicin ($n = 5$), pyrazinamide ($n = 2$),

Table 1 (*continued*)

	ethambutol ($n = 7$), TMP/SMX ($n = 5$), amoxicillin clavulanate ($n = 1$), moxifloxacin ($n = 4$), isoniazid ($n = 5$)

Discussion

Our results show that during the analyzed period, 20.4% of the patients died, with more deaths amongst NCFB patients with associated COPD. The majority of deaths were due to respiratory failure. Univariate analysis showed higher mortality according to age, gender, smoking history, PA status, spirometry, radiological extent/severity, total number of sputum bacteria and underlying etiology. Multivariate analysis resulted in the following risk factors associated with higher mortality: age, number of lobes affected and COPD associated NCFB.

Our analysis with a median follow-up of 5.18 years showed a mortality of 20.4%. These percentages are in line with our previous cross-sectional retrospective analysis and slightly higher than results from the prospective analysis by Loebinger et al. where the 4-year mortality was 9% and the 8.8-year mortality 16.5% [9]. However, the population studied by Loebinger *and colleagues* shows a low prevalence of COPD as 77% were never-smokers and less than 4% had emphysema on HRCT [9]. When we analyze the survival curves of the idiopathic, post-infectious and other etiologies, we can perceive that these are in line with the data of Loebinger et al. Mortality of our NCFB patients (even the best performing etiological subgroups) is still higher than the general population in Belgium, where a mortality of 9.66‰ and 9.51‰ was seen

in 2006 and 2007 respectively [16]. We speculate that the vicious cycle of inflammation, infection and structural damage with inappropriate mucus clearance increases the chances that an infection can lead up to severe respiratory insufficiency as compared to the general population, causing excess mortality.

The higher mortality in older, male and smoking patients was previously acknowledged by several authors [4–7,9]. One possible explanation is the fact that the COPD patients were predominantly male. We also found that active and ex-smokers were predominantly male whereas never smokers were predominantly female. After multivariate correction, age was still significant a factor associated with higher mortality. Apart from the logic increase in mortality with increasing age, another contributing factor might be the overall lower compliance in older patients [17,18]. Whether closer follow-up or better patient education might improve compliance and therefore decrease mortality requires further research.

Loebinger et al. could not assess differences in mortality rates among the different etiologies as the numbers in the several subgroups were too small [9]. Our larger group allowed subanalysis, showing higher mortality rates for patients with associated COPD, even after multivariate analysis. Whether COPD associated bronchiectasis is a distinct COPD phenotype, cannot be concluded from our study as we did not compare COPD patients without bronchiectasis. However, our data add to previous research suggesting that COPD with bronchiectasis is different from
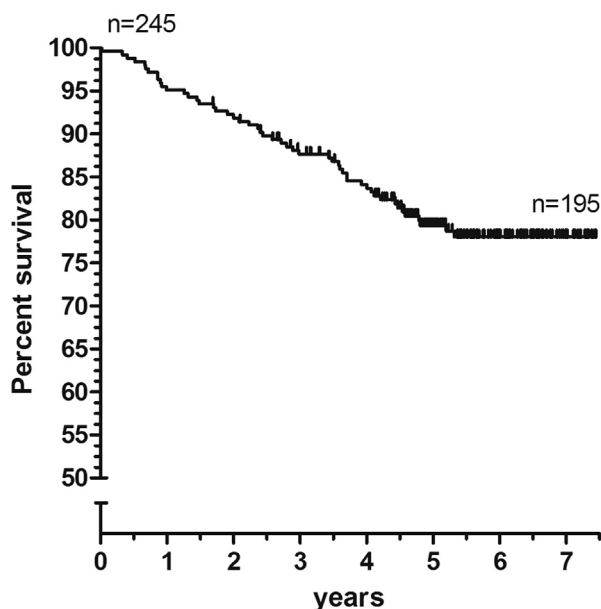

Figure 1 Kaplan–Meier survival curve of the NCFB cohort over the study period: a mortality of 20.4% was seen over a median follow-up time of 5.18 years.
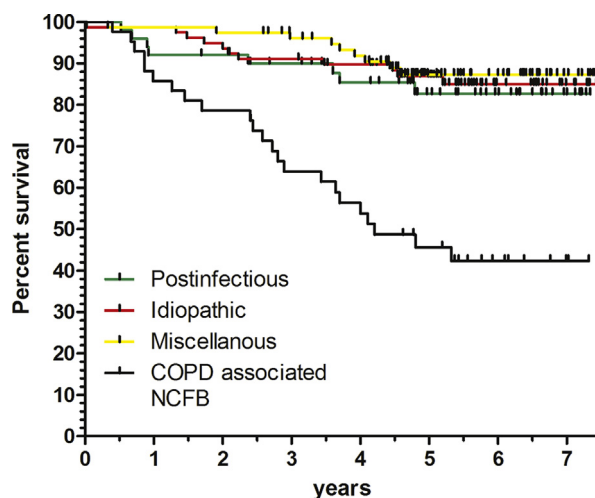

Figure 2 Kaplan–Meier log-rank test survival curve per NCFB etiology over the study period: There was a median follow-up time of 5.18 years and the study period started in June 2006 and ended in November 2013. COPD = Chronic Obstructive Pulmonary Disease; NCFB = Non-cystic fibrosis bronchiectasis.

Table 2 Univariate analysis of factors associated with survival: For socio-economic status ($n = 189$) and PH ($n = 117$) we did not have data from all patients. For non-continuous data, we displayed the classes how they were analyzed. Therefore the hazard ratio reflects the increase for each class increase. M/H = Middle/High; $n°$ = number; V/C = Varicous/Cystic; vs = versus.

	Hazard ratio	95% Confidence interval	Number of patients dead versus alive		p-Value
Age (years)	1.06	1.04–1.09	NA		$p < 0.0001$
Gender	4.16	2.13–8.13	Female	11/124	$p < 0.0001$
Female vs Male			Male	39/121	
Smoking	1.61	1.27–2.05	Non	12/120	$p < 0.0001$
Never vs Passive vs Ex vs Active			Passive	2/8	
			Ex	21/74	
			Active	15/43	
Socio-economic status	0.59	0.30–1.14	Low	24/100	$p = 0.11$
Low vs Middle/High			M/H	14/89	
			Unknown	12/56	
Pulmonary hypertension	1.59	0.87–2.90	Absent	19/64	$p = 0.13$
Absence vs presence			Present	24/53	
			Unknown	7/128	
***Pseudomonas aeruginosa* status**	1.60	1.27–2.00	Never	29/193	$p < 0.0001$
Never vs free vs intermittent			Free	8/23	
vs chronic			Intermittent	3/9	
			Chronic	10/20	
FEV$_1$ (%)	0.97	0.96–0.99	NA		$p < 0.0001$
FVC (%)	0.98	0.97–0.99	NA		$p = 0.001$
$n°$ of exacerbations/year	1.01	0.88–1.15	NA		$p = 0.94$
$n°$ of different bacteria in sputum	1.38	1.23–1.54	NA		$p < 0.0001$
Type	2.55	1.46–4.48	Cylindrical	21/153	$p = 0.001$
Cylindrical vs varicous/cystic			V/C	29/92	
$n°$ of lobes affected	1.95	1.54–2.48	One	0/42	$p < 0.0001$
			Two	6/62	
			Three	12/61	
			Four	13/41	
			Five	19/39	
Long-term azithromycin use	0.61	0.33–1.13	Yes	14/152	$p = 0.11$
			No	36/93	
Long-term antibiotic treatment	0.54	0.29–1.00	Yes	14/146	$p = 0.0513$
			No	36/99	

bronchiectasis in other circumstances [19–21]. The higher mortality might be attributed to the fact that these patients have more severe and more frequent exacerbations, higher degree of airway inflammation, lower lung function and increased colonization [19,22,23]. It is also possible that the diagnosis of bronchiectasis is delayed in NCFB patients with COPD as the COPD itself can explain the majority of their symptoms. Many less severe COPD patients will be managed in the community but still may have bronchiectasis and COPD [22]. Recent work by Martinez-Garcia *and colleagues* evaluated the impact of bronchiectasis on COPD, approaching this problem from a COPD population perspective. They clearly show that bronchiectasis was associated with an independent risk of all-cause mortality in patients with COPD. In their analysis, COPD alone had a mortality of 9.3% whereas our NCFB patients without concomitant COPD had a mortality of 13.3%. More importantly, the combination of COPD and NCFB had similar high mortality rates as our data with a death rate of 37.8% in their study and 55% in our analysis.

This suggests that it is not the NCFB or the COPD alone that causes excess mortality, but the combination of both [24]. These high mortality rates and the diagnostic delay often seen in NCFB with concomitant COPD imply that COPD patients with symptoms suggestive of bronchiectasis, such as frequent infectious exacerbations or chronic mucopurulent/purulent expectorations, need further investigation via HRCT.

Multivariate analysis also underlined that the extent of the disease is a risk factor for higher mortality. Extent of the bronchiectasis was a very significant factor in the paper by Loebinger *and colleagues* but they did not assess HRCT scored in a multivariate way [9].

NCFB patients with an underlying rheumatological disease also had a high mortality of 20% as opposed to most other NCFB etiologies, with the exception of COPD associated NCFB. Swinson et al. previously found that the presence of bronchiectasis in rheumatological disease may be clinically relevant. Patients with rheumatological disease and bronchiectasis were 7.3 times more likely to die during

Table 3 Multivariate Cox regression analysis of factors associated with survival: Significant factors associated with higher mortality in the multivariate analysis are age, number of lobes affected and COPD associated non-cystic fibrosis bronchiectasis. A trend towards significance was seen for active smokers. To account for the interaction between spirometry and COPD we performed both multivariate analyses with and without spirometric data. COPD = Chronic Obstructive Pulmonary Disease; FEV_1 = Forced Expiratory Volume in one second; FVC = Forced Vital Capacity; vs = versus; NCFB = Non-Cystic-Fibrosis Bronchiectasis; $n°$ = Number.

Multivariate cox regression variable	Hazard ratio for death	95% Confidence interval	p-Value
Age (years)	1.045	1.01–1.08	$p = 0.004$
Gender	1.75	0.70–4.35	$p = 0.23$
Male vs female			
Smoking	1.04	0.40–2.68	$p = 0.94$
Ex vs never	3.25	0.63–16.87	$p = 0.16$
Passive vs never	2.55	0.96–6.79	$p = 0.06$
Active vs never			
***Pseudomonas aeruginosa* status**	1.35	0.61–2.97	$p = 0.46$
Chronic colonization vs non-chronic			
Total different bacterial species in all sputa	1.10	0.96–1.25	$p = 0.18$
Type	1.44	0.69–2.98	$p = 0.33$
Varicous/cystic vs cylindrical			
$n°$ of lobes affected	1.53	1.11–2.09	$p = 0.009$
FEV_1 (%)	0.99	0.97–1.01	$p = 0.41$
FVC (%)	1.01	0.99–1.03	$p = 0.46$
Etiology	2.12	1.04–-4.30	$p = 0.038$
COPD associated NCFB vs other			
Multivariate cox regression without FEV_1 and FVC	**Hazard ratio for death**	**95% confidence interval**	**p-Value**
Etiology	2.20	1.15–4.21	$p = 0.017$
COPD associated NCFB vs other			

a 5-year follow-up period than the general population, five times more likely to die than those with rheumatological disease alone and 2.4 times more likely to die than those with bronchiectasis alone [25]. One explanation may be the increased risk for respiratory infections associated with immunomodulatory therapy [26,27]. Another explanation might be the lower FEV_1 in coexisting NCFB and rheumatological disease as opposed to other NCFB patients [25]. This is in line with our previous data, suggesting that rheumatological disease severity scores inversely correlate with lung functional parameters [26].

The lack of association between mortality and SES in the univariate analysis is somewhat hampered by the lack of data. We only had sufficient SES data from 196 patients. There is however a trend towards significance comparing low to middle class status. This is in line with bronchiectasis data from New Zealand, showing that socio-economic deprivation had a negative impact on survival [6].

We further found a higher mortality in patients with PACC and in patients with number of different bacteriological species present in sputum in the univariate analysis. We know from literature that PA infection is more prevalent in patients with more severe bronchiectatic disease and causes lower quality of life and worse lung function [27,28]. PACC is linked with accelerated decline in lung function, more severe exacerbations and higher systemic inflammation [29,30]. Although PACC was not significant in our multivariate model (possibly due to an overadjusted model), PA infection and PACC are important in NCFB. Our univariate analysis showed a parameter estimate of 0.47 for

each increase in *Pseudomonas* colonization class using the criteria of Lee et al. [12] The importance of PACC was recently confirmed by Martínez-García *and colleagues*, using PACC as an element of their bronchiectasis FACED severity score [31]. This was simultaneously confirmed by Chalmers et al. in their Bronchiectasis Severity Index [32]. It is therefore important to stay vigilant for the appearance of PA in sputa using regular sputum cultures and timely eradication. It is not clear if first acquisition of PA in NCFB is different from CF, but recent research by De Soyza *and colleagues* suggests that (in contrast to CF) cross-infection is rare in NCFB patients [33].

Recently, two scoring systems were published addressing the severity of bronchiectasis. The FACED score is an easy tool that scores 7 points using 5 dichotomized variables to predict mortality and includes FEV_1, age, PACC, number of lobes affected and shortness of breath [31]. The Bronchiectasis Severity Index predicts both the chance of future hospitalization and mortality and has been validated in other centers around Europe. For mortality they found that older age, lower FEV_1, prior hospitalization and three or more exacerbations were of significant importance [32]. Both models show that the majority of the factors we found in our univariate analysis play a role in predicting mortality and they are excellent tools to use in daily clinical practice. However, both studies did not investigate the importance of the underlying etiology or associated conditions into their model. We add that associated COPD might play a pivotal role in predicting mortality, but further research with larger populations is needed.

Although PH is a known risk factor for mortality and the percentages of deaths were higher in the patients with PH (42%) versus without PH (28%), there was no significant difference in terms of mortality [34]. This might be hampered by the lack of echocardiographic data in 130 patients. Not only has research shown a high prevalence of PH in COPD patients [35,36], but PH is also known to be of importance in NCFB as right ventricular dysfunction and right ventricular dimensions are greater in cystic NCFB and are positively correlated with systolic pulmonary artery pressure and negatively correlated with partial pressure of oxygen in arterial blood. In more severe NCFB, there is an impaired perfusion with more capillary bed destruction and left-to-right shunt, leading to impaired cardiac function and pulmonary gas exchange [37].

There was no significant difference in mortality whether NCFB patients were taking azithromycin or not. To our knowledge, the effect of azithromycin on mortality has not been assessed previously. An improvement of exacerbation rate, HRCT score and lung function were observed in retrospective studies [38,39], which was recently confirmed by several double-blind, placebo-controlled trials [40,41]. The low number of patients, duration of therapy and lack of a control population in our study limits this subanalysis. More research is needed to establish the effect of azithromycin on mortality in NCFB.

Although women are usually predominant in NCFB series, we saw an equal distribution between men and women. This equal distribution is caused by the predominantly male COPD group, whereas the idiopathic and postinfectious bronchiectasis were predominantly female.

One limitation of our study might be the overadjusted multivariate model as we included all univariate significant results in the multivariate model, adding ten variables to the model having only 50 events. To analyze stability of the significant and non-significant variables, we have omitted certain variables in a second analysis (data not shown). The omission of spirometric values (as they might have an interaction with COPD) and number of bacteria in sputum, showed no change in significance of the variables in the multivariate Cox regression model and little change in HR of the variables. Nonetheless, overadjustment is possible and might underestimate the number of multivariate significant variables.

Another limitation is the absence of a severe respiratory condition in a large percentage of our population, given the rather low number of exacerbations and an overall good lung function. This might account for the absence of multivariate significance of PACC, number of exacerbations and FEV_1 in the mortality analysis, whereas other groups have found these factors to be of significant importance [31,32]. Another reason for the absence of PACC in the multivariate analysis is the significant association we found between number of lobes and PA status (data not shown).

A third limitation might be the fact that some of the patients needed long-term antibiotic treatment for several reasons (treatment for ABPA, *Aspergillus* or (non)-tuberculous *Mycobacteria*). Univariate analysis showed that adding these patients to the patients receiving chronic azithromycin therapy, showed a near-significant trend towards a lower mortality. We did not exclude these patients in our cohort as these patients were in a clinically stable state and exclusion of these patients might give a selected view of the overall NCFB population. These results suggest that adequate antibiotic treatment based on underlying infectious cause or adequate use of long-term macrolide treatment may have an impact on mortality, but more prospective research is needed to confirm these findings.

In conclusion, our 5.18-year mortality analysis showed a mortality rate of 20.4%. Variables associated with an increased probability of mortality in patients with NCFB were age, gender, smoking habits, PACC status, increased total number of different bacterial species in all collected sputa, spirometric values, radiological severity, extent of disease and COPD associated NCFB. Multivariate risk factors associated with lower survival are increasing age, number of lobes affected and COPD associated NCFB.

Conflict of interest

All authors have read and approved the contents of the manuscript and they all contributed importantly to the preparation of the final manuscript. The manuscript, including related data, figures and tables has not been previously published and is not under consideration elsewhere. Finally, none of the authors has a financial relationship with a commercial entity that has an interest in the subject of the presented manuscript.

Funding

Financial disclosure

None of the authors has a financial relationship with a commercial entity that has interest in the subject of the presented manuscript.

Consent

Each patient gave his or her written consent for the collection and use of their clinical data.

Acknowledgment

References

[1] Goeminne P, Dupont L. Non-cystic fibrosis bronchiectasis: diagnosis and management in 21st century. Postgrad Med J 2010;86:493—501.

[2] De Soyza A, Brown JS, Loebinger MR. Research priorities in bronchiectasis. Thorax 2013;68:695—6.

[3] Roberts HJ, Hubbard R. Trends in bronchiectasis mortality in England and Wales. Respir Med 2010;104:981—5.

[4] Dupont M, Gacouin A, Lena H, et al. Survival of patients with bronchiectasis after the first ICU stay for respiratory failure. Chest 2004;125:1815—20.

[5] Finklea JD, Khan G, Thomas S, Song J, Myers D, Arroliga AC. Predictors of mortality in hospitalized patients with acute exacerbation of bronchiectasis. Respir Med 2010;104:816—21.

[6] Roberts ME, Lowndes L, Milne DG, Wong CA. Socioeconomic deprivation, readmissions, mortality and acute exacerbations of bronchiectasis. Intern Med J 2012;42:e129—36.

[7] Keistinen T, Saynajakangas O, Tuuponen T, Kivela SL. Bronchiectasis: an orphan disease with a poorly-understood prognosis. Eur Respir J 1997;10:2784—7.

[8] Goeminne PC, Scheers H, Decraene A, Seys S, Dupont LJ. Risk factors for morbidity and death in non-cystic fibrosis bronchiectasis: a retrospective cross-sectional analysis of CT diagnosed bronchiectatic patients. Respir Res 2012;13:21.

[9] Loebinger MR, Wells AU, Hansell DM, et al. Mortality in bronchiectasis: a long-term study assessing the factors influencing survival. Eur Respir J 2009;34:843—9.

[10] Onen ZP, Gulbay BE, Sen E, et al. Analysis of the factors related to mortality in patients with bronchiectasis. Respir Med 2007;101:1390—7.

[11] Brody AS, Klein JS, Molina PL, Quan J, Bean JA, Wilmott RW. High-resolution computed tomography in young patients with cystic fibrosis: distribution of abnormalities and correlation with pulmonary function tests. J Pediatr 2004;145:32—8.

[12] Lee TW, Brownlee KG, Conway SP, Denton M, Littlewood JM. Evaluation of a new definition for chronic Pseudomonas aeruginosa infection in cystic fibrosis patients. J Cyst Fibros 2003; 2:29—34.

[13] Galie N, Hoeper MM, Humbert M, et al., ESC Committee for Practice Guidelines (CPG). Guidelines for the diagnosis and treatment of pulmonary hypertension: the task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). Eur Heart J 2009;30:2493—537.

[14] Miller MR, Crapo R, Hankinson J, et al. General considerations for lung function testing. Eur Respir J 2005;26:153—61.

[15] Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. Eur Respir J 2005;26:319—38.

[16] Federale Overheidsdienst Economie (FOD), Algmene Directie Statistiek en Economische Informatie (ADSEI) http://statbel.fgov.be/nl/statistieken/cijfers/bevolking/sterfte_leven/sterfte/.

[17] Barat I, Andreasen F, Damsgaard EM. Drug therapy in the elderly: what doctors believe and patients actually do. Br J Clin Pharmacol 2001;51:615—22.

[18] Wong MC, Lau RK, Jiang JY, Griffiths SM. Discontinuation of angiotensin-converting enzyme inhibitors: a cohort study. J Clin Pharm Ther 2012;37:335—41.

[19] Martinez-Garcia MA, Soler-Cataluna JJ, Donat SY, et al. Factors associated with bronchiectasis in patients with COPD. Chest 2011;140:1130—7.

[20] Novosad SA, Barker AF. Chronic obstructive pulmonary disease and bronchiectasis. Curr Opin Pulm Med 2013;19:133—9.

[21] O'Donnell AE. Bronchiectasis in patients with COPD: a distinct COPD phenotype? Chest 2011;140:1107—8.

[22] O'Brien C, Guest PJ, Hill SL, Stockley RA. Physiological and radiological characterisation of patients diagnosed with chronic obstructive pulmonary disease in primary care. Thorax 2000;55:635—42.

[23] Patel IS, Vlahos I, Wilkinson TM, et al. Bronchiectasis, exacerbation indices, and inflammation in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2004;170:400—7.

[24] Martinez-Garcia MA, de la Rosa Carrillo D, Soler-Cataluna JJ, et al. Prognostic value of bronchiectasis in patients with moderate-to-severe chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2013;187:823—31.

[25] Swinson DR, Symmons D, Suresh U, Jones M, Booth J. Decreased survival in patients with co-existent rheumatoid arthritis and bronchiectasis. Br J Rheumatol 1997;36:689—91.

[26] Goeminne PC, Verschueren P, Scheers H, Dupont LJ. Safety of immunomodulatory therapy in patients with bronchiectasis associated with rheumatic disease and IBD: a retrospective and cohort analysis. Clin Rheumatol 2012;31:367—73.

[27] Davies G, Wells AU, Doffman S, Watanabe S, Wilson R. The effect of Pseudomonas aeruginosa on pulmonary function in patients with bronchiectasis. Eur Respir J 2006;28:974—9.

[28] Wilson CB, Jones PW, O'Leary CJ, Hansell DM, Cole PJ, Wilson R. Effect of sputum bacteriology on the quality of life of patients with bronchiectasis. Eur Respir J 1997;10:1754—60.

[29] Martinez-Garcia MA, Soler-Cataluna JJ, Perpina-Tordera M, Roman-Sanchez P, Soriano J. Factors associated with lung function decline in adult patients with stable non-cystic fibrosis bronchiectasis. Chest 2007;132:1565—72.

[30] Goeminne PC, Vandooren J, Moelants EA, et al. The sputum colour chart as a predictor of lung inflammation, proteolysis and damage in non-cystic fibrosis bronchiectasis: a case-control analysis. Respirology 2013. http://dx.doi.org/10.1111/resp.12219 [Epub ahead of print].

[31] Martínez-García MA, de Gracia J, Vendrell Relat M, et al. Multidimensional approach to non-cystic fibrosis bronchiectasis. The FACED score. Eur Respir J. http://dx.doi.org/10.1183/09031936.00026313 [Epub ahead of print].

[32] Chalmers JD, Goeminne P, Aliberti S, et al. The bronchiectasis severity Index: an international derivation and validation study. Am J Respir Crit Care Med 2013. http://dx.doi.org/10.1164/rccm.201309-1575OC [Epub ahead of print].

[33] De Soyza A, Perry A, Hall AJ, et al. Molecular epidemiological analysis suggests cross infection with Pseudomonas aeruginosa is rare in non-cystic fibrosis bronchiectasis. Eur Respir J 2013. http://dx.doi.org/10.1183/09031936.00167813 [Epub ahead of print].

[34] Devaraj A, Wells AU, Meister MG, Loebinger MR, Wilson R, Hansell DM. Pulmonary hypertension in patients with bronchiectasis: prognostic significance of CT signs. AJR Am J Roentgenol 2011;196:1300—4.

[35] Minai OA, Fessler H, Stoller JK, et al. Clinical characteristics and prediction of pulmonary hypertension in severe emphysema. Respir Med 2013. http://dx.doi.org/10.1016/j.rmed.2013.11.006 [Epub ahead of print].

[36] Minai OA, Chaouat A, Adnot S. Pulmonary hypertension in COPD: epidemiology, significance, and management. Chest 2010;137:39S—51S.

[37] Alzeer AH, Al-Mobeirek AF, Al-Otair HA, Elzamzamy UA, Joherjy IA, Shaffi AS. Right and left ventricular function and pulmonary artery pressure in patients with bronchiectasis. Chest 2008;133:468—73.

[38] Anwar GA, Bourke SC, Afolabi G, Middleton P, Ward C, Rutherford RM. Effects of long-term low-dose azithromycin in patients with non-CF bronchiectasis. Respir Med 2008;102:1494—6.

[39] Goeminne PC, Soens J, Scheers H, De Wever W, Dupont LJ. Effect of macrolide on lung function and computed tomography (CT) score in non-cystic fibrosis bronchiectasis. Acta Clin Belg 2012;67:338—46.

[40] Wong C, Jayaram L, Karalus N, et al. Azithromycin for pre-
vention of exacerbations in non-cystic fibrosis bronchiectasis
(EMBRACE): a randomised, double-blind, placebo-controlled
trial. Lancet 2012;380:660−7.

[41] Altenburg J, de Graaff CS, Stienstra Y, et al. Effect of azi-
thromycin maintenance treatment on infectious exacerba-
tions among patients with non-cystic fibrosis bronchiectasis:
the BAT randomized controlled trial. JAMA 2013;309:1251−9.