ORIGINAL ARTICLE

The Bronchiectasis Severity Index

An International Derivation and Validation Study

James D. Chalmers[1], Pieter Goeminne[2], Stefano Aliberti[3], Melissa J. McDonnell[4,5], Sara Lonni[3], John Davidson[4], Lucy Poppelwell[1], Waleed Salih[1], Alberto Pesci[3], Lieven J. Dupont[2], Thomas C. Fardon[1], Anthony De Soyza[4,5], and Adam T. Hill[6]

[1]Tayside Respiratory Research Group, University of Dundee, Dundee, United Kingdom; [2]Respiratory Medicine, University Hospital Gasthuisberg, Leuven, Belgium; [3]Department of Health Science, University of Milan Bicocca, Clinica Pneumologica, AO San Gerardo, Monza, Italy; [4]Adult Bronchiectasis Service and Sir William Leech Centre for Lung Research, Freeman Hospital, Newcastle upon Tyne Hospitals, Heaton, Newcastle, United Kingdom; [5]Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, United Kingdom; and [6]Department of Respiratory Medicine Royal Infirmary of Edinburgh and the University of Edinburgh, Edinburgh, United Kingdom

Abstract

Rationale: There are no risk stratification tools for morbidity and mortality in bronchiectasis. Identifying patients at risk of exacerbations, hospital admissions, and mortality is vital for future research.

Objectives: This study describes the derivation and validation of the Bronchiectasis Severity Index (BSI).

Methods: Derivation of the BSI used data from a prospective cohort study (Edinburgh, UK, 2008–2012) enrolling 608 patients. Cox proportional hazard regression was used to identify independent predictors of mortality and hospitalization over 4-year follow-up. The score was validated in independent cohorts from Dundee, UK (n = 218); Leuven, Belgium (n = 253); Monza, Italy (n = 105); and Newcastle, UK (n = 126).

Measurements and Main Results: Independent predictors of future hospitalization were prior hospital admissions, Medical Research Council dyspnea score greater than or equal to 4, $FEV_1 <$ 30% predicted, *Pseudomonas aeruginosa* colonization, colonization with other pathogenic organisms, and three or more lobes involved on high-resolution computed tomography. Independent predictors of mortality were older age, low FEV_1, lower body mass index, prior hospitalization, and three or more exacerbations in the year before the study. The derived BSI predicted mortality and hospitalization: area under the receiver operator characteristic curve (AUC) 0.80 (95% confidence interval, 0.74–0.86) for mortality and AUC 0.88 (95% confidence interval, 0.84–0.91) for hospitalization, respectively. There was a clear difference in exacerbation frequency and quality of life using the St. George's Respiratory Questionnaire between patients classified as low, intermediate, and high risk by the score ($P < 0.0001$ for all comparisons). In the validation cohorts, the AUC for mortality ranged from 0.81 to 0.84 and for hospitalization from 0.80 to 0.88.

Conclusions: The BSI is a useful clinical predictive tool that identifies patients at risk of future mortality, hospitalization, and exacerbations across healthcare systems.

Keywords: bronchiectasis; mortality; *Pseudomonas aeruginosa*; exacerbation; prediction

At a Glance Commentary

Scientific Knowledge on the Subject: There are no recognized clinical severity criteria for non–cystic fibrosis bronchiectasis.

What This Study Adds to the Field: This study derives and validates a multidimensional clinical prediction tool, the Bronchiectasis Severity Index (BSI), from a large international multicenter study of 1,310 patients with bronchiectasis. The BSI is a useful clinical predictive tool that identifies patients at risk of future mortality, hospital admissions, and exacerbations across healthcare systems.

(Received in original form September 2, 2013; accepted in final form December 10, 2013)

Supported by the Medical Research Council, UK; fellowship support from the Medical Research Council and the Wellcome Trust (J.D.C.); fellowship support from the European Respiratory Society/European Lung Foundation (M.J.M.); and a Higher Education Funding Council for England senior lectureship and support from the National Institute for Health Research Biomedical Research Centre (A.D.S.). L.J.D. is a senior research fellow of the Fonds Wetenschappelijk Onderzoek.

Author Contributions: All authors participated in study design, data analysis, and interpretation of the data. All authors were involved in writing and revising the article before submission.

Correspondence and requests for reprints should be addressed to James D. Chalmers, M.B. Ch.B., Tayside Respiratory Research Group, University of Dundee, Dundee DD1 9SY, UK. E-mail: jchalmers@dundee.ac.uk

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

Am J Respir Crit Care Med Vol 189, Iss 5, pp 576–585, Mar 1, 2014

Originally Published in Press as DOI: 10.1164/rccm.201309-1575OC on December 12, 2013
Internet address: www.atsjournals.org

Non–cystic fibrosis (CF) bronchiectasis (hereafter referred to as bronchiectasis) is a chronic respiratory disorder characterized by recurrent cough, sputum production, and respiratory infections (1). Pathologically, patients have abnormally dilated bronchi leading to impairment of host defense, chronic colonization with bacteria, and airways inflammation (2, 3).

Although patients are sometimes described as having mild, moderate, or severe bronchiectasis, there is no accepted definition of these terms. They are often applied in reference to the radiological appearance of disease. Radiological appearance is likely to be insufficient to capture the complexity of disease impact in bronchiectasis (4).

Clinical decision making relies on accurately identifying patients at high risk of future mortality, hospital admissions, and exacerbations. Such a model has been successful for guideline development in chronic obstructive pulmonary disease (COPD), in which different treatment strategies are recommended for different Global Initiative for Chronic Obstructive Lung Disease stages of disease and in other respiratory disorders in which treatments are targeted to patients with a worse prognosis (5–7). There are currently no severity scoring systems for use in bronchiectasis.

There is a need to define which patients are most likely to benefit from new treatments, with an increasing number of clinical trials of inhaled and oral therapies in bronchiectasis (8–11). A severity classification system could theoretically allow targeting of therapies to the patients most likely to benefit.

The aim of this study was develop a severity index for bronchiectasis using four important, well recognized end-points: mortality, frequency of exacerbations, hospital admissions, and health-related quality of life.

Methods

Derivation Cohort

The clinical prediction tool was derived using data from a prospective cohort study conducted at a regional specialist bronchiectasis service based at the Royal Infirmary of Edinburgh, UK (2008–2012). The study was approved by the South East Scotland Research Ethics Committee. Consecutive patients were enrolled on the basis of a diagnosis of bronchiectasis made by high-resolution computed tomography (HRCT) and a clinical history consistent with bronchiectasis (12). The primary objective of the original study was to evaluate predictors of outcome in bronchiectasis, including clinical and genetic predictors. As the goal of this present analysis was to derive a clinical prediction tool using routinely available clinical data, genetic predictors or biomarkers that are not widely available were excluded from the present analysis (13, 14). Patients were excluded if they had active malignancy at enrollment, CF, active mycobacterial disease (including active nontuberculous mycobacteria [NTM]), HIV, or a primary diagnosis of pulmonary fibrosis/sarcoidosis with secondary traction bronchiectasis. Patients receiving long-term oral or inhaled antibiotic therapy at enrollment were also excluded.

Clinical Assessments

At the time of clinical assessment all patients were clinically stable, with no antibiotic use in the preceding 4 weeks. All patients underwent spirometry (FEV_1 and FVC with the highest of three technically satisfactory measurements recorded). The underlying etiology of bronchiectasis was determined after testing recommended by the British Thoracic Society (BTS) guidelines (3).

Radiological Severity

Radiological severity of bronchiectasis was assessed using a modified Reiff score, which assesses the number of lobes involved (with the lingula considered to be a separate lobe) and the degree of dilatation (tubular = 1, varicose = 2, and cystic = 3). The maximum score is 18 and minimum score is 1. This score has been used previously in studies of bronchiectasis (13–16).

Bacteriology

All bacteriology was performed on spontaneous early-morning sputum samples as previously described (2). Chronic colonization was defined by the isolation of potentially pathogenic bacteria in sputum culture on two or more occasions, at least 3 months apart in a 1-year period (14, 16, 17). The predominant pathogen was the organism grown most frequently over the study period. Patients were asked to provide sputum samples at least twice a year at clinic reviews. Patients who were unable to provide sputum samples due to absence of a productive cough were classified as noncolonized for the purposes of analysis.

End-points

Mortality. At the end of the 4-year follow-up period, mortality was determined using a computer database linked to national death records. Survival status was confirmed for 100% of participants. Cause of death was determined and assigned as bronchiectasis related or unrelated after individual case review.

Hospitalization for severe exacerbations. Severe exacerbations were defined according to the BTS guidelines, and unscheduled hospitalizations or emergency department visits for severe bronchiectasis exacerbations or complications were recorded from patient histories and verified using an administrative database that records all regional hospital admissions (3).

Exacerbations. Exacerbations were defined according to the BTS definition as an acute deterioration with increasing sputum volume and purulence and/or systemic upset (3). Frequency of exacerbations requiring antibiotic treatment were determined from patient histories and verified against electronic general practice prescription records.

Quality of life. Patients completed the St. George's Respiratory Questionnaire (18) as a measure of quality of life. The widely used minimal important clinical difference is a change of 4 units (18).

Validation Cohorts

The Bronchiectasis Severity Index (BSI) was validated in independent cohorts of patients with bronchiectasis from four centers: Dundee (n = 218) and Newcastle (n = 126) in the UK (19), Leuven in Belgium (n = 253) (20), and Monza in Italy (n = 105). Details of data collection in each of these studies are described in the online supplement. Validation cohorts were convenience cohorts collected and analyzed independently of the derivation study. Each applied definitions of colonization and assessments based on the derivation cohort.

Statistical Analysis and Derivation of Clinical Prediction Tool

Normally distributed data are presented as mean with SD, whereas nonnormally

distributed data are presented as median with interquartile range. The chi-squared test and Mann Whitney *U* test were used for comparison of categorical and numerical data, respectively. For comparisons of more than two groups, one-way analysis of variance or the Kruskal-Wallis test were used as appropriate. The independent relationship of clinical variables with mortality and hospital admissions over the study period was determined using separate Cox proportional hazard regression models. Variables that were associated with the outcome at *P* less than 0.2 on univariate analysis were considered for entry into the multivariate models. Variables were dichotomized using the Youden index to identify the optimal cut-off or using previous cut-offs identified in the bronchiectasis literature (21). In all analyses, missing data for predictors were assumed to be normal. Less than 0.1% of data were missing in the five databases, and no outcome data were missing.

To derive a prediction tool for bronchiectasis severity, the authors identified common variables that predicted mortality and hospital admissions. These variables were then formed into a prediction tool using the rounded averaged β-coefficient to award "points" for each variable as previously described (7). The performance of the resulting model for mortality and hospital admissions was assessed using the area under the receiver operator characteristic curve (AUC). For all analyses, *P* less than 0.05 was considered statistically significant.

Results

The prospective derivation cohort included 608 patients. The majority were classified as having idiopathic or postinfective bronchiectasis (386 patients). Underlying etiologies and comorbidities are shown in Table 1.

Mortality and Hospitalizations during the Study

There were 62 deaths in the derivation cohort over 4 years (10.2%). Causes of death are shown in the online supplement. Hospital admissions or emergency department visits were recorded in 189 patients during follow-up over 4 years. During the study period, 81 patients had more than one hospital admission, whereas the remainder had a single episode recorded. The mean frequency of exacerbations per patient per year during follow-up was 1.8 per year (SD, 1.4).

Demographic Characteristics

The relationship between demographic characteristics and outcomes for the derivation cohort are shown in Table 1. As

Table 1: Demographics and Comorbidities Associated with Clinical Outcomes in Bronchiectasis

	N	4-yr Mortality Rate	Hospitalizations	Annual Exacerbation Frequency	SGRQ
Age, yr					
<30 (ref)	17	0 (0%)	2 (11.8%)	1.56 (1.4)	26.0 (22.2)
30–49	50	1 (2%)	11 (22.0%)	1.74 (1.4)	41.4 (21.6)
50–69	268	11 (4.1%)	82 (30.6%)	1.94 (1.4)	42.3 (23.9)
70–79	203	29 (14.3%)	64 (31.5%)	1.78 (1.4)	45.8 (22.8)
80+	68	22 (32.4%)	30 (44.1%)	1.73 (1.2)	46.5 (22.1)
P value		<0.0001	0.03	0.5	0.008
Sex					
Male (ref)	243	29 (11.9%)	73 (30.0%)	1.85 (1.42)	42.2 (24.0)
Female	365	33 (9.0%)	116 (31.8%)	1.82 (1.32)	44.0 (22.7)
P value		0.2	0.6	0.8	0.4
BMI					
<18.5	42	13 (31.0%)	22 (52.4%)	2.44 (1.9)	47.5 (27.4)
18.5–25 (ref)	227	21 (9.1%)	71 (30.9%)	1.84 (1.3)	40.8 (22.2)
25–30	214	15 (7.0%)	55 (25.7%)	1.62 (1.2)	40.2 (21.7)
30+	125	13 (10.4%)	41 (32.8%)	1.93 (1.5)	50.7 (24.8)
P value		<0.0001	0.008	0.003	<0.0001
Underlying cause					
Idiopathic/postinfective (ref)	386	39 (10.1%)	110 (28.5%)	1.89 (1.4)	42.0 (23.3)
Previous TB	82	11 (13.4%)	33 (40.2%)	1.50 (1.0)	41.8 (25.6)
Previous ABPA	49	3 (6.1%)	20 (40.8%)	1.64 (1.1)	45.8 (18.4)
Rheumatoid arthritis	44	5 (11.4%)	13 (29.5%)	1.98 (1.6)	46.8 (23.0)
Inflammatory bowel disease	14	2 (14.3%)	6 (42.9%)	1.70 (1.4)	54.3 (19.5)
Others	33	2 (6.1%)	7 (21.2%)	2.11 (1.7)	49.6 (24.0)
P value		0.7	0.1	0.1	0.1
Comorbidities					
Chronic cardiac disease	139	27 (19.4%)*	41 (29.5%)	1.70 (1.3)	46.1 (22.4)
Cerebrovascular disease	63	16 (25.4%)	35 (55.6%)*	1.73 (1.4)	48.0 (23.1)
Chronic renal failure	36	6 (16.7%)	14 (38.9%)	1.40 (1.1)	44.3 (21.2)
Diabetes mellitus	67	6 (9.0%)	13 (19.4%)	1.81 (1.3)	44.9 (23.6)
Current smokers	42	4 (9.5%)	18 (42.9%)	2.12 (1.5)	42.4 (20.4)

Definition of abbreviations: ABPA = allergic bronchopulmonary aspergillosis; BMI = body mass index; ref = reference; SGRQ = St. George's Respiratory Questionnaire; TB = tuberculosis.

P values refer to comparisons between groups using chi-squared test (categorical data) or analysis of variance (continuous data).

*$P < 0.05$, comparisons made with patients without this comorbidity. All other relationships not statistically significant.

expected, there was a strong relationship between age and mortality. There was no significant relationship between sex and mortality. There was a strong relationship between body mass index (BMI) and mortality, with a 31.0% mortality rate in patients with a BMI less than 18.5 kg/m^2. Chronic cardiac disease was associated with mortality but not with hospital admissions, exacerbation frequency, or quality of life.

Pulmonary Function Tests

Based on FEV_1/FVC ratio, 301 patients (49.5%) had airflow obstruction, restrictive spirometry was present in 114 patients (18.8%), and normal spirometry was present in 193 patients (31.7%).

Based on the Youden index, FEV_1 % predicted was most discriminatory for mortality and hospital admissions and was used for subsequent analyses of lung function. Lower FEV_1/FVC ratio, FEV_1, and FVC % predicted were all strongly associated with mortality. Similarly, patients with lower lung function were more frequently hospitalized and had an increased annual exacerbation frequency and worse quality of life. The data for FEV_1 are shown in Table 2, and the data for FVC % predicted and data for patients with obstruction, restriction, and normal spirometry are shown in Table E1 in the online supplement.

Hospital Admissions, Exacerbations, and Exercise Capacity

At study enrollment, 133 patients gave a history of hospitalization or emergency department visits with a severe exacerbation or respiratory tract infection in the preceding 2 years. The distribution of patients according to annual exacerbation frequency is shown in Table 2. This shows that a prior history of hospital admissions or the annual frequency of exacerbations

Table 2: Spirometry, Previous Hospital Admissions, Exacerbations, and Baseline Medical Research Council Dyspnea Score as Predictors of Future Morbidity and Mortality

	N	4-yr Mortality	Hospitalizations	Exacerbations	SGRQ
FEV_1, % predicted					
>80	255	15 (5.9%)	44 (17.3%)	1.60 (1.22)	34.7 (21.5)
50–80	220	20 (9.1%)	71 (32.3%)	1.85 (1.41)	43.4 (20.9)
30–50	110	19 (17.3%)	59 (53.6%)	2.24 (1.46)	58.5 (21.1)
<30	23	9 (39.1%)	15 (65.2%)	2.37 (1.36)	66.3 (21.5)
P value		<0.0001	<0.0001	<0.0001	<0.0001
History of hospitalization for severe exacerbations					
Yes	133	33 (24.8%)	123 (92.5%)	2.59 (1.5)	60.8 (22.0)
No	475	29 (6.1%)	66 (13.9%)	1.62 (1.2)	38.4 (21.0)
P value		<0.0001	<0.0001	<0.0001	<0.0001
Frequency of outpatient exacerbations in previous year*					
0	245	19 (7.8%)	59 (24.1%)	1.09 (0.8)	36.3 (21.4)
1	127	7 (5.5%)	28 (22.0%)	1.38 (0.8)	41.1 (20.8)
2	97	11 (11.3%)	30 (30.9%)	2.05 (0.9)	48.2 (22.8)
3	47	4 (8.5%)	18 (38.3%)	2.42 (1.0)	46.1 (25.5)
4 or more	92	22 (23.9%)	54 (58.7%)	3.90 (1.4)	58.9 (21.8)
P value		0.0001	<0.0001	<0.0001	<0.0001
MRC dyspnea score					
1	228	16 (7.0%)	26 (11.4%)	1.59 (1.3)	33.2 (20.9)
2	121	11 (9.1%)	29 (24.0%)	1.67 (1.2)	44.6 (21.9)
3	124	10 (8.1%)	50 (40.3%)	2.01 (1.5)	46.7 (21.7)
4	87	12 (13.8%)	49 (56.3%)	1.91 (1.4)	52.8 (21.2)
5	48	14 (29.2%)	35 (72.9%)	2.78 (1.4)	61.9 (22.0)
P value		0.0001	<0.0001	<0.0001	<0.0001
Bacteriology and colonization					
Chronic colonization	440	52 (11.8%)	169 (38.4%)	2.04 (1.4)	45.6 (23.7)
Not colonized	168	10 (6.0%)	20 (12.0%)	1.29 (0.9)	37.8 (20.2)
P value		0.03	<0.0001	<0.0001	<0.0001
Specific organisms					
Haemophilus influenzae	177	10 (5.6%)	61 (34.5%)	2.03 (1.5)	45.1 (22.0)
Pseudomonas aeruginosa	70	15 (21.2%)†	62 (88.6%)†	2.85 (1.5)†	60.7 (21.7)†
Streptococcus pneumoniae	35	2 (5.7%)	11 (31.4%)†	2.13 (1.5)	49.3 (21.6)
Moraxella catarrhalis	63	5 (7.9%)	26 (41.3%)†	2.08 (1.3)†	48.4 (22.1)†
Staphylococcus aureus (excluding MRSA)	43	5 (11.6%)	14 (32.6%)†	2.04 (1.7)	43.7 (21.6)†
MRSA	8	5 (62.5%)†	5 (62.5%)†	3.10 (2.4)†	50.7 (33.3)†
Gram-negative *Enterobacteriaceae*	40	6 (15.0%)	21 (52.5%)†	2.29 (1.5)†	55.2 (21.2)†

Definition of abbreviations: MRC = Medical Research Council; MRSA = methicillin-resistant *Staphylococcus aureus*; SGRQ = St. George's Respiratory Questionnaire.

A proportion of patients were colonized with more than one pathogen; therefore, for individual organisms the mortality rates are expressed as a percentage of all patients colonized with that pathogen and may add up to more than the total number of events in the population.

*Outpatient exacerbations excludes exacerbations managed in hospital.

†For microbiology, statistically significant differences are highlighted. $P < 0.05$ compared to the not-colonized group.

Table 3: Results of the Cox Proportional Hazard Regression Analysis for Mortality and Hospitalization

Severity Marker	HR (95% CI) for Hospital Admissions during Follow-up	HR (95% CI) for Mortality	Score Points
Age, yr			
<50	1.0 (reference)	1.0 (reference)	0
50–69	1.38 (0.73–2.56)	2.21 (0.28–17.5)	2
70–79	1.50 (0.79–2.82)	8.57 (1.15–63.63)	4
80+	1.76 (0.89–3.50)	23.16 (3.09–173.7)	6
BMI			
<18.5	1.23 (0.73–2.08)	2.25 (1.09–4.67)	2
18.5–25	1.0 (reference)	1.0 (reference)	0
26–29	0.90 (0.62–1.30)	0.91 (0.46–1.81)	0
30 or more	1.14 (0.76–1.70)	1.38 (0.68–2.81)	0
FEV_1 % predicted			
>80	1.0 (reference)	1.0 (reference)	0
50–80	1.17 (0.74–1.85)	1.34 (0.67–2.67)	1
30–49	1.40 (0.68–2.85)	1.58 (0.72–3.46)	2
<30	1.52 (1.03–2.25)	4.47 (1.60–12.53)	3
Hospital admission before study			
No	1.0 (reference)	1.0 (reference)	0
Yes	13.5 (9.40–19.46)	2.43 (1.30–4.53)	5
Exacerbations before the study			
0	1.0 (reference)	1.0 (reference)	0
1–2	1.67 (0.78–3.58)	1.78 (0.80–3.98)	0
3 or more	2.25 (0.89–5.70)	2.03 (1.02–4.03)	2
MRC dyspnea score			
1–3	1.0 (reference)	1.0 (reference)	0
4	2.42 (1.66–3.52)	1.05 (0.50–2.20)	2
5	2.69 (1.59–4.53)	1.15 (0.50–2.63)	3
Pseudomonas colonization			
No	1.0 (reference)	1.0 (reference)	0
Yes	2.16 (1.36–3.43)	1.58 (0.75–3.34)	3
Colonization with other organisms			
No	1.0 (reference)	1.0 (reference)	0
Yes	1.66 (1.12–2.44)	1.10 (0.54–2.24)	1
Radiological severity: ⩾3 lobes involved or cystic bronchiectasis			
No	1.0 (reference)	1.0 (reference)	0
Yes	1.48 (1.02–2.15)	1.05 (0.57–1.94)	1

Definition of abbreviations: BMI = body mass index; CI = confidence interval; HR = hazard ratio; MRC = Medical Research Council.
All factors founded to be significantly associated with either mortality or hospital admissions were included in the derivation of the severity score.

predicts future mortality, hospital admissions, exacerbations, and quality of life. Further analysis identified a strong relationship between baseline Medical Research Council dyspnea score and future mortality, hospital admissions, exacerbations, and quality of life.

Colonization Status and Bacteriology

Mortality was significantly higher in patients with chronic colonization compared with noncolonized patients. The mortality rate varied significantly depending on the colonizing organism, with the highest mortality rates associated with the isolation of *Pseudomonas aeruginosa* and methicillin-resistant *Staphylococcus aureus* (Table 2).

Radiological Severity

The analysis of radiological severity is presented in Table E2. The data show no significant relationship between radiological severity and mortality ($P = 0.3$) but a significant relationship between the Reiff score and hospital admissions. This relationship was statistically significant above a score of 3 or more (indicating three or more lobes involved or a lobe with cystic bronchiectasis). There was a weak but statistically significant relationship with quality of life, but the relationship with exacerbations was not statistically significant ($P = 0.06$; Table E2).

Development of the BSI in the Derivation Cohort

The Cox proportional hazard regression models for hospital admission for severe exacerbations and mortality are shown in Table 3. This model identified a prior history of hospitalization to be the strongest predictor of future hospitalization risk. Independent of this, Medical Research Council dyspnea score, FEV_1 less than 30% predicted, and colonization with *P. aeruginosa* or other organisms were independent predictors of hospital admissions. Mortality was significantly associated with prior hospitalizations, increasing age, BMI less than 18.5 kg/m^2, FEV_1 % predicted, and three or more exacerbations per year.

Several factors were not associated with mortality or hospital admissions after adjustment for the other included variables, including etiology of bronchiectasis, sex, comorbidities, smoking status, and inhaled corticosteroid use (Table 3).

Classification of Patients According to the BSI

Patients were classified into tertiles designated low (0–4 points, n = 191),

intermediate (5–8 points, n = 224), and high BSI scores (9 or more points, n = 193). The relationship between these severity classes and mortality and morbidity are shown in Figure 1.

The AUC for mortality was 0.80 (0.74–0.86) and the AUC for hospitalization was 0.88 (0.84–0.91). There was a clear difference in exacerbation frequency and quality of life between patients classified as low, intermediate, and high BSI scores ($P < 0.0001$) for all comparisons (Figure 1).

The above data represent predictions over the full 4 years of follow-up. An analysis was performed using data from annual follow-up visits to predict events in the subsequent year (e.g., data from follow-up in 2009 was used to predict events from 2009–2010, and so on). The AUC for mortality was: 0.79 (0.66–0.91) for 2008 to 2009, 0.75 (0.62–0.87) for 2009 to 2010, 0.82 (0.72–0.91) for 2010 to 2011, and 0.80 (0.71–0.89) for the period 2011 to 2012. This indicates that the score worked similarly for annual prediction as for longer-term prediction.

For hospital admissions, the annual AUCs were: 0.87 (0.84–0.91) for 2008 to 2009, 0.86 (0.82–0.89) for 2009 to 2010, 0.88 (0.82–0.94) for 2010 to 2011, and 0.87 (0.78–0.96) for the period 2011 to 2012. This confirms the usefulness of the BSI in predicting the likelihood of both short- and long-term hospital admissions.

Validation of the BSI in Independent Cohorts

The four independent cohorts are described in Table 4 and in the online supplement. For prediction of mortality, data are shown in Figures 2A and 2B, demonstrating progressive increases in mortality with increasing severity index group. The AUCs for mortality are shown in Figure 2D and confirmed good discrimination for predicting mortality using the BSI. No AUC was calculated for the Monza, Italy cohort as there were only two deaths. Similarly, each cohort with available data showed a progressive increase of hospitalization with BSI severity class, and the AUCs in Figure 2D confirmed a high degree of discrimination (AUC, 0.80–0.88). No hospitalization data were available in the Leuven cohort.

Three cohorts had data for exacerbation frequency during follow-up (Figure 2C). Each of these showed a progressive increase in exacerbation frequency with BSI severity class ($P < 0.0001$ for Newcastle and Dundee cohorts, $P = 0.03$ for Monza cohort).

In contrast to the derivation cohort, the Dundee, Newcastle, and Leuven cohorts included patients receiving long-term antibiotic therapy. The frequency of antibiotic therapy was 41.3% in the Dundee cohort, 40.5% in Newcastle, and 43.1% in Leuven. In these cohorts, long-term antibiotic therapy was not independently predictive of mortality or hospitalizations. Hazard ratio (HR) was 0.66 (95% CI, 0.34–1.31) in the Leuven cohort and HR was 1.43 (95% CI, 0.54–1.81) in the Newcastle cohort for mortality. For hospital admissions, the HR was 0.63 (95% CI, 0.36–1.11) in the Newcastle cohort and HR was 1.34 (95% CI, 0.81–2.23) in the Dundee cohort. The BSI score predicted mortality and hospital admissions in current users of long-term antibiotics similarly to the primary analysis, suggesting this was not a major confounder. The AUC for mortality in long-term antibiotic users was 0.82, 0.75, and 0.80 in Dundee, Newcastle, and Leuven, respectively. For hospital

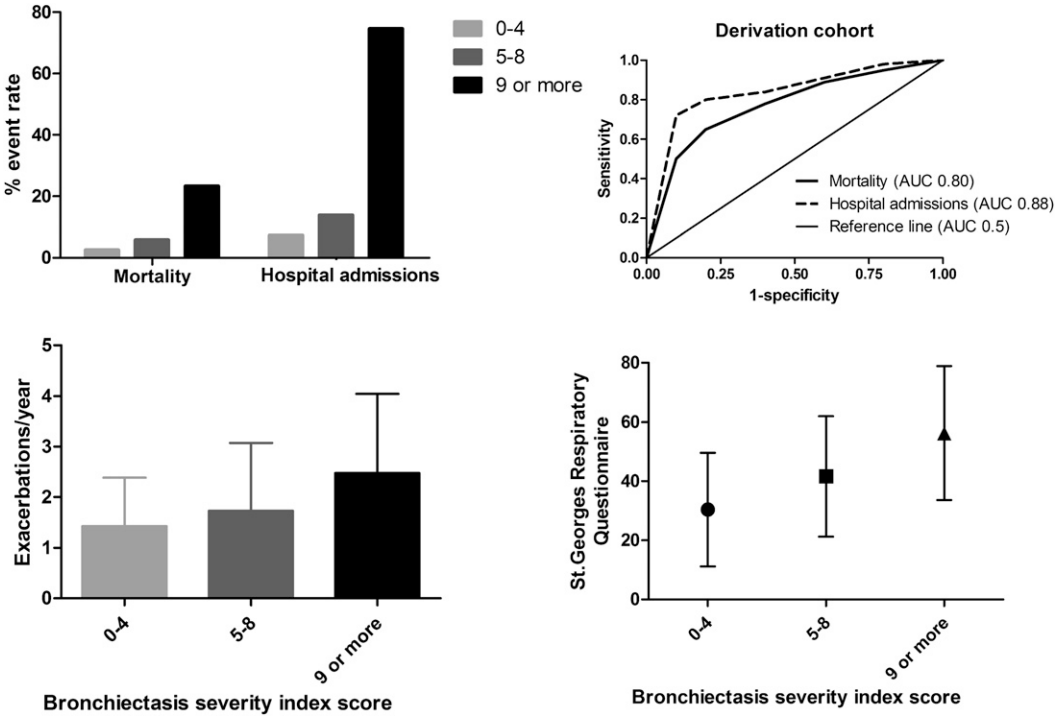

Figure 1. The performance of the Bronchiectasis Severity Index in predicting mortality, hospital admissions, exacerbations, and quality of life. All between-group comparisons were statistically significant ($P < 0.0001$). The exacerbation and quality-of-life data are presented as mean with SD. AUC = area under the receiver operator characteristic curve.

Table 4: Characteristics of the Validation Cohorts

Cohort	Dates of Enrollment	N	Age (*yr*) Median (IQR)	Male Sex N (%)	FEV_1 % Predicted Median (IQR)	*Pseudomonas aeruginosa* Colonization n (%)	Duration of Follow-up (*mo*)	End-points Assessed	Etiology n (%)	Outcome Frequency (%)
Dundee, Scotland, UK	2011	218	66 (55–77)	98 (45.0)	71 (51–88)	29 (13.3)	24	Mortality Hospital admissions Exacerbation frequency	Idiopathic, 91 (42) ABPA, 21 (10) Postinfective, 20 (9) CTD, 12 (6)	Mortality, 2.3 Hospital admissions, 26.6
Leuven, Belgium	2006–2012	253	68 (56–78)	127 (50.2)	72 (50–91)	20 (7.9)	49 (mean)	Mortality	Idiopathic, 78 (31) Postinfective, 50 (20) COPD, 42 (17) CTD, 25 (10)	Mortality, 16.6
Monza, Italy	2011–2012	105	67 (58–74)	45 (43.0)	75 (53–98)	21 (20.0)	12	Mortality Hospital admissions Exacerbation frequency	Idiopathic, 35 (33) Postinfective, 31 (30) COPD, 23 (22) IBD, 4 (4)	Mortality, 1.9 Hospital admissions, 31.4
Newcastle, England, UK	2009	126	61 (54–69)	51 (40.5)	64 (30–84)	13 (10.3)	40 (mean)	Mortality Hospital admissions Exacerbation frequency	Idiopathic, 52 (41) Postinfective, 28 (22) COPD, 12 (10) ABPA, 8 (6)	Mortality, 13.5 Hospital admissions, 40.4

Definition of abbreviations: ABPA = allergic bronchopulmonary aspergillosis; COPD = chronic obstructive pulmonary disease; CTD = connective tissue disease; IBD = inflammatory bowel disease; IQR = interquartile range.

admissions it was 0.80 and 0.76 in Dundee and Newcastle, respectively.

Discussion

The present study is the first multicenter international study to describe a clinical prediction tool for bronchiectasis. We derived the BSI in a prospective cohort study over 4 years and validated in several independent cohorts of patients with bronchiectasis. Overall, this study evaluated the score in 1,310 patients with bronchiectasis across five cohorts, making this the largest and most diverse assessment of bronchiectasis severity so far reported. The BSI accurately stratified the risk of mortality, hospital admissions, future risk of exacerbations, and quality of life.

Most respiratory diseases have a disease-specific severity assessment tool, designed for guiding therapy or stratifying risk of complications (5–7). No such tool exists for bronchiectasis. New treatments are increasingly available for patients with bronchiectasis, with growing evidence for the efficacy of long-term macrolide therapy and inhaled antibiotics (8–11). However, these therapies have attendant risks (e.g., antimicrobial resistance and toxicity) as well as significant healthcare costs and treatment burdens (22). A key challenge in bronchiectasis management lies in the identification of patients at high risk of developing bronchiectasis complications who may benefit from intensification of therapy (23, 24). Whether using a risk-stratification tool such as the BSI can achieve improvements in clinical practice now requires prospective evaluation.

This score is likely to contribute to clinical decision making for patients with bronchiectasis, for example, in identifying high-risk patients who may benefit from more intensive follow-up or aggressive therapy, such as the administration of long-term antibiotics. The score may prove cost-efficient in reducing healthcare use and saving valuable resources with the identification of patients at low risk of complications who may not require regular secondary care follow-up or who can be seen less frequently (3, 24). From a research perspective, the BSI will allow a comparison of cohorts across different studies by describing them in terms of risk of complications and will be useful to identify groups of patients likely to benefit from

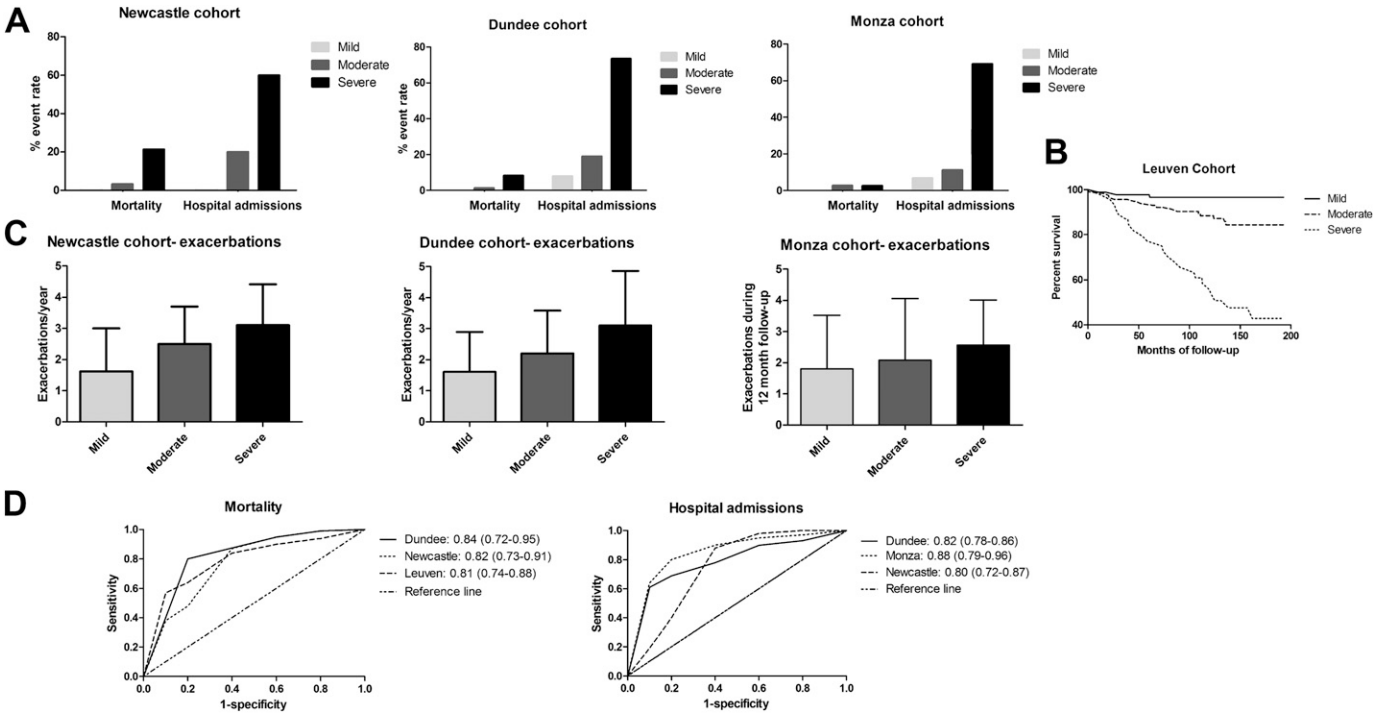

Figure 2. Validation of the Bronchiectasis Severity Index (BSI) in external cohorts. (*A*) Mortality and hospital admissions according to mild (0–4 points), moderate (5–8 points), and severe (>8 points) risk BSI groups. (*B*) Kaplan-Meier survival curves (mortality) in the mild, moderate, and severe groups ($P < 0.0001$ by log rank test) in the Leuven cohort. (*C*) Exacerbation frequency in the mild, moderate, and severe groups according to the BSI ($P < 0.0001$ for Newcastle and Dundee cohorts, $P = 0.03$ for Monza cohort). (*D*) Receiver operator characteristic curves for mortality and hospital admissions according to the BSI.

novel therapies for enrollment into clinical trials.

Three recent trials of macrolides in bronchiectasis all showed a reduction in exacerbations with macrolide treatment versus placebo (9–11). The Effectiveness of Macrolides in Patients with Bronchiectasis Using Azithromycin to Control Exacerbations (EMBRACE) trial enrolled patients with one or more exacerbations in the previous year, the Bronchiectasis and Low-Dose Erythromycin Study (BLESS) trial required two exacerbations in the previous year, and the Bronchiectasis and Long-Term Azithromycin Treatment (BAT) trial required three exacerbations in the previous year and a positive sputum culture (9–11). BTS guidelines empirically recommend consideration of long-term antibiotic treatment for patients with three or more exacerbations in the previous year (3). Macrolide use is associated with a significant increase in adverse events, with 40% of macrolide-treated patients experiencing gastrointestinal side effects in the BAT trial (11). Macrolides have also been linked with uncommon adverse events, including an increased frequency of cardiovascular events (25), and undoubtedly promote antibiotic resistance (22). Therefore, identifying patients most likely to benefit from antibiotic treatment, with a favorable risk:benefit ratio, is one potential application of a severity tool. This requires future prospective analysis in further longitudinal studies.

A strength of the BSI score is that the predictors are readily available and routinely collected clinical parameters that do not require any advanced imaging or pulmonary function testing, with HRCT scanning performed as standard. The derivation and validation cohorts included a wide spectrum of disease severity in bronchiectasis, ranging from patients with infrequent exacerbations and well-preserved lung function to patients with radiologically defined cystic pattern multilobar bronchiectasis, frequent exacerbations, and marked airflow obstruction. The large sample size and broad inclusion criteria make this prediction tool applicable to a wide range of patients with bronchiectasis. The score was validated in four cohorts—two from the UK, one from Italy, and one from Belgium—demonstrating its generalizability on an international scale. Each of the validation cohorts used similar definitions and assessments to the derivation cohort, but nevertheless there were differences between the cohorts, including the use of long-term antibiotic therapy. Further prospective validation of the BSI in independent cohorts would be desirable. For the purposes of analysis, we classified patients into similar-sized mild, moderate, and severe groups similar to prior COPD prognostic models. Determining the optimal cut-off of the BSI score for use in clinical decision making will require further studies.

A recent study followed 91 patients with bronchiectasis enrolled in a clinical study for 13 years and found a mortality rate of 29.7% (26). Independent predictors of mortality in this cohort included age, *P. aeruginosa* colonization, pulmonary function, and the St. George's respiratory questionnaire, all of which support the findings of the present study (26). Onen and colleagues reported data from 98 patients with bronchiectasis in which there were 16 deaths and found age, BMI, and severity of dyspnea to be the strongest predictors of mortality (27).

This study has limitations: the derived score is relatively complex, awarding different point values for each of the predictors and including multiple predictors. To aid calculation of the score, an online calculator is accessible at http://www.bronchiectasisseverity.com. The study excluded patients with active NTM disease, and therefore the validity of this tool in patients with bronchiectasis due to active NTM cannot be determined. The derivation cohort also excluded patients receiving long-term antibiotic therapy, which is increasingly being regarded as a standard of care for patients with severe disease. Our analysis in the validation cohorts where antibiotics were widely used suggests this did not significantly confound the analysis. Only four patients in the derivation study were excluded due to NTM, as this is an infrequent underlying cause in UK centers (16, 28). In contrast, very high rates of NTM have been reported in the United States registry (29). This tool will require further international validation including patients with NTM. Additional variables are likely to be associated with mortality beyond those included in the current BSI score. These may include time since diagnosis of bronchiectasis or the presence of pulmonary hypertension, neither of which was recorded routinely in this study (20). In addition, our study was primarily of patients with idiopathic and postinfective bronchiectasis and would not be powered to detect anything other than very large effects on survival in bronchiectasis due to less common etiologies, such as allergic bronchopulmonary aspergillosis or rheumatological diseases. Investigating the effects of less common etiologies on prognosis will require very large multicenter registries (29). We used a simple radiological classification system to evaluate the severity of disease on HRCT. This score has limitations, as it only takes into account the number of lobes involved and the degree of dilatation (15). This score has been widely used in studies of non-CF bronchiectasis but takes into account far fewer variables than scoring systems used in CF, such as the Bhalla score (30). We are unable to address whether adding additional radiological variables would improve the BSI.

The predictors identified in this study are clinically intuitive and consistent with previous studies. The score is therefore likely to be applicable to other secondary care populations with bronchiectasis. Further studies determining how this score may impact clinical practice are now needed.

Conclusions

This study has derived and validated a novel disease-specific severity index for predicting future risk of mortality, hospital admissions, exacerbations, and quality of life in patients with bronchiectasis. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Acknowledgment: The authors thank Giulia Suigo, M.D., and Giulia Bonaiti, M.D., from the Health Science Department, University of Milan Bicocca, and Mr Paul McAlinden, Sir William Leech Centre for Lung Research, Newcastle upon Tyne Hospitals, for assistance with data collection. They also thank the UK Bronchiectasis Research and Academic Network and the European Multicentre Bronchiectasis Audit and Research Collaboration (EMBARC) for advice and support in developing this study.

References

1. Chalmers JD, Hill AT. Mechanisms of immune dysfunction and bacterial persistence in non-cystic fibrosis bronchiectasis. *Mol Immunol* 2013; 55:27–34.
2. Chalmers JD, Smith MP, McHugh BJ, Doherty C, Govan JR, Hill AT. Short- and long-term antibiotic treatment reduces airway and systemic inflammation in non-cystic fibrosis bronchiectasis. *Am J Respir Crit Care Med* 2012;186:657–665.
3. Pasteur MC, Bilton D, Hill AT; British Thoracic Society Bronchiectasis non-CF Guideline Group. British Thoracic Society guideline for non-CF bronchiectasis. *Thorax* 2010;65:i1–i58.
4. McShane PJ, Naureckas ET, Tino G, Strek ME. Non-cystic fibrosis bronchiectasis. *Am J Respir Crit Care Med* 2013;188:647–656.
5. Lange P, Marott JL, Vestbo J, Olsen KR, Ingebrigtsen TS, Dahl M, Nordestgaard BG. Prediction of the clinical course of chronic obstructive pulmonary disease, using the new GOLD classification: a study of the general population. *Am J Respir Crit Care Med* 2012;186:975–981.
6. Chalmers JD, Singanayagam A, Akram AR, Mandal P, Short PM, Choudhury G, Wood V, Hill AT. Severity assessment tools for predicting mortality in hospitalised patients with community-acquired pneumonia: systematic review and meta-analysis. *Thorax* 2010;65:878–883.
7. du Bois RM, Weycker D, Albera C, Bradford WZ, Costabel U, Kartashov A, Lancaster L, Noble PW, Raghu G, Sahn SA, *et al*. Ascertainment of individual risk of mortality for patients with idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2011;184:459–466.
8. Murray MP, Govan JRW, Doherty CJ, Simpson AJ, Wilkinson TS, Chalmers JD, Greening AP, Haslett C, Hill AT. A randomized controlled trial of nebulized gentamicin in non-cystic fibrosis bronchiectasis. *Am J Respir Crit Care Med* 2011;183:491–499.
9. Wong C, Jayaram L, Karalus N, Eaton T, Tong C, Hockey H, Milne D, Fergusson W, Tuffery C, Sexton P, *et al*. Azithromycin for prevention of exacerbations in non-cystic fibrosis bronchiectasis (EMBRACE): a randomised, double-blind, placebo-controlled trial. *Lancet* 2012; 380:660–667.
10. Serisier DJ, Martin ML, McGuckin MA, Lourie R, Chen AC, Brain B, Biga S, Schlebusch S, Dash P, Bowler SD. Effect of long-term, low-dose erythromycin on pulmonary exacerbations among patients with non-cystic fibrosis bronchiectasis: the BLESS randomized controlled trial. *JAMA* 2013;309:1260–1267.
11. Altenburg J, de Graaff CS, Stienstra Y, Sloos JH, van Haren EH, Koppers RJ, van der Werf TS, Boersma WG. Effect of azithromycin maintenance treatment on infectious exacerbations among patients with non-cystic fibrosis bronchiectasis: the BAT randomized controlled trial. *JAMA* 2013;309:1251–1259.
12. 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;145:32–38.
13. Chalmers JD, McHugh BJ, Docherty C, Govan JR, Hill AT. Vitamin-D deficiency is associated with chronic bacterial colonisation and disease severity in bronchiectasis. *Thorax* 2013;68:39–47.
14. Chalmers JD, McHugh BJ, Doherty C, Smith MP, Govan JR, Kilpatrick DC, Hill AT. Mannose binding lectin deficiency is associated with disease severity in non-cystic fibrosis bronchiectasis: a prospective study. *Lancet Respir Med* 1:224–232.
15. Reiff DB, Wells AU, Carr DH, Cole PJ, Hansell DM. CT findings in bronchiectasis: limited value in distinguishing between idiopathic and specific types. *AJR Am J Roentgenol* 1995;165: 261–267.
16. Pasteur MC, Helliwell SM, Houghton SJ, Webb SC, Foweraker JE, Coulden RA, Flower CD, Bilton D, Keogan MT. An investigation into causative factors in patients with bronchiectasis. *Am J Respir Crit Care Med* 2000;162:1277–1284.
17. 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.
18. Wilson CB, Jones PW, O'Leary CJ, Cole PJ, Wilson R. Validation of the St. George's Respiratory Questionnaire in bronchiectasis. *Am J Respir Crit Care Med* 1997;156:536–541.

19. Hester KL, Macfarlane JG, Tedd H, Jary H, McAlinden P, Rostron L, Small T, Newton JL, De Soyza A. Fatigue in bronchiectasis. *QJM* 2012;105:235–240.
20. 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.
21. Youden WJ. Index for rating diagnostic tests. *Cancer* 1950;3:32–35.
22. Serisier DJ. Risks of population antimicrobial resistance associated with chronic macrolide use for inflammatory airway diseases. *Lancet Respiratory Medicine* 2013;1:262–274.
23. Wilson R, Wells AU. Azithromycin in bronchiectasis: when should it be used? *Lancet* 2012;380:627–629.
24. De Soyza A, Brown JS, Loebinger MR; Bronchiectasis Research & Academic Network. Research priorities in bronchiectasis. *Thorax* 2013;68:695–696.
25. Schembri S, Williamson PA, Short PM, Singanayagam A, Akram AR, Taylor JK, Singanayagam A, Hill AT, Chalmers JD. Cardiovascular events after clarithromycin use in lower respiratory tract infections: analysis of two prospective cohort studies. *BMJ* 2013;346:f1235.
26. Loebinger MR, Wells AU, Hansell DM, Chinyanganya N, Devaraj A, Meister M, Wilson R. Mortality in bronchiectasis: a long-term study assessing the factors influencing survival. *Eur Respir J* 2009;34: 843–849.
27. Onen ZP, Gulbay BE, Sen E, Yildiz OA, Saryal S, Acican T, Karabiyikoglu G. Analysis of the factors related to mortality in patients with bronchiectasis. *Respir Med* 2007;101: 1390–1397.
28. Fowler SJ, French J, Screaton NJ, Foweraker J, Condliffe A, Haworth CS, Exley AR, Bilton D. Nontuberculous mycobacteria in bronchiectasis: prevalence and patient characteristics. *Eur Respir J* 2006;28:1204–1210.
29. Aksamit TR, Carretta E, Daley CL, O'Donnell AE, Thomashow B, Dominik R, Olivier KN, Knowles MR, Griffith DE, Barker AF, *et al*. The Bronchiectasis Research Registry: a collaborative research cohort for non-cystic fibrosis bronchiectasis [abstract]. *Am J Respir Crit Care Med* 2012;185:A8654.
30. Bhalla M, Turcios N, Aponte V, Jenkins M, Leitman BS, McCauley DI, Naidich DP. Cystic fibrosis: scoring system with thin-section CT. *Radiology* 1991;179:783–788.