Predicting mortality in bronchiectasis using bronchiectasis severity index and FACED scores: a 19-year cohort study

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ABSTRACT The clinical course of bronchiectasis is unpredictable, posing a challenge both in clinical practice and in research. Two mortality prediction scores, the bronchiectasis severity index (BSI) and FACED scores, have recently been developed. The aim of this study was to assess the ability of these scores to predict long-term mortality and to compare the two scores.

The study was a single-centre retrospective cohort analysis consisting of 91 subjects originally recruited in 1994. BSI and FACED scores were calculated at the time of enrolment and long-term mortality ascertained. Data was available for 74 patients with a median of 18.8 years of follow-up.

Both scoring systems had similar predictive power for 5-year mortality (area under receiver operator characteristic curve (AUC) 0.79 for BSI and 0.8 for FACED). Both scores were able to predict 15-year mortality with the FACED score showing slightly superior predictive power (AUC 0.82 *versus* 0.69, p=0.0495).

This study provides further validation of the FACED and BSI scores for the prediction of mortality in bronchiectasis and demonstrates their utility over a longer period than originally described. Whilst both scores had excellent predictive power, the FACED score was superior for 15-year mortality.

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Introduction

Bronchiectasis is a chronic and debilitating illness characterised by dilatation of the bronchial lumen that predisposes to infection [1]. Recurrent infection leads to tissue damage and inflammation that leads to excess mucus production and delayed mucociliary clearance, predisposing the patient to recurrent and chronic infections [2]. This in turn creates a cycle of further tissue damage and infection [3], leading to recurrent exacerbations, hospitalisations and loss of lung function.

A variety of underlying factors may give rise to bronchiectasis ranging from previous pulmonary infection (particularly in childhood) to causes amenable to specific treatment (*e.g.* hypogammaglobulinaemia). In many cases the aetiology is not identified despite thorough investigation [4, 5]. The clinical course is unpredictable; generally the disease progresses slowly, but in a minority of cases progression is much more rapid [6]. Such heterogeneity poses a challenge both in clinical practice and in the characterisation of subjects for observational studies and clinical trials. Whilst several individual factors have been associated with poor outcomes in bronchiectasis [4, 6–8], more recently two multidimensional severity scores have been developed: the bronchiectasis severity index (BSI) score and the FACED score (see online supplementary material) [9, 10]. Both scores have been validated in multiple, large cohorts, and have been shown to accurately predict mortality over 4 (BSI) and 5 years (FACED) of follow-up.

The Royal Brompton Hospital has compiled data on a cohort of subjects with bronchiectasis since 1994 [11]. The aim of this study was to test the ability of BSI and FACED scores to predict long-term mortality in this cohort and to compare the two systems.

Method

Design

The study was a single-centre retrospective cohort analysis. The study cohort consisted of 91 subjects with bronchiectasis who were originally recruited in 1994 to assess the validity of the St George's Respiratory Questionnaire (SGRQ) in bronchiectasis [11] and later studied to determine predictors of mortality in bronchiectasis [6]. The diagnosis of bronchiectasis was confirmed on high-resolution computed tomography (HRCT) [12–14]. Subjects were assessed whilst in a stable clinical state.

Data to calculate BSI and FACED scores were taken from original study records supplemented by a review of patient notes where required. The scores were calculated as described elsewhere [9, 10]. Forced expiratory volume in 1 s (FEV_1) was determined in the pulmonary function laboratory at the time of study enrolment. Body mass index (BMI) was not recorded as part of the original study; this was calculated using heights and weights recorded as close to the date of study entry as possible. The number of affected lobes was calculated from HRCT by two specialist radiologists blinded to patient details. Colonisation with bacteria was defined as "the isolation of potentially pathogenic bacteria in sputum culture on two or more occasions, at least 3 months apart in a 1-year period". Where less than two samples were provided, the subject was deemed not colonised. An exacerbation of bronchiectasis was defined according to British Thoracic Society criteria as "an acute deterioration with worsening local symptoms (cough, increased sputum volume, purulence, or change of viscosity, with or without increasing wheeze, breathlessness, haemoptysis) and/or systemic upset".

In addition to the calculation of both severity scores, subjects were also categorised as mild (BSI $\leqslant$4, FACED $\leqslant$2), moderate (BSI 5–8, FACED 3–4) and severe (BSI $\geqslant$9, FACED $\geqslant$5) disease according to each scoring system.

Mortality was ascertained as of November 2013 and dates of death obtained from electronic patient records. For patients no longer at our institution, data was obtained *via* their general practitioner or hospital and death certificates were reviewed wherever possible.

Statistical analysis

Data were pre-processed using Microsoft Excel for Mac 2011 software (Microsoft, Redmond, WA, USA) and then imported into R version 3.0.4 [15] for further analysis. Receiver operating characteristic (ROC) curves were calculated using the pROC package [16] and area under the curve (AUC) compared using DeLong's test for two correlated ROC curves. Optimum threshold values were identified as those giving the highest Youden's index (sensitivity+(1−specificity)). Kaplan–Meier curves were generated using the survival package [17] and compared using the log-rank test. Mortality between groups with different severity scores was compared using univariate Cox proportional hazards analysis. For comparisons between groups of subjects, the t-test was used for parametric variables, the Wilcoxon rank-sum test for nonparametric variables and proportions were compared using Fisher's exact test.

Results

Of the 91 patients recruited to the mortality study, three were lost to follow-up and 14 were excluded as incomplete clinical data did not allow calculation of BSI and/or FACED scores. Analyses were conducted on the remaining 74 patients. The median duration of follow-up from enrolment was 18.8 years (range 18.3–19.1 years). Patient demographics are shown in table 1.

The BSI score classified 31% of subjects as severe compared with only 8% by the FACED score (table 2). One subject with a mild BSI score was classed as severe by FACED score, whereas 11 subjects with mild disease by FACED score had a severe BSI score. There was a significant association between severity classification based on the BSI and FACED scores (Fisher's exact test, p=0.021). Details of the contribution made by each variable to each score according to severity category are shown in table 3.

There were 26 deaths in 74 subjects (35%) during the study period. The median age at death was 67.4 years (interquartile range (IQR) 60.7–75.4 years) and median survival time from enrolment was 9.7 years (IQR 5.9–11.6 years). Data on the cause of death was available for 24 of the 26 deceased subjects. Of these, 18 had a respiratory disease identified as a factor contributing or leading to their death and bronchiectasis was specified in 14 (58%). Mortality varied substantially according to BSI or FACED score (table 4), from 21% and 16% in those with mild scores to 57% and 83% for those with severe scores, respectively.

Survival analysis

Kaplan–Meier survival curves for mortality according to BSI and FACED scores are shown in figure 1. There was little separation of the survival curves between with a mild and moderate BSI score (log-rank test, p=0.575), but those with a severe BSI score had significantly reduced survival (log-rank test, p=0.017 *versus* mild and p=0.023 *versus* moderate groups). For the FACED score, both the moderate and severe groups had significantly reduced survival compared with the mild group (log-rank test, p<0.001 for both comparisons). Although there was also separation of the curves between moderate and severe groups, this was not significant (log-rank test, p=0.140).

The results of univariate Cox proportional hazards analysis are shown in table 4. Mortality was significantly raised in both the moderate and severe FACED groups compared with mild disease. Mortality in the severe BSI group, but not in the moderate BSI group, was significantly raised compared with those in the mild group.

Receiver operating characteristic analysis

The AUC for 5-year mortality was similar for BSI and FACED scores. As the duration of follow-up increased, the AUC for 10- and 15-year mortality remained high for the FACED score but declined slightly for the BSI score (fig. 2). For 15-year mortality, the AUC for the FACED score was significantly higher

TABLE 1 Demographics of study cohort

Age years	52.5±12.4
FEV_1 % predicted	68.8±27.7
BMI kg·m^{-2}	23.4±3.9
MRC dyspnoea score	2.1±0.9
Lobes affected	3.4±1.5
Exacerbations in previous year	4.4±4.4
Hospitalisations in last 2 years	0.5±1.3
Microbiological colonisation status	
Pseudomonas aeruginosa	16 (22)
Haemophilus influenzae	9 (12)
Streptococcus pneumoniae	3 (4)
Staphylococcus aureus	1 (1)
Branhamella catarrhalis	1 (1)
Aetiology of bronchiectasis	
Idiopathic	41 (55)
Post-infective	19 (26)
Allergic bronchopulmonary aspergillosis	5 (7)
Young's syndrome	4 (5)
Common variable immunodeficiency	3 (4)
Primary ciliary dyskinesia	2 (3)

Data are presented as mean±SD or n (%). FEV_1: forced expiratory volume in 1 s; BMI: body mass index; MRC: Medical Research Council.

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than the BSI score (0.82 *versus* 0.69; DeLong's test for two correlated ROC curves, p=0.0495) (table 5). For 15-year mortality, the optimum threshold of >2.5 for the FACED score gave a specificity of 84% and sensitivity 70.8%; for the BSI score, a threshold of >9.5 gave a specificity of 92% and sensitivity 37.5%.

TABLE 2 Classification of subjects by bronchiectasis severity index (BSI) and FACED scores

BSI	FACED		
	Mild	Moderate	Severe
Mild	17	1	1
Moderate	21	10	1
Severe	11	8	4

Data are presented as n.

TABLE 3 Contribution of individual variables to FACED and bronchiectasis severity index (BSI) scores

	FACED score			BSI score		
	Mild (0–2)	Moderate (3–4)	Severe (5–7)	Mild (0–4)	Moderate (5–8)	Severe (9+)
Age years						
<50	22 (45)	8 (42)	1 (22)	11 (58)	14 (44)	7 (30)
50–69	25 (51)	8 (42)	3 (50)	8 (42)	14 (44)	13 (57)
70–79	2 (4)	3 (16)	2 (33)	0 (0)	4 (13)	3 (13)
⩾80	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
FEV_1 % predicted						
<30	2 (4)	3 (16)	2 (33)	1 (5)	4 (13)	2 (9)
30–49	2 (4)	12 (63)	3 (50)	2 (11)	9 (28)	7 (30)
50–80	18 (37)	3 (16)	1 (22)	4 (21)	9 (28)	10 (43)
>80	27 (55)	1 (5)	0 (0)	12 (63)	10 (31)	4 (17)
BMI $kg \cdot m^{-2}$						
<18.5	1 (2)	2 ((11)	0 (0)	0 (0)	0 (0)	3 (13)
18.5–25	36 (73)	15 (79)	5 (87)	15 (79)	24 (75)	15 (65)
26–30	9 (18)	1 (5)	0 (0)	3 (16)	6 (19)	3 (13)
>30	3 (6)	1 (5)	1 (22)	1 (5)	2 (6)	2 (6)
MRC dyspnoea score						
0–2	36 (73)	12 (63)	0 (0)	15 (79)	25 (78)	8 (35)
3	11 (22)	7 (37)	4 (66)	4 (21)	7 (22)	11 (48)
4	2 (4)	0 (0)	2 (33)	0 (0)	0 (0)	4 (17)
5	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Lobes affected						
1	6 (12)	1 (5)	0 (0)	3 (16)	2 (6)	2 (6)
2	16 (33)	3 (16)	0 (0)	5 (26)	8 (25)	6 (26)
⩾3 or cystic bronchiectasis	27 (55)	15 (79)	6 (100)	11 (58)	22 (69)	15 (65)
Exacerbations in previous year						
0	3 (6)	2 (11)	1 (22)	3 (16)	3 (9)	0 (0)
1–2	17 (35)	5 (26)	3 (50)	13 (68)	7 (22)	6 (26)
⩾3	29 (59)	12 (63)	2 (33)	3 (16)	22 (69)	17 (74)
Hospitalisations in last 2 years						
Yes	15 (31)	3 (16)	1 (22)	0 (0)	7 (22)	12 (52)
No	34 (69)	16 (84)	5 (87)	19 (100)	25 (78)	11 (48)
Microbiological colonisation status						
Pseudomonas aeruginosa	6 (12)	5 (26)	5 (83)	1 (5)	7 (22)	8 (35)
Haemophilus influenzae	6 (12)	3 (16%)	0 (0)	2 (11)	5 (16)	2 (9)
Streptococcus pneumoniae	2 (4)	1 (5)	0 (0)	0 (0)	3 (9)	0 (0)
Staphylococcus aureus	1 (2)	0 (0)	0 (0)	1 (5)	0 (0)	0 (0)
Branhamella catarrhalis	1 (2)	0 (0)	0 (0)	1 (5)	0 (0)	0 (0)
None	33 (67)	10 (53)	1 (17)	14 (74)	27 (84)	13 (57)

Data are presented as n (%). FEV_1: forced expiratory volume in 1 s; BMI: body mass index; MRC: Medical Research Council.

TABLE 4 Univariate Cox proportional hazard analysis of bronchiectasis severity index (BSI) and FACED scores for mortality during the study period according to BSI and FACED category

	Subjects n	Mortality n (%)	Hazard ratio (95% CI)	p-value
BSI				
Mild	19	4 (21%)	Reference	
Moderate	32	9 (28%)	1.40 (0.43–4.54)	0.577
Severe	23	13 (57%)	3.66 (1.19–11.24)	0.023
FACED				
Mild	49	8 (16%)	Reference	
Moderate	19	13 (68%)	5.90 (2.43–14.32)	<0.001
Severe	6	5 (83%)	12.49 (3.98–39.18)	<0.001

Discordant severity classification

Within the severe BSI group, mortality was lowest in those with a mild FACED score (18%) compared with those with a moderate or severe FACED score (88% and 100%, respectively). Cox proportional hazards analysis found a significantly raised risk of death associated with both moderate (hazard ratio 8.86; p=0.008) and severe (hazard ratio 22.51; p=0.001) FACED scores. Within the mild FACED group, mortality was marginally lower in those with a mild BSI score (12%) compared with those with a moderate or severe BSI score (19% and 18%, respectively); however, the overall number of deaths within this group was low.

11 subjects were assigned a severe BSI score, but a mild FACED score (table 2). The mortality in these subjects was 18% compared with 16% in subjects with a mild FACED score and a mild or moderate BSI score and 92% in subjects with a severe BSI score and moderate or severe FACED score. Compared with participants with a severe BSI score and moderate or severe FACED score, these participants were younger (mean age 51.82 *versus* 62 years; p=0.019), had better lung function (mean FEV_1 % predicted 75.36 *versus* 49.58; p=0.014), less extensive bronchiectasis (median number of affected lobes 2 *versus* 4; p=0.009) and nonsignificantly higher BMI (mean 24.74 *versus* 21.33 $kg \cdot m^{-2}$; p=0.06). There was no significant difference in Medical Research Council (MRC) dyspnoea score. Fewer subjects had chronic *Pseudomonas* infection (18% *versus* 58%) and more had chronic infection with other organisms (18% *versus* 0%), although neither difference was significant. The majority (82%) of participants in this group had been hospitalised within the preceding 2 years, compared with 25% of those with a severe BSI score and a moderate or severe FACED score (Fisher's exact test, p=0.0123) The number of exacerbations within the previous 2 years was not significantly higher (median 4 *versus* 3.5; p=0.534).

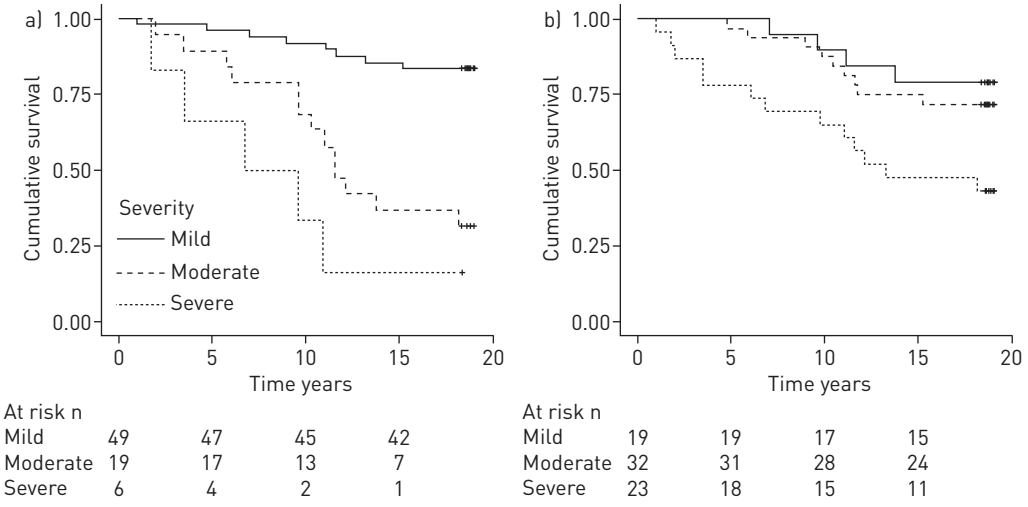

FIGURE 1 Kaplan–Maier curves for mortality during the study period corresponding to a) FACED score and b) bronchiectasis severity index score category.

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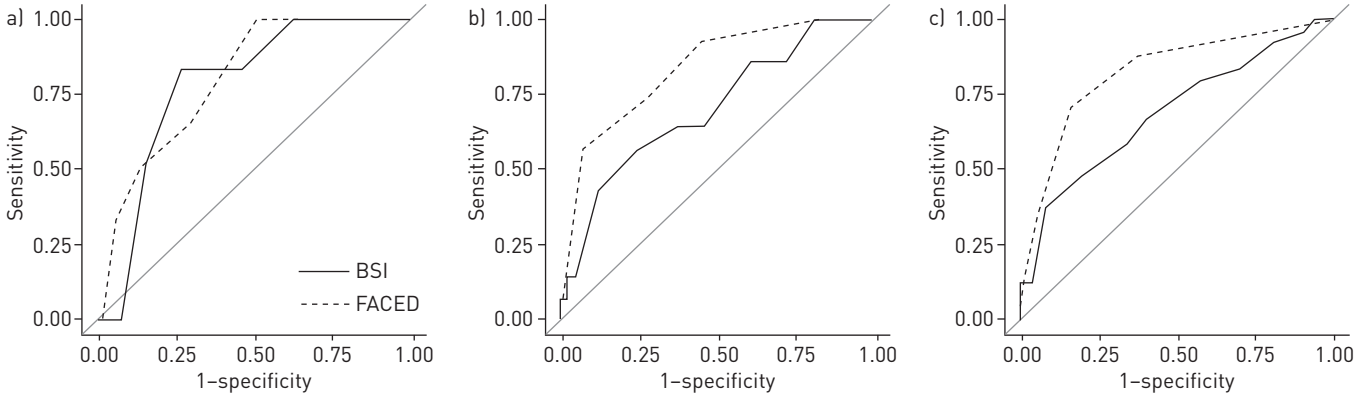

FIGURE 2 Receiver operating characteristic curves for bronchiectasis severity index (BSI) and FACED score for a) 5-, b) 10- and c) 15-year mortality.

Respiratory disease-related mortality

The analysis was repeated looking only at deaths where a respiratory cause was felt to be contributory. At all time points both scoring systems were still able to predict mortality with AUC 0.79, 0.71 and 0.69 for the BSI score and 0.80, 0.84 and 0.82 for the FACED score at 5, 10 and 15 years, respectively. The difference in AUC between BSI and FACED scores was not statistically significant at any time point.

Discussion

This study demonstrates the ability of both BSI and FACED scores to predict mortality in bronchiectasis at up to 15 years of follow-up. The FACED score had a greater AUC for the prediction of 15-year mortality and greater separation of survival curves. In a subgroup with discordant severity classification, mortality was more similar to that indicated by the FACED score than the BSI score.

Several individual factors have been found to be associated with mortality in bronchiectasis. A retrospective study conducted at our centre on the current patient cohort found chronic *Pseudomonas aeruginosa* infection, SGRQ score, total lung capacity (TLC), residual volume/TLC ratio and transfer factor were independently associated with mortality over a 13-year follow-up [6]. A prospective study in Turkey found many markers of disease severity which were predictive of mortality over a 4-year follow-up; the highest risk was associated with radiographic disease extent, MRC dyspnoea score and lack of vaccination against influenza or pneumococcus [7].

Moving beyond single factors, BSI and FACED scores both use multiple markers of disease severity to capture the complex and heterogeneous nature of bronchiectasis, and were validated in large independent cohorts [9, 10]. All the factors identified as significant predictors of mortality and used to create the FACED score (FEV_1, age, *Pseudomonas* infection status, extent of bronchiectasis and MRC dyspnoea score) were also identified as significant in the development of the BSI, which also added BMI, colonisation with other bacteria, and previous hospitalisations and admissions as predictive variables. The additional aim of the BSI to predict exacerbations and hospitalisation may account for the larger number of variables used.

These data confirm that both scoring systems are excellent predictors of medium-term mortality in subjects with bronchiectasis, finding very similar AUC values to those reported in their original cohorts. For the BSI score, the AUC for 4-year mortality was 0.85 with a mortality rate of 7% (data not shown) compared with an AUC of 0.8 in the original study cohort with a mortality of 10%. For the FACED score, the AUC for 5-year mortality was 0.8 with a mortality rate of 8% compared with an AUC 0.87 in original

TABLE 5 Comparison of receiver operating characteristics (ROCs) for mortality at different time points between bronchiectasis severity index (BSI) and FACED scores

Mortality	BSI	FACED	p-value
5-year	0.79 (0.64–0.94)	0.80 (0.65–0.95)	0.876
10-year	0.71 (0.55–0.86)	0.84 (0.72–0.95)	0.082
15-year	0.69 (0.55–0.82)	0.82 (0.72–0.93)	0.049

Data are presented as area under the curve (95% CI), unless otherwise stated. p-values calculated using DeLong's test for two correlated ROC curves.

study cohort with a mortality of 19%. Impressively, both scoring systems were able to predict long-term mortality and to identify patients with a significantly reduced survival at up to 15 years.

The survival of those with a moderate BSI score was not significantly different to that of the mild group. In contrast, a moderate FACED score identified a distinct patient group with mortality between that of the mild and severe groups, although there was overlap in the 95% confidence interval for hazard ratios in the moderate and severe groups perhaps due to the small size of the latter. The FACED score also had a better predictive value for 15-year mortality. In the shorter term, at 5 and 10 years, the AUC was higher for the FACED score, but this did not reach significance.

In many cases the BSI assigned higher scores than FACED with the result that the severe BSI group was much larger than the corresponding FACED group (23 *versus* 6 subjects) and had a lower mortality during the study (57% *versus* 83%). Similarly there were fewer subjects with a mild BSI score than with a mild FACED score (19 *versus* 49 subjects) and mortality in this group was higher (21% *versus* 16%). These differences are likely to account for the higher AUC and greater separation of survival curves seen with the FACED score. The superior AUC for the prediction of 15-year mortality and the low mortality in subjects with a discordant severity classification suggests that the milder scores assigned by FACED may be more appropriate in the prediction of mortality.

11 subjects were classed as severe by BSI score, but mild by FACED score. The principle factors contributing to this were the high rates of exacerbation and hospitalisation seen in this group despite their relative lack of other markers of severity. The mortality in this group was low and these subjects appear to be the driving force for the lower mortality observed in the severe BSI group compared with the equivalent FACED group.

In the derivation of the BSI score [3], previous hospitalisation was associated with a far higher risk of future hospitalisation (hazard ratio 13.5, 95% CI 9.40–19.46) than mortality (hazard ratio 2.43, 95% CI 1.30–4.53), but this factor contributes heavily to the total score. Of the nine subjects with severe BSI scores and previous hospitalisation, none would have been classed as severe without the contribution of this factor. This group may therefore represent a subgroup where the raised BSI score is reflective of an increased risk of hospitalisation only and not increased mortality; however, we do not have hospitalisation data for out cohort. One explanation for this is that a variety of factors lead to the decision to admit a patient, many of which are independent of disease severity, such as their level of social support, access to intravenous antibiotics in the community or individual patient preference.

The main limitation of our study lies in its retrospective nature and relatively small number of participants. The collected data is limited to that which was obtained at the time of the original study and data for other outcomes of interest such as exacerbations was not gathered. Figures for exacerbations and hospitalisations over 2 years prior to recruitment were difficult to obtain retrospectively, leading to the exclusion of 14 patients due to missing data. There is the possibility that the included subjects are not representative of the whole cohort; however, the mortality rate did not significantly differ between those subjects excluded due to missing data and those included in the analysis (8/14 *versus* 26/74; Fisher's exact test, p=0.143) nor did the median age of death (62.2 *versus* 67.4 years; t-test, p=0.217).

The size of the cohort is constrained by the number of subjects recruited to the original study, which limits the statistical power to detect differences in AUC between the two scoring systems. Our cohort was powered to detect a difference in AUC of 0.15 (from a reference AUC of 0.7) with 80% power and a 95% confidence level [18]. Given the observed differences in AUC of 0.13 at 10 and 15 years (table 5), the study was underpowered to demonstrate a difference between AUC and the lack of statistical significance seen at 10 years may therefore be due to type II error. The difference in AUC seen at 5 years was minimal and is far below the powered detectable difference; however, even if this were statistically significant, it is not clinically meaningful.

The second limitation concerns our study population. Subjects with nontuberculous mycobacterial infection and those taking antibiotic prophylaxis were included in our study, but excluded from the BSI derivation cohort, although the BSI validation cohorts included such patients. The FACED study derivation cohort was recruited soon after the diagnosis of bronchiectasis was made, whereas our cohort was primarily composed of patients with known bronchiectasis already in our service and in many cases on treatment. However, these differences also serve to demonstrate that these scores are applicable to a wider bronchiectasis population outside those originally described.

This study provides independent validation of the FACED and BSI scores for the prediction of mortality in bronchiectasis, and demonstrates their utility over a far longer follow-up period than previously described. It is also the first comparison of the two scores and shows the FACED score to have some advantage in the prediction of survival over the long term. Whilst mortality is clearly an important outcome, interventions in bronchiectasis have primarily aimed at reducing exacerbations and hospitalisations, preserving lung function,

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and increasing quality of life. An advantage of the BSI is that is has also been shown to predict exacerbations and hospitalisations, whereas the ability of the FACED score to predict these outcomes has yet to be tested. However, from a practical perspective the FACED score requires less data and its simplicity makes it easier to calculate. It may be that the two systems complement one another by reflecting different aspects of bronchiectasis severity. Such tools will be valuable for stratification in clinical trials and for targeting individuals who may benefit most from intervention.

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