

Heterogeneity of non-cystic-fibrosis bronchiectasis in multiethnic Singapore: A prospective cohort study at a tertiary pulmonology centre

Si Ling Young¹*MRCP*, Youxin Puan¹*MRCP*, Si Yuan Chew¹*MRCP*, Haja Mohideen Salahudeen Mohamed²*FRCR*, Pei Yee Tiew¹*MRCP*, Gan Liang Tan³*MRCP*, Mariko Siyue Koh¹*MRCP*, Ken Cheah Hooi Lee¹*MRCP*

ABSTRACT

Introduction: Non-cystic fibrosis bronchiectasis (NCFB) is a highly heterogenous disease. We describe the clinical characteristics of NCFB patients and evaluate the performance of Bronchiectasis Severity Index (BSI) in predicting mortality.

Methods: Patients attending the bronchiectasis clinic between August 2015 and April 2020 with radiologically proven bronchiectasis on computed tomography were recruited. Clinical characteristics, spirometry, radiology, microbiology and clinical course over a median period of 2.4 years is presented.

Results: A total of 168 patients were enrolled in this prospective cohort study. They were predominantly women (67.8%), Chinese (87.5%) and never-smokers (76.9%). Median age of diagnosis was 64 years (interquartile range 56–71) and the most common aetiology was “idiopathic” bronchiectasis (44.6%). Thirty-nine percent had normal spirometries. Compared to female patients, there were more smokers among the male patients (53.8% versus 8.5%, $P<0.001$) and a significantly larger proportion with post-tuberculous bronchiectasis (37.0% vs 15.8%, $P=0.002$). Fifty-five percent of our cohort had a history of haemoptysis. Lower body mass index, presence of chronic obstructive pulmonary disease, ever-smoker status, modified Reiff score, radiological severity and history of exacerbations were risk factors for mortality. Survival was significantly shorter in patients with severe bronchiectasis ($BSI\geq 9$) compared to those with mild or moderate disease ($BSI<9$). The hazard ratio for severe disease ($BSI\geq 9$) compared to mild disease ($BSI 0-4$) was 14.8 (confidence interval 1.929–114.235, $P=0.01$).

Conclusion: The NCFB cohort in Singapore has unique characteristics with sex differences. Over half the patients had a history of haemoptysis. The BSI score is a useful predictor of mortality in our population.

Ann Acad Med Singap 2021;50:556-65

Keywords: Bronchiectasis, exacerbations, gender, haemoptysis, mortality, Reiff score, sex

INTRODUCTION

Bronchiectasis is a chronic lung disease of significant morbidity and mortality. The pathological hallmarks of the disease are abnormal dilatation of airways resulting from recurrent inflammation, airway obstruction and mucous plugging.¹ The past 2 decades have seen a significant increase in its prevalence, exceeding the threshold of 5 per 10,000 persons for the definition of an “orphan disease”.²⁻⁷ In the UK, a rising incidence and prevalence was reported across nearly all age groups between 2004 and 2013, most notably among women above 70 years of age.² A similar

growing trend is reported in the US.³ There is less epidemiologic data on non-cystic fibrosis bronchiectasis (NCFB) in Asian countries. A cross-sectional survey from China reported a 1.2% prevalence of bronchiectasis among those aged 40 years and older.⁶ More recently, Choi et al. reported a prevalence of 464 patients per 100,000 person-years with NCFB in South Korea, with a mean age of 63.8 ± 13.1 years.⁷ These observations suggest that unlike cystic fibrosis that predominantly affects Caucasians, NCFB occurs commonly in both Caucasians and Asians, especially in the older age groups.

¹ Department of Respiratory and Critical Care Medicine, Singapore General Hospital, Singapore

² Department of Diagnostic Radiology, Singapore General Hospital, Singapore

³ Department of Respiratory and Critical Care Medicine, Sengkang General Hospital, Singapore

Correspondence: Dr Si Ling Young, Department of Respiratory and Critical Care Medicine, Singapore General Hospital, Outram Road, Singapore 169608.

Email: siling.young@mohh.com.sg

CLINICAL IMPACT

What is New

- This is one of the first studies describing the characteristics of non-cystic fibrosis bronchiectasis (NCFB) patients in Singapore, highlighting key features such as a high incidence of haemoptysis among these patients.
- The Bronchiectasis Severity Index (BSI) is a useful prognostic marker in our NCFB population.

Clinical Implications

- This study highlights the heterogeneity of NCFB and importance of further research to identify phenotypes that may help guide future management.
- The BSI can aid clinicians in their communication with NCFB patients regarding the prognosis of their disease.

Geographic variation in the aetiology and microbiology of NCFB has been described, such as the higher prevalence of idiopathic and post-infectious NCFB patients reported in European and Asian countries,⁸ compared to the US where NCFB was frequently associated with immune dysregulation.⁹ For microbiology, the rates of *Pseudomonas aeruginosa* and *Hemophilus influenzae* colonisation vary across the US, Europe and Asia Pacific region. Non-tuberculous mycobacterium (NTM) colonisation was found in 63% of NCFB patients in the US bronchiectasis research registry,¹⁰ but much lower rates were reported in Chinese studies.⁹ Other organisms like *Klebsiella pneumoniae* were significantly prevalent in NCFB patients in Thailand and South Korea.^{11,12}

The heterogeneity of NCFB is further reflected in its diversity in clinical presentation, radiologic involvement, spirometry patterns and prognosis as reported by the various global registries on patients with NCFB.^{10,13-17} Such heterogeneity has led to a keen interest to identify phenotypes and endotypes with the aim of individualising treatment to improve outcomes.¹⁸ To date, information about the NCFB population in Singapore remains scarce. In this study, we describe the characteristics of NCFB patients in Singapore and evaluated the performance of Bronchiectasis Severity Index (BSI) in predicting mortality.

METHODS

Consecutive subjects (aged ≥ 21 years) with diagnosis of bronchiectasis based on computed tomography

(CT), and attending the bronchiectasis clinic in Singapore General Hospital, a tertiary hospital in Singapore, were recruited into this prospective cohort study from 2017. The patients underwent a systematic evaluation of potential underlying aetiologies with a thorough assessment of disease symptoms, past history of sino-pulmonary infections including tuberculosis, ear infections, gastro-oesophageal reflux, subfertility, autoimmune disease and inflammatory bowel disease. Serum immunoglobulins and full blood count were performed for all patients, in accordance with the British Thoracic Society and European Respiratory Society guidelines.^{19,20} Other investigations such as autoimmune markers, alpha-1-antitrypsin level, and genetic testing for cystic fibrosis were performed if relevant clinical features were present. The aetiology of bronchiectasis was determined on the basis of the aforementioned investigations by the treating physician via a clinical-radiological approach. Spirometry results, respiratory microbiology and exacerbation history from time of diagnosis were also collected. Interpretation of spirometry was in accordance with the 2005 American Thoracic Society interpretative strategies for lung function tests.²¹ Bacterial colonisation was defined by the growth of the same bacteria on 2 or more occasions at least 3 months apart on either sputum or broncho-alveolar lavage specimens.

The CT images were independently reviewed by an experienced thoracic radiologist, and the morphological characteristics and severity of bronchiectasis were determined. The modified Reiff score was used to assess the number of lobes involved and degree of dilatation.^{22,23} The left lingula was considered a separate lobe. The extent of bronchiectasis within each lobe was also graded with a score of 1, 2 or 3, according to the proportion of airways involved: <25%, 25–50% and >50%, respectively. A radiology severity score was obtained by a summation of scores for all the lobes.

Exacerbation was defined as a deterioration in 3 or more of the following symptoms for at least 48 hours—cough, sputum volume or consistency, sputum purulence, breathlessness or exercise tolerance, fatigue and haemoptysis—associated with a requirement for treatment with antibiotics, which is modified from the original definition by Hill et al.²⁴ A history of haemoptysis was defined as the patient having reported any amount of haemoptysis before in their lifetime that is attributed to bronchiectasis. Clinically significant haemoptysis referred to haemoptysis requiring bronchoscopy, intubation, bronchial artery embolisation or surgery. The BSI score was first derived and validated by Chalmers et al. and provided an easily

Table 1. Clinical characteristics of patients with NCFB in Singapore and mortality subgroup analysis

Characteristic	Baseline characteristics (N=168)	Mortality group (n=18)	Survival group (n=150)	P value
Age at diagnosis, median (IQR), years	64 (56–71)	56 (54–60)	64 (57–71)	0.693
BMI, median (IQR)	19.3 (17.3–21.8)	18.5 (18.1–21.5)	19.3 (17.3–21.7)	0.003
Female, no. (%)	114 (67.8)	11 (61.1)	103 (68.7)	0.517
Smoking status, no. (%)				
Never	123 (76.9)	8 (53.3)	113 (78.5)	0.030
Active	4 (2.5)	0 (0.0)	4 (2.8)	0.513
Ever	33 (20.6)	7 (46.7)	26 (18.1)	0.009
Asthma, no. (%)	15 (8.9)	0 (0.0)	15 (10.0)	0.160
COPD, no. (%)	9 (5.3)	3 (16.7)	6 (4.0)	0.024
Aetiology, no. (%)				
Idiopathic	75 (44.6)	5 (27.8)	70 (46.7)	0.128
Post-TB	42 (25.0)	6 (33.3)	32 (21.3)	0.250
Post-infectious	38 (22.6)	5 (27.8)	37 (24.7)	0.773
FEV1 % predicted (baseline), median (IQR)	79 (63–95)	70 (51–84)	80 (65–95)	0.138
Spirometry pattern, no. (%)				
Normal	52 (39.0)	3 (25.0)	49 (40.5)	0.294
Restrictive	29 (21.8)	5 (41.7)	24 (19.8)	0.081
Obstructive	15 (11.2)	1 (8.3)	14 (11.6)	0.735
Non-specific	13 (9.7)	1 (8.3)	12 (9.9)	0.860
Microbiology, no. (%)				
<i>Pseudomonas aeruginosa</i>	35 (22.3)	6 (33.3)	29 (20.9)	0.232
<i>Pseudomonas aeruginosa colonisation</i>	24 (15.2)	5 (29.4)	19 (14.4)	0.113
<i>Klebsiella pneumoniae</i>	16 (10.2)	1 (5.6)	15 (10.8)	0.490
<i>Hemophilus influenzae</i>	6 (3.8)	1 (5.6)	5 (3.6)	0.683
<i>Staphylococcus aureus</i>	10 (6.4)	3 (16.7)	7 (5.0)	0.057
NTM	74 (46.3)	12 (66.7)	62 (43.7)	0.065
Radiology, no. (%)				
Upper lobes	103 (61.3)	14 (77.8)	89 (59.3)	0.129
Middle lobes	146 (86.9)	17 (94.4)	129 (86.0)	0.316
Lower lobes	129 (76.7)	14 (77.8)	115 (76.7)	0.916
Lobes involved, median (IQR)	3 (2–4)	4 (3–4)	3 (2–4)	0.004
Radiology severity score, median (IQR)	6 (4–9)	7 (4–9)	6 (5–6)	0.007
Modified Reiff score, median (IQR)	4 (3–5)	4 (3–4)	4 (3–5)	0.015
Radiology pattern, no. (%)				
Cylindrical	132 (78.5)	12 (66.7)	120 (80.0)	0.193
Cystic	22 (13.0)	5 (27.8)	17 (11.3)	0.051
Varicose	14 (8.3)	1 (5.6)	13 (8.7)	0.652
Exacerbations in the past year, no. (%)	45 (25.7)	10 (55.6)	35 (23.3)	0.004
Haemoptysis ever, no. (%)	92 (54.7)	8 (44.4)	84 (56.0)	0.352
Significant haemoptysis, no. (%)	36 (21.4)	3 (16.7)	33 (22.0)	0.602
BSI score, median (IQR)	6 (5–8)	8 (6–9)	6 (5–8)	<0.001
CAT score, median (IQR)	12.5 (8.0–19.0)	18.0 (17.5–22.5)	12.0 (8.0–19.0)	0.081
Aetiology of death in mortality group, no (%)				
Pneumonia			4 (22.2)	
Bronchiectasis			1 (5.6)	
Colorectal cancer			1 (5.6)	
Coroner's case or unknown			12 (66.7)	

BMI: body mass index; BSI: Bronchiectasis Severity Index; CAT: COPD assessment test; COPD: chronic obstructive pulmonary disease; IQR: interquartile range; NCFB: non-cystic fibrosis bronchiectasis; NTM: non-tuberculous mycobacteria; TB: tuberculosis
P values in bold are significant

accessible clinical score to aid in prognostication of patients with NCFB, which can influence clinical decision making and management.²³ This was a composite score of clinical variables used to classify bronchiectasis severity, and prospectively validated to predict 1- and 4-year morbidity and mortality. The BSI scores, as well as chronic obstructive pulmonary disease (COPD) assessment test scores were obtained.^{23,25} Mortality outcome was defined in this study as the point of death from any cause. In calculating the clinical scores, missing data for variables were assumed to be normal. All data were entered into a secure digital platform (Research Electronic Data Capture).

Statistical analyses were done using SPSS Statistics software version 23.0 (IBM Corp, Armonk, US). Chi-square test and Mann-Whitney U test were applied in the comparison of categorical and continuous data, respectively. Data were expressed as median (interquartile range) for non-normally distributed continuous variables. Kaplan-Meier survival curves were plotted to determine the relationship between BSI severity grades and mortality, and hazard ratios were obtained using Cox proportional hazard regression models. Statistical significance was defined as a *P* value less than or equal to 0.05.

RESULTS

A total of 168 subjects were recruited. The clinical characteristics are presented in Table 1. There was preponderance of women (67.8%) and Chinese ethnicity (87.5%). The median age at diagnosis was 64 years (56–71). Most subjects were never-smokers (76.9%). Nearly half the subjects had idiopathic bronchiectasis (44.6%). Those with known aetiologies included 37 post-tuberculosis (TB) (33.3%), 42 post-infectious (25.0%), 8 autoimmune-related (4.8%), 2 cilia dysmotility (1.2%) and 2 immunoglobulin deficiency (1.2%). One subject had alpha-1-antitrypsin level measured, which was normal. None underwent genetic testing for cystic fibrosis. The median follow-up period was 2.4 years (1.3–3.4).

Spirometry

A normal spirometry was most commonly observed (39.0%). Eleven percent of subjects had an obstructive pattern, and 21.8% showed restriction. The median *forced expiratory volume in the first second* (FEV1) predicted was 79% (63–95).

Microbiology

Thirty-five (22.3%) subjects had at least 1 growth of *Pseudomonas aeruginosa* from a respiratory specimen.

Sixteen (10.2%) subjects had *Klebsiella pneumoniae* and 6 (3.8%) had *Hemophilus influenzae*. Seventy-four subjects (46.3%) had sputum positive for NTM. The most common NTM isolated was *Mycobacterium abscessus* (41.9%), followed by *M. fortuitum* (25.7%), *M. avium* complex (20.3%), and *M. kansasii* (8.1%). Eighteen (24.3%) subjects were initiated on NTM treatment, of whom 14 completed the course of treatment. Two patients did not complete treatment due to intolerable side effects, and 2 were still undergoing treatment at the time of this writing. The median treatment duration was 12 months (10–18).

Radiology

The median number of lobes involved was 3 (2–4). The median modified Reiff score was 4 (3–5), and median radiology severity score was 6 (4–9). Majority had middle lobe involvement (86.9%). The most common radiological pattern observed was a cylindrical pattern (78.5%), followed by cystic pattern (13.0%).

Clinical history

Fifty-seven subjects (33.9%) had no history of exacerbations. Eight subjects (4.8%) had 3 or more exacerbations per year in their lifetime. Seventy-two subjects (60.0%) had a COPD assessment test score of 10 and above. Eighteen subjects (10.7%) had demised during the period of follow-up. Ninety-two (54.7%) subjects had a history of haemoptysis, of which 36 (21.4%) were clinically significant.

Sex differences

There were more smokers (51.8% vs 7.9%, *P*<0.001) and subjects with obstructive spirometry patterns (20.8% vs 5.9%, *P*=0.009) observed among men (Table 2). Men were also more likely to have post-TB as the aetiology for bronchiectasis (37.0% vs 15.8%, *P*=0.002) and upper lobe disease (75.9% vs 54.4%, *P*=0.007). Women had a higher prevalence of NTM (55.0% vs 27.5%, *P*=0.001).

Comparison of patients with and without a history of haemoptysis

Ninety-two subjects (54.7%) had a history of haemoptysis (Table 3). Subjects with haemoptysis tend to have a normal spirometry (48.6% vs 27.9%, *P*=0.015) with higher baseline FEV1 (84L [67–100] vs 72L [63–87], *P*=0.004), as compared to subjects without haemoptysis, who tend to have a restrictive pattern (29.5% vs 15.3%, *P*=0.048). More subjects without haemoptysis had asthma (14.5% vs 4.3%, *P*=0.022). The use of anticoagulation or antiplatelets was not associated with the development of haemoptysis.

Table 2. Comparison of female and male NCFB patients in Singapore

Characteristics	Female (n=113)	Male (n=54)	P value
Age, median (IQR), years	62 (56–69)	69 (60–74)	0.115
BMI, median (IQR)	19.3 (17.4–21.2)	19.1 (17.0–26.2)	0.658
Smoking status, no. (%)			
Active	0 (0)	4 (7.4)	0.004
Previous	9 (7.9)	24 (44.4)	<0.001
Never	97 (85.8)	24 (44.4)	<0.001
Aetiology, no. (%)			
Idiopathic	55 (48.2)	20 (37.0)	0.172
Post-infectious	31 (27.2)	11 (20.4)	0.340
Post-TB	18 (15.8)	20 (37.0)	0.002
Comorbidities, no. (%)			
Asthma	11 (9.6)	4 (7.4)	0.634
COPD	3 (2.6)	6 (11.1)	0.023
Spirometry, no. (%)			
Normal	40 (47.1)	12 (25.0)	0.012
Restrictive	19 (22.4)	10 (20.8)	0.838
Obstructive	5 (5.9)	10 (20.8)	0.009
Non-specific	7 (8.2)	6 (12.5)	0.426
FEV1 % predicted (baseline), median (IQR)	83 (68–98)	69 (61–94)	0.004
Sputum cultures, no. (%)			
<i>Pseudomonas aeruginosa</i>	26 (24.3)	9 (18.0)	0.377
<i>Klebsiella pneumoniae</i>	8 (7.5)	8 (16.0)	0.100
<i>Hemophilus influenzae</i>	5 (4.7)	1 (2.0)	0.416
<i>Staphylococcus aureus</i>	7 (6.5)	3 (6.0)	0.897
NTM	60 (55.0)	14 (27.5)	0.001
Radiology, no. (%)			
Cylindrical	90 (78.9)	42 (77.8)	0.863
Cystic	14 (12.3)	8 (14.8)	0.649
Varicose	10 (8.8)	4 (7.4)	0.765
Involvement, no. (%)			
Upper lobes	62 (54.4)	41 (75.9)	0.007
Middle lobes	102 (89.5)	44 (81.5)	0.152
Lower lobes	88 (77.2)	41 (75.9)	0.856
Lobes involved, median (IQR)	3 (2–4)	4 (2–5)	0.358
Radiology severity score, median (IQR)	6 (4–8)	8 (5–12)	0.107
Modified Reiff score, median (IQR)	4 (2–5)	4 (3–6)	0.263
Haemoptysis, no. (%)	64 (56.1)	28 (51.9)	0.602
Significant haemoptysis, no. (%)	29 (25.4)	7 (13.0)	0.066
BSI score, median (IQR)	6 (4–8)	7 (6–9)	0.022
CAT score, median (IQR)	13 (8–20)	13 (7–18)	0.394

BMI: body mass index; BSI: Bronchiectasis Severity Index; CAT: COPD assessment test; COPD: chronic obstructive pulmonary disease; IQR: interquartile range; NCFB: non-cystic fibrosis bronchiectasis; NTM: non-tuberculous mycobacteria; TB: tuberculosis
P values in bold are significant

Mortality outcomes

Causes of death are shown in Table 1. The most common aetiology of death was pneumonia (4, 22.2%). The cause of death was not available in 12 patients who died outside our institution. Our national policy on patient data confidentiality does not allow investigators to obtain information from national records for the purpose of research. Lower BMI, concomitant COPD, modified Reiff score, radiological

severity, exacerbations and BSI scores correlated with mortality. Growth or colonisation of *Pseudomonas aeruginosa* was not associated with mortality. The hazard ratio for moderate grade BSI (BSI 5–8) compared to mild grade BSI (BSI 0–4) was 1.6 (confidence interval [CI] 0.188–15.053, $P=0.642$), and for severe grade BSI (BSI \geq 9) compared to mild grade BSI was 14.8 (CI 1.929–114.235, $P=0.01$) (Table 4). The Kaplan-Meier survival curve

Table 3. Comparison of NCFB patients with and without a history of haemoptysis

Characteristics	Haemoptysis (n=92)	No haemoptysis (n=76)	P value
Age, median (IQR), years	65 (56–71)	63 (56–73)	0.554
BMI, median (IQR)	19.0 (16.9–21.1)	20.2 (17.9–23.4)	0.247
Female gender, no. (%)	64 (69.6)	50 (65.8)	0.602
Smoking status, no. (%)			
Active	3 (3.4)	1 (1.4)	0.438
Previous	21 (23.6)	12 (17.1)	0.319
Never	64 (71.9)	57 (81.4)	0.162
Aetiology, no. (%)			
Idiopathic	41 (44.6)	34 (44.7)	0.982
Post-infectious	21 (22.8)	21 (27.6)	0.474
Post-TB	25 (27.2)	13 (17.1)	0.121
Asthma, no. (%)	4 (4.3)	11 (14.5)	0.022
COPD, no. (%)	6 (6.5)	3 (3.9)	0.461
Spirometry, no. (%)			
Normal	35 (48.6)	17 (27.9)	0.015
Restrictive	11 (15.3)	18 (29.5)	0.048
Obstructive	7 (9.7)	8 (13.1)	0.538
Non-specific	7 (9.7)	6 (9.8)	0.982
FEV1 % predicted (baseline)	84 (67–100)	72 (63–87)	0.004
Sputum cultures, no. (%)			
<i>Pseudomonas aeruginosa</i>	22 (24.7)	13 (19.1)	0.403
<i>Klebsiella pneumoniae</i>	8 (9.0)	8 (11.8)	0.569
<i>Hemophilus influenzae</i>	3 (3.4)	3 (5.9)	0.736
<i>Staphylococcus aureus</i>	8 (9.0)	2 (2.9)	0.124
NTM	44 (48.9)	30 (42.9)	0.448
Radiology pattern, no. (%)			
Cylindrical	73 (79.3)	59 (77.6)	0.787
Cystic	8 (8.7)	14 (18.4)	0.063
Varicose	11 (12.0)	3 (3.9)	0.062
Involvement, no. (%)			
Upper lobes	53 (51.5)	50 (48.5)	0.305
Middle lobes	81 (55.5)	65 (44.5)	0.488
Lower lobes	71 (55.0)	58 (45.0)	0.544
Lobes involved, median (IQR)	3 (2–4)	4 (2–5)	0.080
Radiology severity score, median (IQR)	6 (4–9)	7 (5–10)	0.326
Modified Reiff score, median (IQR)	4 (2–5)	4 (3–6)	0.073
Use of antiplatelets or anticoagulation, no. (%)	11 (12.1)	12 (15.8)	0.489
BSI score, median (IQR)	7 (5–9)	6 (4–8)	0.398
CAT score, median (IQR)	12 (5–19)	15 (8–20)	0.433

BMI: body mass index; BSI: Bronchiectasis Severity Index; CAT: COPD assessment test; COPD: chronic obstructive pulmonary disease; IQR: interquartile range; NCFB: non-cystic fibrosis bronchiectasis; NTM: non-tuberculous mycobacteria; TB: tuberculosis
P values in bold are significant

Table 4. Hazard ratios of Bronchiectasis Severity Index (BSI) severity grades

BSI	Hazard ratios	95% confidence interval	P value
Grade 1: Mild	Reference	Reference	Reference
Grade 2: Moderate	1.682	0.188–15.052	0.642
Grade 3: Severe	14.844	1.929–114.235	0.01

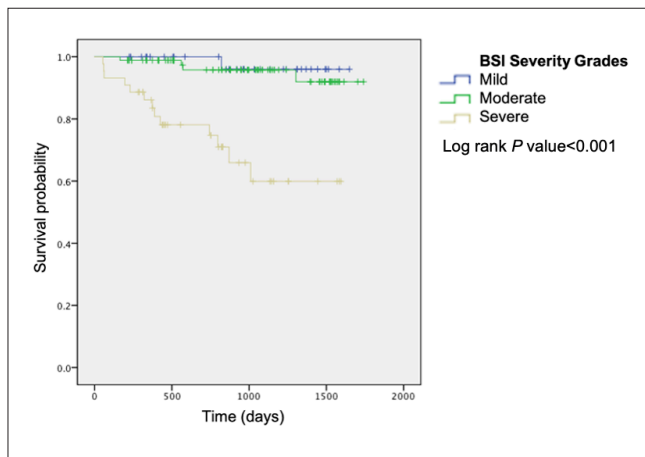


Fig. 1. Kaplan-Meier survival curves according to Bronchiectasis Severity Index (BSI) severity grades.

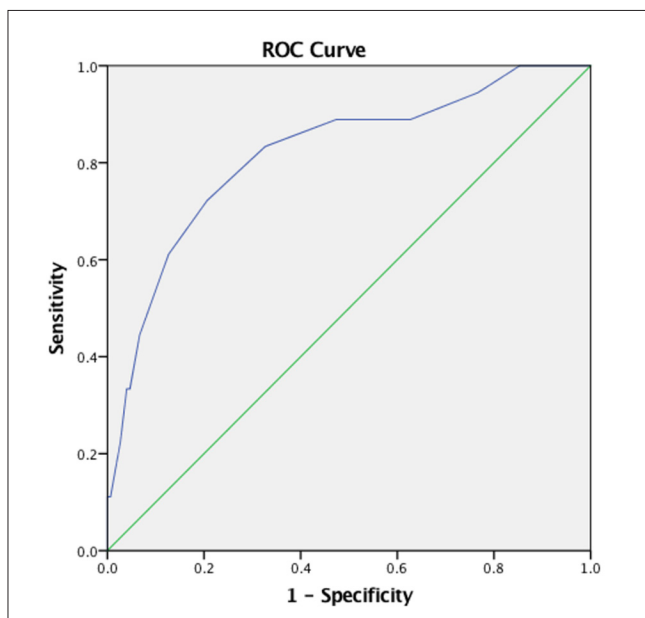


Fig. 2. Receiver operating characteristic curve for mortality according to Bronchiectasis Severity Index score.
ROC: receiver operating characteristic

demonstrated a lower survival at the median overall follow-up period of 2.4 years for subjects with severe BSI grade as compared to those with mild or moderate grades ($P < 0.001$) (Fig. 1). The receiver operating characteristic curve for mortality according to BSI score demonstrates an area under the curve of 0.818 (Fig. 2).

DISCUSSION

We observed a disproportionate Chinese majority and female predominance in our study, which is one of the first reports describing characteristics of NCFB patients in a multiethnic Southeast Asian population.

Most patients had normal spirometry patterns, and fewer than 2 exacerbations per year. There was a high prevalence of NTM, *P. aeruginosa* and *K. pneumonia* infection. Over half the patients had a history of haemoptysis, and approximately one-fifth of the patients had clinically significant haemoptysis. There is a higher proportion of NCFB among Chinese (87.5%) compared to other races and this is out of proportion to Singapore's ethnic distribution (74.3% Chinese, 13.5% Malays and 9.0% Indians, according to Singapore Department of Statistics' 2020 figures). The reason for this is unknown but postulated to be due to differences in disease aetiology and sputum microbiology.²⁶ We are unable to confirm these findings due to the small number of non-Chinese patients in our cohort.

Female preponderance of NCFB has been widely described in various global registries including the UK, US and Australia.^{10,13,18} Reasons postulated for this sex distribution include the smaller conducting airways in females, as well as the effects of oestrogen and progesterone on mucociliary clearance.²⁷ However, the sex ratio is reversed in TB-endemic countries like China, India and Pakistan.^{6,14,16} In these countries, TB is a significant cause of NCFB and is more common among men.²⁸ NCFB patients in India and Pakistan are also younger—83.1% of Pakistani patients are younger than 60, and the mean age of diagnosis in India was 56 (41–66)—compared to the European cohort with mean age of 67 (57–74).^{14,16} Factors such as the incidence of childhood pulmonary infections (including TB) and poor access to healthcare may contribute to the earlier onset, higher burden and increased severity of the disease.^{29,30} Southeast Asia accounts for over 40% of the global TB incidence.³¹ Despite a high incidence of TB in Singapore (47 per 100,000 population), the overall mean age of diagnosis of NCFB remains comparable to the UK and US.^{10,18} In the current study, 40% of the NCFB patients with known aetiology were due to previous TB infection. Idiopathic and post-TB bronchiectasis were equally common as aetiology of NCFB among male patients. On the other hand, the proportion of female patients with idiopathic bronchiectasis was thrice that of post-TB bronchiectasis. The higher frequency of male patients with post-TB bronchiectasis is likely due to a significantly higher TB prevalence among the men in Singapore (70.7% vs 29.3%).³²

Other significant sex differences observed were smoking status and sputum microbiology. Most female NCFB patients were never-smokers (90.7%), compared to 46.2% in males ($P < 0.001$). This sex difference

in smoking habits is similarly reflected in the larger proportion of COPD (11.1% vs 2.6%, $P=0.023$), and obstructive spirometry (20.8% vs 5.9%, $P=0.009$) seen in the male NCFB patients. The frequency of positive microbiology for NTM was significantly higher among females (55.0% vs 27.5%, $P=0.001$).

The spirometry findings of the present study contradict previous reports that NCFB patients often have an obstructive lung pattern.³³ Proposed mechanisms for the airway obstruction include collapse of the major airways during expiration, bronchial wall thickening, presence of endobronchial secretions and obliterative bronchitis.³⁴ However, a high proportion of smokers in some older studies might have contributed to the high frequency of airway obstruction observed. Other studies assessing lung function in NCFB patients have reported that obstructive and restrictive spirometry were both associated with increased disease severity and hospitalisation rate.³³ The high proportion of patients with normal spirometry and fairly preserved FEV1 may signal better clinical outcomes in our NCFB population.

Nearly half the NCFB patients (46.3%) in our study had positive NTM culture, which is higher than the NTM prevalence (11.2%) reported in China.⁶ Our NTM prevalence is more comparable to that of the US, which was 63% with a predominance of *M. avium* complex (37%).¹⁰ In our population, *M. abscessus* was the most common mycobacterium species isolated (18.6%). The most common bacterium isolated in our population is *P. aeruginosa* (22.3%), which is comparable to other NCFB registries.^{10,14-16} Notably, *K. pneumoniae* is not widely reported in the microbiological characteristics of patients in US or European registries, and its overall incidence appears to be low. In our study, we observed an incidence of 10.2%, comparable to the Thai (14%) and Korean (22.4%) cohorts.^{11,12} *K. pneumoniae* is associated with less mortality, exacerbations and hospitalisation rates than *P. aeruginosa*.³⁵⁻³⁷ The lung microbiome composition appears to affect response to anti-inflammatory therapy. In the erythromycin group in the Bronchiectasis and Low-dose Erythromycin Study (BLESS), patients with a *Haemophilus*-dominated microbiome had fewer exacerbations compared to those with *Pseudomonas*-dominated microbiome.³⁸ There may be a geographical or racial predisposition that affects colonisation and further research into the bronchiectasis microbiome is imperative.

Interestingly, more than half of our patients (54.7%) had a history of haemoptysis, 40% of whom were

clinically significant. This is significantly higher than the prevalence of 20.9% and 23% that were reported in studies from Pakistan and the US, respectively.^{10,16} In bronchiectasis, chronic airway inflammation causes hypertrophy and tortuosity of the vessels accompanying the airways.^{39,40} Haemoptysis occurs due to the rupture of these vessels, usually in the setting of an acute infection or exacerbation. Despite our understanding of the pathophysiology, it remains uncertain why haemoptysis occurs more frequently in some patients but not others. We did not find an association between haemoptysis and the presence of hypertrophied bronchial arteries on computed tomography imaging in our population, which may suggest the presence of other factors affecting the development of haemoptysis. Other factors associated with haemoptysis in NCFB include the use of inhaled anticholinergics and short-acting beta agonists,⁴¹ presence of cystic pattern of on CT⁴² and post-TB aetiology.³⁷ However, these findings were not replicated in our study.

Lower BMI, smoking status, history of exacerbations, modified Reiff scores and radiological severity were associated with mortality in our study, which is in keeping with results from previous studies.^{23,43} BSI scores were calculated and showed to be a good predictor of mortality, with an area under the curve (AUC) value of 0.818 that was similar to the derivation and validation cohorts of the original study (AUC of 0.80 and 0.81–0.84, respectively). The Kaplan-Meier survival curve and hazard ratios showed a significant difference in mortality when comparing patients with mild (BSI 0–4) and severe (BSI >9) bronchiectasis. Our results validate the use of BSI as a prognostic indicator in our local population. The inclusion of further markers of radiological severity such as a composite of lobar severity grades as we have done in our study may further refine the accuracy and utility of such clinical scores.

The limitations of this study include the relatively small cohort of patients, the potential selection bias due to recruitment of participants from a single study centre, and incomplete data, as in most real-world clinical studies. A multicentre study would likely provide more comprehensive information about characteristics of the NCFB population in Singapore. Causal inference between the variables analysed should also be made with caution given the relatively short follow-up period. The labels of post-infectious and post-TB aetiologies are based on self-reported histories of pulmonary infections or TB, and may have an element of recall bias. However, as far as possible,

objective evidence of previous pulmonary TB infection was documented. Similarly, there was a degree of reliance on self-reporting of bronchiectasis exacerbations and haemoptysis. We were unable to perform analysis for respiratory-specific mortality as the cause of death was not available for a significant proportion of the non-survivors. There may be interpretation bias introduced as the radiological assessment was performed by a sole radiologist. The strengths of the study include its prospective nature, and a broad inclusion criteria to reflect real-world clinical practice.

CONCLUSIONS

The NCFB population in Singapore has a female and Chinese predominance. Sex differences were found and haemoptysis was common. The BSI score is a useful predictor of mortality in our population. Future research and longitudinal data should focus on better understanding of the Asian bronchiectasis microbiome and cause of haemoptysis in NCFB.

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