Evaluation of disease severity in bronchiectasis using impulse oscillometry

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ABSTRACT Although the diagnostic value of impulse oscillometry (IOS) in bronchiectasis for the differential diagnosis of healthy subjects has been researched, the usefulness of each IOS parameter for predicting disease severity in bronchiectasis has not been thoroughly investigated. In addition, the usefulness of IOS in patients with nontuberculous mycobacteria (NTM) infection has not been reported. This study aimed to determine the predictive significance of respiratory impedance and detect the other most significant IOS parameters for predicting disease severity in bronchiectasis patients and to validate the usefulness of IOS in patients with NTM infection.

A total of 206 patients with bronchiectasis who attended clinics at the National Hospital Organization Osaka Toneyama Medical Center were included. Chest high-resolution computed tomography, spirometry and IOS were performed. Hospital admissions, mortality and disease severity indices for bronchiectasis (Bronchiectasis Severity Index (BSI), FACED, and E-FACED scores) were calculated to assess disease severity. The patients were divided into subgroups with and without NTM infection, and subgroup analyses were performed.

Respiratory reactance, especially resonant frequency (f_{res}), correlated with both BSI and FACED score better than respiratory resistance. Inspiratory but not expiratory impedance was strongly correlated with BSI, FACED and E-FACED scores. Inspiratory f_{res} was the most useful predictor, increasing as the disease became more severe. The usefulness of IOS was almost equivalent in patients both with and without NTM infection.

Inspiratory reactance measured by IOS is useful for estimating disease severity in bronchiectasis. Inspiratory f_{res} best predicts disease severity in bronchiectasis patients both with and without NTM infection.

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Inspiratory reactance measured by impulse oscillometry may be useful for estimating disease severity of bronchiectasis. Inspiratory f_{res} can be used to evaluate severity in the disease both with and without NTM infection. https://bit.ly/3fvG0Rn

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Introduction

Bronchiectasis is a chronic respiratory disease. Its symptoms include recurrent cough, sputum and respiratory infections [1]. The host-mediated inflammatory response to foreign material and bacteria induces tissue damage and subsequent bronchiectasis, which is associated with abnormal mucus clearance and bacterial colonisation [2, 3]. In particular, *Pseudomonas aeruginosa* colonisation (*Pseudomonas* colonisation) is one of the independent predictors of poor prognosis [4–7]. Although there was no accepted definition of the disease severity of bronchiectasis, Bronchiectasis Severity Index (BSI), FACED and E-FACED scores have been developed [6, 8, 9]. These are novel scores with great accuracy that combine spirometry and the Medical Research Council (MRC) dyspnoea scale, which can evaluate various clinical outcomes, including hospital admissions and mortality [6, 8, 10]. However, the scores are difficult to obtain from patients at the first visit and without regular visits because they require several sputum cultures to confirm bacterial colonisation and the BSI and E-FACED score further require histories of exacerbations and hospital admissions. Therefore, pulmonary function tests (PFTs), including spirometry and impulse oscillometry (IOS), could remain important for evaluating disease severity in bronchiectasis effortlessly.

IOS, which involves measurements of within-breath changes in respiratory impedance, measures respiratory resistance (R_{rs}) and respiratory reactance (X_{rs}). R_{rs} represents the sum of the airway resistance and viscous resistance of lung and thoracic tissue [11], while X_{rs} reflects the dynamic elastance and inertia of the respiratory system [12]. Measurement of respiratory impedance by IOS is less time-consuming and technically easier to perform than spirometry because it is measured at rest under conditions of minimal respiratory effort [13]. In addition, IOS can show complementary information of the lungs and might be useful in the assessment of respiratory mechanics [14].

Regarding bronchiectasis, the majority of reports for IOS are in paediatric cystic fibrosis (CF) populations, with reports of the disease in adults being rare [13, 15]. Guan *et al.* [16] first reported the usefulness of IOS as a tool for differentiating bronchiectasis patients from healthy subjects in adults. The study revealed that an increased number of abnormal IOS parameters indicates poor clinical conditions [16]. They also demonstrated that IOS had a high diagnostic value for mild-to-moderate bronchiectasis [17]. In particular, IOS parameters that indicate small airways were reportedly useful for the diagnosis [17]. Despite these preceding studies, the usefulness of IOS for evaluating the disease severity of bronchiectasis in adults has never been thoroughly investigated. In addition, the usefulness of IOS for patients with nontuberculous mycobacteria (NTM) infection has never been reported. The information obtained from IOS might be a useful tool for predicting the clinical outcomes of bronchiectasis adult patients and assessing the respiratory physiology of bronchiectasis.

The objectives of the present study were as follows: 1) to investigate the usefulness of IOS as a tool for predicting two important clinical outcomes in patients with bronchiectasis: hospital admissions and mortality; 2) to identify any IOS parameters significant for predicting hospital admissions, mortality, and the severity indices associated with bronchiectasis; and 3) to assess the potential relationships between NTM infection and IOS parameters, hospital admissions and mortality in bronchiectasis patients.

Methods

Subjects

A total of 405 Japanese patients with bronchiectasis who attended clinics at the National Hospital Organization (NHO) Osaka Toneyama Medical Center between February 2013 and October 2019 were screened in this study. The patients were diagnosed with bronchiectasis based on their clinical symptoms (cough, purulent sputum and haemoptysis) and chest high-resolution computed tomography (HRCT) findings. Patients who did not undergo spirometry or IOS within 3 months from the time of diagnosis were excluded. Moreover, patients were excluded if they had CF, malignant tumours, severe heart diseases, severe cerebral diseases or primary diagnoses of pulmonary fibrosis/sarcoidosis with secondary traction bronchiectasis. The qualified 206 patients underwent the examinations and evaluations described in the following sections.

Study design

Respiratory impedance was measured in all patients using IOS, and spirometry was performed on the same day. Short-acting β_2-agonists were not used for at least 12 h before tests in all patients. Long-acting β_2-agonists (LABAs) and long-acting antimuscarinic agents (LAMAs) were not withdrawn before the measurement of PFTs. Chest HRCT scans were conducted with 1-mm section thickness and within 12 months from the IOS and spirometric measurements. Bacterial colonisation was defined as the presence of at least two sputum of the same pathogen at least 3 months apart in a 1-year period [18]. The patients were divided into a subgroup with NTM infection (NTM subgroup) and without NTM infection (non-NTM subgroup) based on the presence of symptoms, radiological abnormalities, and microbiological cultures that excluded other potential aetiologies [19]. Correlations between IOS parameters, spirometric parameters and the disease severity indices (BSI, FACED and E-FACED scores) were analysed. The IOS parameters were then compared with the disease severity indices for their usefulness in predicting disease severity. This comparison was made regarding the total patients, the NTM subgroup and the non-NTM subgroup. The Institutional Review Board of the NHO Osaka Toneyama Medical Center approved the study protocols and chose an opt-out system for obtaining patients' informed consent (approval number: TNH-2019042).

Measurement of respiratory impedance using IOS

Respiratory impedance was measured at rest with broadband IOS using a commercially available device (Mostgraph-01, Chest M.I. Co., Ltd., Tokyo, Japan). The methods were performed according to the standard recommendations [11]. Partitioned (inspiratory and expiratory) and average IOS parameters were measured. As indicators of the frequency dependence of R_{rs}, R_{rs} at 5 and 20 Hz (R_5 and R_{20}, respectively) and the difference between these (R_5–R_{20}) were used. In addition, X_{rs} at 5 Hz (X_5), resonant frequency (f_{res}) and low-frequency reactance area (ALX) were used as indicators of respiratory reactance. f_{res} indicates the point at which X_{rs} crosses zero and elasticity and inertia balance each other, and ALX is defined as the integral of X_5 to f_{res} [14].

Spirometry

The patients underwent spirometry using the CHESTAC 8800 spirometer (Chest MI, Inc., Tokyo, Japan) according to the recommendations of the American Thoracic Society [20]. The predicted vital capacity (VC) and forced expiration volume in 1 s (FEV_1) were calculated according to the formula for Japanese subjects developed by the Japanese Respiratory Society [21].

The BSI, FACED and E-FACED scores

The BSI, FACED and E-FACED scores were calculated for all patients in the present study. All indices included age, MRC/modified MRC dyspnoea scale, FEV_1% predicted, number of pulmonary lobes with bronchiectasis and *Pseudomonas* colonisation [6, 8, 9]. The BSI incorporated body mass index (BMI), exacerbations, hospital admissions and colonisation with other organisms, in addition to the variables described above, and was calculated by summing the scores of each. The final BSI score ranged from 0 to 26, with a score between 0 and 4 indicating a mild case of the disease, between 5 and 8 indicating a moderate case, and 9 or more indicating a severe case [6]. The FACED score incorporated the five abovementioned variables and was calculated by summing the scores of each. The final FACED score ranged from 0 to 7, with a score between 0 and 2 indicating a mild case of the disease, between 3 and 4 indicating a moderate case, and between 5 and 7 indicating a severe case [8]. The E-FACED score was calculated by adding the score of hospital admissions to the FACED score. The final E-FACED score ranged from 0 to 9, with a score between 0 and 3 indicating a mild case of the disease, between 4 and 6 indicating a moderate case, and between 7 and 9 indicating a severe case [8, 9].

Assessment of disease severity of bronchiectasis

The disease severity of bronchiectasis was assessed according to hospital admissions and mortality. Exacerbations were defined as the patients' status that requires antibiotic therapy, (*i.e.* the presence of increased sputum purulence, increased sputum volume or change in viscosity) and increased pulmonary symptoms [22]. Unscheduled hospital admissions due to exacerbations of bronchiectasis were recorded [22]. Exacerbations, hospital admissions due to exacerbations and survival status were measured for all patients within 4 years from their first visit. In cases of mortality, cause of death was determined and assigned as bronchiectasis related or unrelated [6]. All the data were collected by individual case review.

Statistical analysis

The Mann–Whitney *U*-test, t-test and Chi-squared test were used for comparison of IOS parameters among the two subgroups and necessary sample size was calculated to present the statistical power. The Kruskal–Wallis test was used for comparison of IOS parameters among patients with mild-to-severe bronchiectasis stratified by the BSI, FACED and E-FACED scores. Spearman's rank correlation coefficient and univariate analyses were used for bivariate correlation analysis between IOS parameters, spirometric parameters, the BSI, FACED and E-FACED scores. Multiple stepwise linear regression analysis was performed to detect IOS parameters that were significant determinants of the BSI, FACED and E-FACED scores. After detecting the most significant IOS parameters, the receiver operating characteristic (ROC) curves of these IOS parameters were compared to FEV_1, the BSI, FACED and E-FACED scores for predicting hospital admissions and mortality using the DeLong test [23]. Univariate and multivariate analyses and the Mann–Whitney *U*-test were used for subgroup and interaction analyses. For all analyses,

TABLE 1 Patients' baseline characteristics (n=206)

Parameter	Bronchiectasis patients	
Age years	70.55±11.09	24 to 89
Male/female n	64/142	
Height cm	157.3±8.2	134.7 to 175.9
Weight kg	49.6±10.0	30.0 to 81.0
BMI kg·m^{-2}	19.95±3.18	13.0 to 35.3
Never-smokers	142 (68.93)	
Medications		
LAMA	33 (16.02)	
LABA	54 (26.21)	
ICS	50 (24.27)	
Theophylline	15 (7.28)	
Macrolides	140 (67.96)	
Mucolytics	129 (62.62)	
Underlying cause		
MAC	86 (41.75)	
Idiopathic/post-infective	74 (35.92)	
Previous TB	17 (8.25)	
Other NTM	12 (5.83)	
Rheumatoid arthritis	11 (5.34)	
ABPA	3 (1.46)	
Others	3 (1.46)	

Data are presented as mean±SD along with the minimum and maximum values (right hand column) or n (%), unless otherwise stated. BMI: body mass index; LABA: long-acting β_2-agonist; LAMA: long-acting muscarinic antagonist; ICS: inhaled corticosteroid; MAC: *Mycobacterium avium* complex; TB: tuberculosis; NTM: nontuberculous mycobacteria; ABPA: allergic bronchopulmonary aspergillosis.

TABLE 2 Clinical characteristics of bronchiectasis patients (n=206)

Parameter	Bronchiectasis patients	
Spirometry		
FEV_1 L	1.59±0.68	0.53 to 3.75
FEV_1 % predicted	75.2±25.4	18.2 to 131.1
FEV_1/FVC %	70.9±15.0	27.6 to 100.0
VC L	2.26±0.85	0.64 to 4.65
VC %	80.1±22.2	22.3 to 121.7
Three or more exacerbations per year	40 (20.93)	
Hospital admission within 4 years	91 (44.17)	
Mortality within 4 years	20 (9.71)	
MRC dyspnoea score	2.38±1.41	
***Pseudomonas* colonisation**	54 (26.21)	
Colonisation with other organisms	143 (69.42)	
Pulmonary lobes with bronchiectasis or cystic bronchiectasis n	3.32±1.33	
Bronchiectasis Severity Index	10.18±5.42	
Mild (0–4)	33 (16.02)	
Moderate (5–8)	53 (25.73)	
Severe (>9 or more)	120 (58.25)	
FACED score	2.76±1.78	
Mild (0–2)	90 (43.69)	
Moderate (3–4)	84 (40.78)	
Severe (5–7)	32 (15.53)	
E-FACED score	3.15±2.17	
Mild	126 (61.17)	
Moderate	61 (29.61)	
Severe	19 (9.22)	

Data are presented as mean±SD along with the minimum and maximum values (right hand column) or n (%), unless otherwise stated. FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; VC: vital capacity; MRC: Medical Research Council; *Pseudomonas* colonisation: *Pseudomonas aeruginosa* colonisation.

TABLE 3 Baseline characteristics of patients with and without nontuberculous mycobacteria (NTM) infection (n=206)

Parameter	Non-NTM subgroup (n=108)	NTM subgroup (n=98)	p-value
Age years	70.74±12.12	70.34±9.88	0.7947
Male/female n	43/65	21/77	0.0043
BMI kg·m^{-2}	20.25±3.42	19.62±2.87	0.1542
VC %	75.53±23.49	85.21±19.55	0.0016
FEV_1 % predicted	70.92±27.34	79.95±22.27	0.0104
Three or more exacerbations per year	21 (19.44)	19 (19.39)	0.9919
Hospital admission within 4 years	53 (49.07)	38 (38.78)	0.1385
Mortality within 4 years	14 (12.96)	6 (6.12)	0.0986
MRC dyspnoea score	2.65±1.48	2.08±1.27	0.0038
***Pseudomonas* colonisation**	44 (40.74)	10 (10.20)	<0.0001
Colonisation with other organisms	47 (43.52)	98 (100.00)	<0.0001
Pulmonary lobes with bronchiectasis or cystic bronchiectasis	3.39±1.37	3.24±1.30	0.4405
Bronchiectasis Severity Index	11.05±5.68	9.23±4.99	0.0163
Mild (0–4)	15 (13.89)	18 (18.37)	0.1370
Moderate (5–8)	23 (21.30)	30 (30.61)	
Severe (>9 or more)	70 (64.81)	50 (51.02)	
FACED score	3.17±1.85	2.31±1.59	0.0005
Mild (0–2)	38 (35.19)	52 (53.06)	0.0049
Moderate (3–4)	46 (42.59)	38 (38.78)	
Severe (5–7)	24 (22.22)	8 (8.16)	
E-FACED score	3.56±2.25	2.69±2.01	0.0043
Mild	57 (52.78)	69 (70.41)	0.0228
Moderate	37 (34.26)	24 (24.49)	
Severe	14 (12.96)	5 (5.10)	

Data are presented as mean±SD or n (%), unless otherwise stated. BMI: body mass index; VC: vital capacity; FEV_1: forced expiratory volume in 1 s; MRC: Medical Research Council; *Pseudomonas* colonisation: *Pseudomonas aeruginosa* colonisation.

p-values <0.05 were considered statistically significant. All statistical analyses were performed using EZR version 1.38 (based on R version 3.5.2) and R commander version 2.5-1, Saitama, Japan; [24].

Results

Baseline characteristics

Among the 206 patients included in the present study, 98 patients were in the NTM subgroup, while 108 were in the non-NTM subgroup. Many of the patients had been treated with LAMAs, LABAs, inhaled corticosteroids (ICSs), theophylline, macrolides and/or mucolytics (table 1). Overall, 20 mortalities (9.71%) and 44 hospital admissions (44.17%) were recorded within 4 years of the first patients' initial visits. The use ratio of macrolides was high in this study compared with previous studies because the present study included patients with NTM colonisation or infection [6, 8, 16]. The average VC and FEV_1/forced vital capacity (FVC) were lower than VC (male, 3.37 L; and female, 2.75 L) and FEV_1/FVC (male, 77.7%; and female, 77.6%) of healthy Japanese subjects (table 2, [21]). The baseline inspiratory IOS parameters indicated overall lower SD compared with expiratory parameters (supplementary table 1).

In the NTM subgroup, the ratio of females and FEV_1% predicted were higher than in the non-NTM subgroup. The MRC dyspnoea scale, *Pseudomonas* colonisation, BSI, FACED and E-FACED scores were all lower than in the non-NTM subgroup (table 3). The frequency distributions of disease severity stratified by the BSI were not significantly different, but the mild disease ratio stratified by the FACED and E-FACED scores was higher in NTM subgroup (table 3). The difference was probably due to the scoring methods of age and *Pseudomonas* colonisation because the BSI weights these scores heavier than the FACED and E-FACED scores [6, 8, 9]. There was no significant difference between the NTM and non-NTM subgroups for age, BMI, exacerbations, pulmonary lobes with bronchiectasis or cystic bronchiectasis, hospital admissions (38.78% in the NTM subgroup and 49.07% in the non-NTM subgroup; p=0.1385) or mortality (6.12% in the NTM subgroup and 12.96% in the non-NTM subgroup; p=0.0986; table 3). Given that the necessary sample sizes required to present the statistical power were 768 for

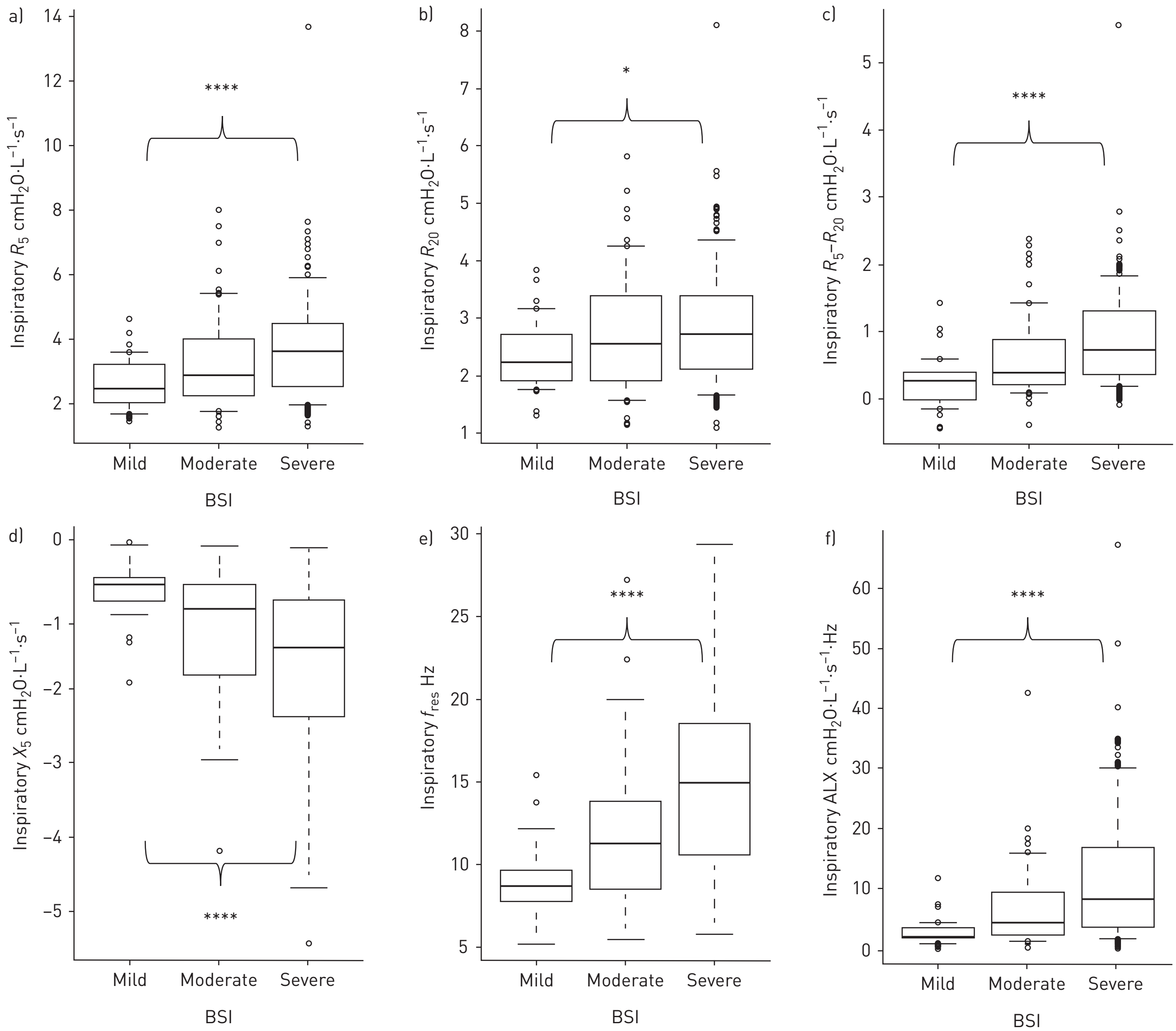

FIGURE 1 Results of inspiratory impedance at rest stratified by the Bronchiectasis Severity Index (BSI) (n=206). a) inspiratory respiratory system resistance at 5 Hz (R_5), b) inspiratory respiratory system resistance at 20 Hz (R_{20}), c) inspiratory R_5–R_{20}, d) inspiratory respiratory system reactance at 5 Hz (X_5), e) inspiratory resonant frequency (f_{res}), and f) inspiratory low-frequency reactance area (ALX). *: p<0.05; ****: p<0.0001, as measured by the Kruskal–Wallis test.

hospital admissions and 636 for mortality, the insignificant difference of hospital admissions and mortality between the two subgroups might have been attributed to the small number of subjects.

Correlations of IOS parameters with spirometric parameters

VC, FVC and even FEV_1 correlated the strongest with respiratory reactance (supplementary table 2). In addition, respiratory reactance correlated with FEV_1/FVC stronger than respiratory resistance. This showed that respiratory reactance reflected restrictive ventilation deficiency and airflow obstruction in bronchiectasis.

Identification of IOS parameters relevant to the BSI, FACED and E-FACED scores

Respiratory reactance had a stronger correlation than respiratory resistance with the BSI, FACED and E-FACED scores (supplementary tables 3–5). Among resistance parameters, R_{20} had the weakest correlation and expiratory R_{20} showed no apparent correlation. R_5–R_{20} had the strongest correlation of all the resistance parameters; however, even this correlation was weaker than respiratory reactance. Therefore, respiratory reactance rather than resistance correlated with the disease severity indices in bronchiectasis patients.

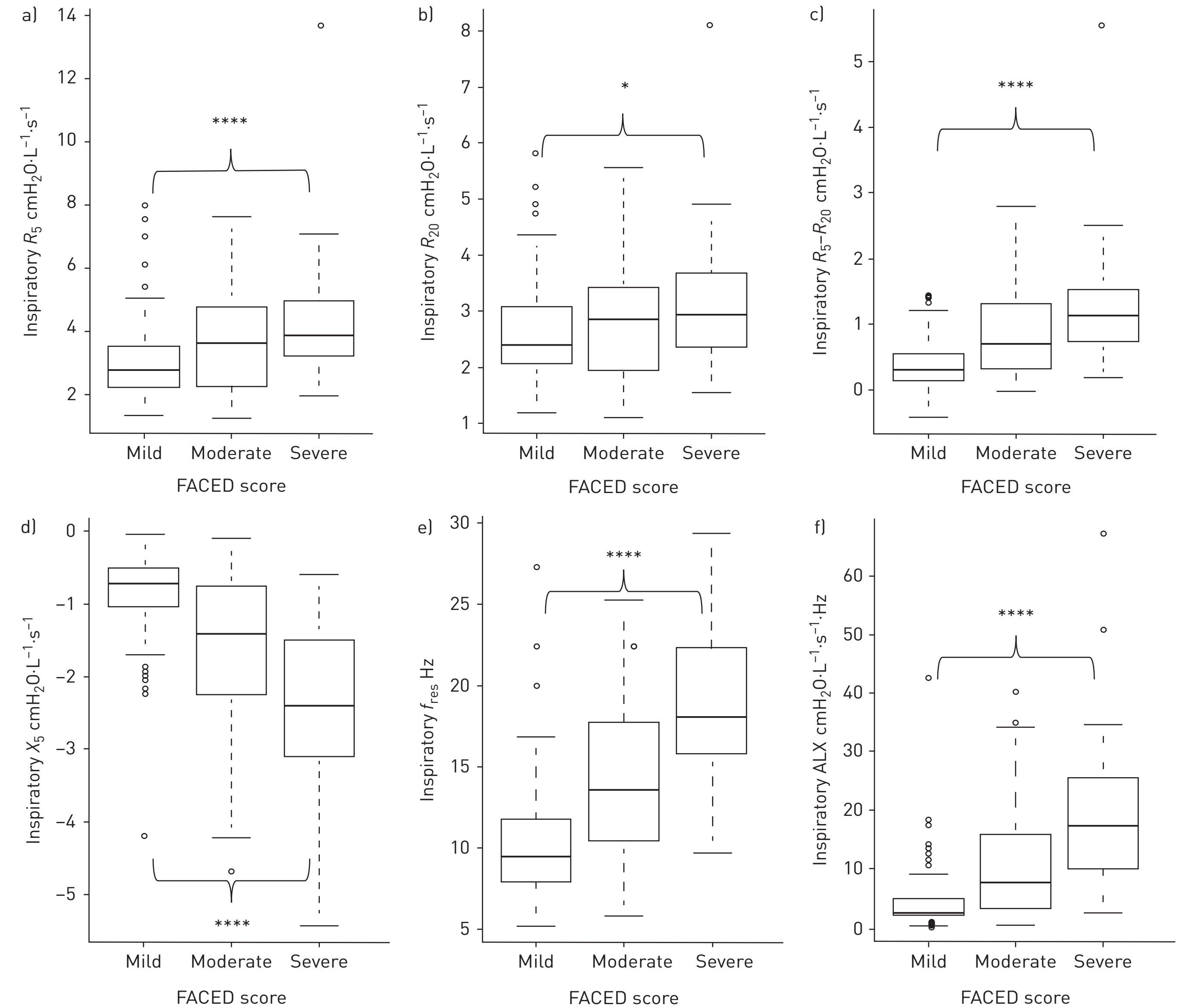

FIGURE 2 Results of inspiratory impedance at rest stratified by the FACED score (n=206). a) inspiratory respiratory system resistance at 5 Hz (R_5), b) inspiratory respiratory system resistance at 20 Hz (R_{20}), c) inspiratory R_5–R_{20}, d) inspiratory respiratory system reactance at 5 Hz (X_5), e) inspiratory resonant frequency (f_{res}), and f) inspiratory low-frequency reactance area (ALX). *: p<0.05; ****: p<0.0001, as measured by the Kruskal–Wallis test.

Regarding reactance parameters, f_{res} had the best correlation with all the disease severity indices (supplementary tables 3–5). Moreover, inspiratory but not expiratory impedance was correlated with both scores. Inspiratory IOS parameters stratified by the BSI and FACED and E-FACED scores are shown in figures 1 and 2, and supplementary figure 1. Multiple stepwise linear regression analyses also identified inspiratory f_{res} as the most significant determinant of the disease severity indices (supplementary table 6). Overall, inspiratory f_{res} was the most significant determinant of the disease severity indices.

Detection of IOS parameters correlated with hospital admissions and mortality

The ROC curves for predicting hospital admissions and mortality in bronchiectasis patients indicated that the area under curve (AUC) of respiratory reactance was higher than that of respiratory resistance (supplementary tables 7 and 8). Of note, the AUC of inspiratory f_{res} was the highest of all the reactance parameters (AUC=0.672 for hospital admissions and AUC=0.781 for mortality). The cut-off values of inspiratory f_{res} for predicting hospital admissions and mortality were 13.120 and 14.180, respectively (p<0.0001). Inspiratory rather than expiratory IOS parameters indicated higher AUC for predicting both hospital admissions and mortality, a trend similar to that shown in the analyses of the relationship

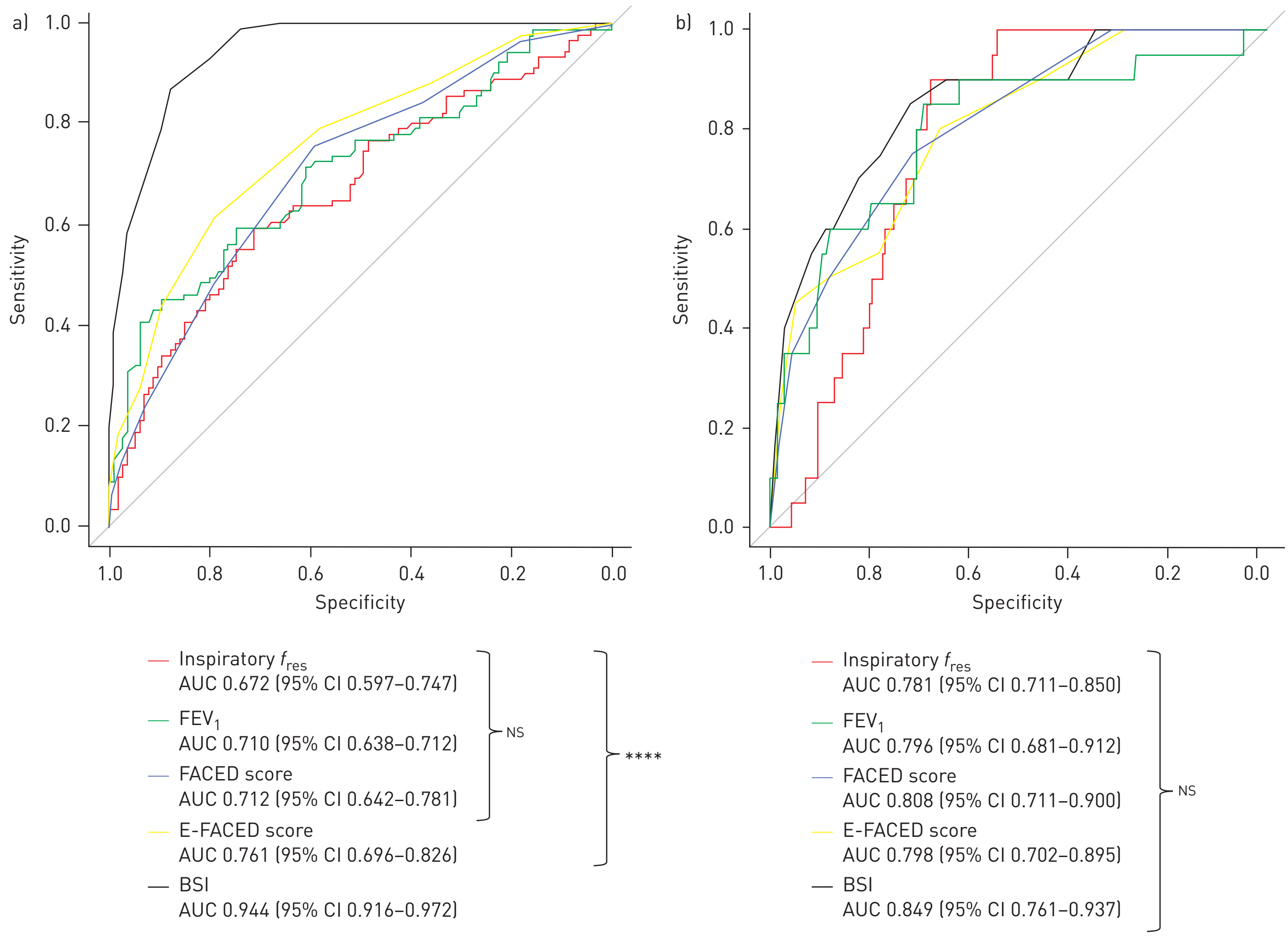

FIGURE 3 Receiver operating characteristic (ROC) curves for predicting hospital admissions and mortality (n=206). a) ROC curves for predicting hospital admissions within 4 years. b) ROC curves for predicting mortality within 4 years. AUC: area under curve; BSI: Bronchiectasis Severity Index; FEV$_1$: forced expiratory volume in 1 s; f_{res}: resonant frequency; NS: nonsignificant. ****: p<0.0001 as measured by the DeLong test.

between respiratory impedance and the disease severity indices. In addition, no treatment has significantly affected the correlation of inspiratory f_{res} with hospital admissions and mortality (supplementary table 9). Given these analyses, inspiratory f_{res} was identified as the most significant determinant of disease severity in bronchiectasis.

Comparison of the predictive usefulness of inspiratory f_{res}, BSI, FACED and E-FACED scores

No apparent difference was observed between inspiratory f_{res} (AUC=0.672 for hospital admissions and AUC=0.781 for mortality) and FACED score (AUC=0.712 for hospital admissions and AUC=0.808 for mortality, figure 3). Thus, the predictive usefulness of inspiratory f_{res} was almost equivalent to FACED score. Although the AUC for hospital admissions was greater for BSI (AUC=0.944; p<0.0001), the AUC of inspiratory f_{res} and BSI for mortality (AUC=0.849) were not significantly different (p=0.1368).

Validation of inspiratory f_{res} for predicting disease severity in the NTM subgroup

Between the subgroups, reactance but not resistance parameters were significantly different (figure 4). In particular, in the NTM subgroup, inspiratory f_{res} and ALX were lower and X_5 was less negative (all p-values <0.05), indicating the better reactance of this subgroup. The AUC for predicting hospital admissions and mortality were almost equivalent between the NTM and non-NTM subgroups (table 4). The results demonstrated that inspiratory f_{res} was useful for predicting disease severity in bronchiectasis patients with NTM infection.

Although the predictive usefulness was almost equivalent, the cut-off values of inspiratory f_{res} for predicting hospital admissions and mortality were lower in the NTM subgroup (10.500 for hospital

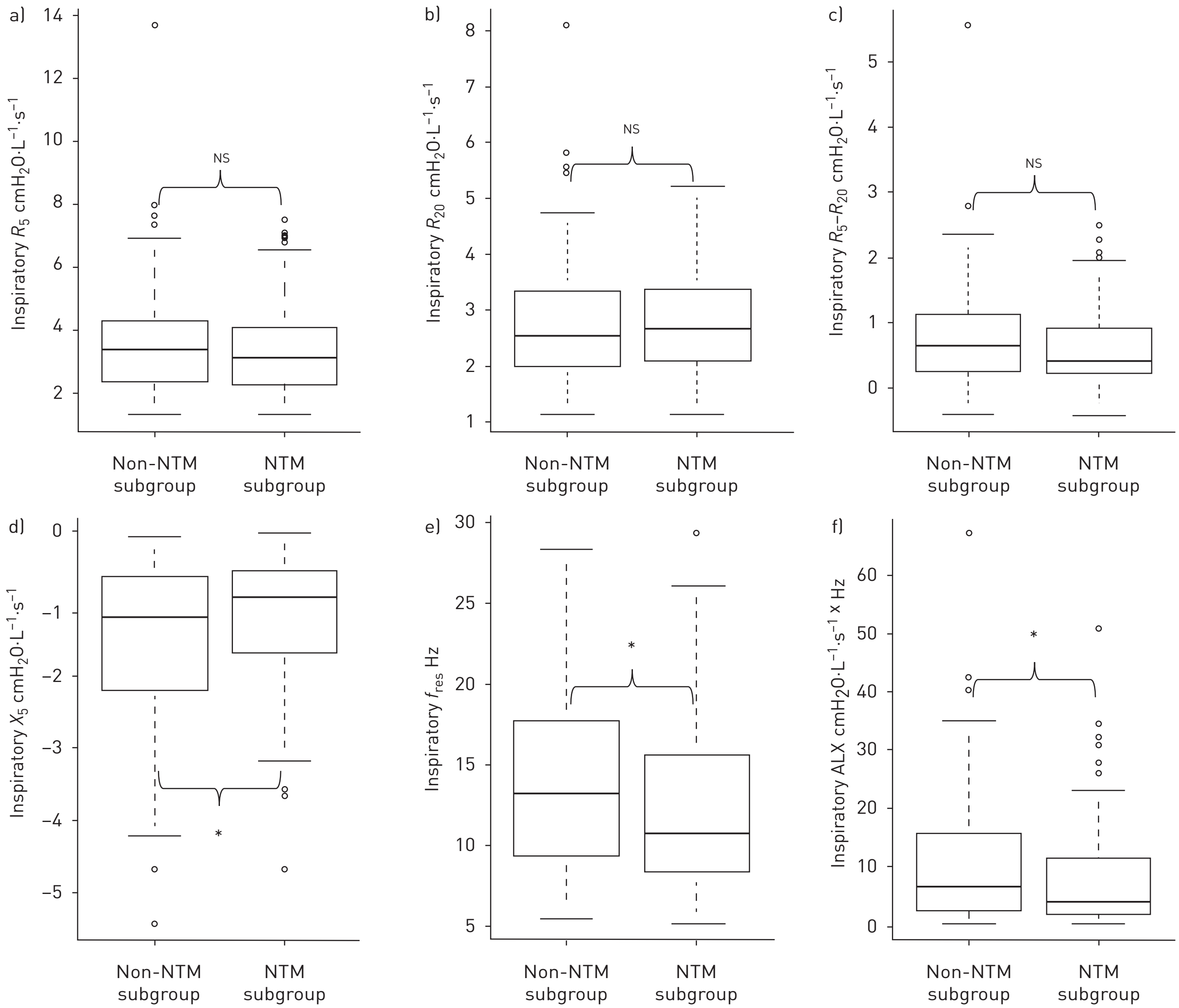

FIGURE 4 Results of inspiratory impedance at rest stratified by nontuberculous mycobacteria (NTM) infection (n=206). a) inspiratory respiratory system resistance at 5 Hz (R_5), b) inspiratory respiratory system resistance at 20 Hz (R_{20}), c) inspiratory R_5–R_{20}, d) inspiratory respiratory system reactance at 5 Hz (X_5), e) inspiratory resonant frequency (f_{res}), and f) inspiratory low-frequency reactance area (ALX). NTM subgroup (n=98) and non-NTM subgroup (n=108). *: p<0.05 as measured by the Mann–Whitney *U*-test.

TABLE 4 Receiver operating characteristic curve of inspiratory resonant frequency in patients with or without nontuberculous mycobacteria (NTM) infection for predicting hospital admissions and mortality (n=206)

Subgroup	Area under curve	p-value	95% CI		Cut-off value	Sensitivity	Specificity
			Lower limit	Upper limit			
Hospital admission within 4 years							
NTM subgroup	0.666	0.0185	0.556	0.776	10.500	0.567	0.763
Non-NTM subgroup	0.675	0.0008	0.570	0.779	14.180	0.709	0.642
Mortality within 4 years							
NTM subgroup	0.819	0.0182	0.699	0.939	11.750	0.620	1.000
Non-NTM subgroup	0.732	0.0204	0.635	0.828	14.430	0.617	0.929

NTM subgroup (n=98) and non-NTM subgroup (n=108).

admissions and 11.750 for mortality, and 14.180 for hospital admissions and 14.430 for mortality in the non-NTM subgroup). Given the baseline characteristics of the NTM subgroup that were significantly different from the non-NTM subgroup, sex and *Pseudomonas* colonisation were hypothesised to affect inspiratory f_{res} (table 3). However, only NTM infection, age and pulmonary lobes with bronchiectasis correlated independently with inspiratory f_{res} (supplementary table 10). Hence, the results showed that the cut-off values of inspiratory f_{res} for hospital admissions and mortality could be independently affected by NTM infection.

Discussion

The present study highlights three major findings regarding the usefulness of IOS in bronchiectasis: 1) respiratory impedance measured by IOS, particularly respiratory reactance, is useful for evaluating disease severity; 2) inspiratory but not expiratory impedance is useful for evaluating disease severity; and 3) IOS is useful for evaluating disease severity of bronchiectasis both with and without NTM infection. To the best of our knowledge, this was the largest study that investigates the usefulness of IOS for predicting disease severity in bronchiectasis and the first study that demonstrates the usefulness of IOS in patients with NTM infection.

In bronchiectasis patients, respiratory impedance has been reported to be effective for diagnosis and not to change between convalescence and acute exacerbations [16]. Thus, the present study included bronchiectasis patients regardless of their clinical condition. In addition, it has been demonstrated that respiratory resistance might be an indicator of poorer clinical conditions [16]. In particular, R_5–R_{20}, which is considered to reflect small airway conditions, was reported to be useful for the diagnosis of bronchiectasis [17]. However, no study has yet reported on the usefulness of each IOS parameter for predicting the disease severity and prognosis in patients with bronchiectasis. Given the results of the present study, both respiratory reactance and R_5–R_{20} were demonstrated to be useful for estimating the disease severity, with both statistical and clinical significance. Of note, all the reactance parameters were more useful than the resistance parameters (including R_5–R_{20}) for predicting hospital admissions, mortality and the disease severity indices. Given the correlation of respiratory impedance with spirometric parameters, the usefulness of respiratory reactance might have been attributed to the combined correlations with restrictive ventilation deficiency and airflow obstruction (supplementary table 2). Although, in the present study, IOS and spirometry were not as useful as the BSI for predicting hospital admissions, inspiratory f_{res} and FEV_1 were equally useful as the FACED score as a predictor of hospital admissions and mortality. PFTs, including IOS and spirometry, might be appropriate for monitoring in bronchiectasis because the disease severity indices include variables with small fluctuations (*e.g.* age and *Pseudomonas* colonisation). FEV_1 declines gradually and thus might be preferred for monitoring in bronchiectasis [25]; however, given the effortless measurement, inspiratory f_{res} could be useful as a complementary score for evaluating and monitoring disease severity in bronchiectasis patients.

The present study also found that inspiratory impedance correlated better than expiratory impedance with the disease severity of bronchiectasis. Although the mechanism remains unclear, patients with chronic obstructive pulmonary disease, asthma and interstitial lung disease have also been reported to show wider variation in expiratory impedance [26, 27]. The present study implies that measurement of IOS could be affected by the variation of expiration regardless of patients' aetiology. Therefore, inspiratory impedance might be used when evaluating disease severity in patients with bronchiectasis. However, further investigations are necessary to validate the results and assess the mechanism.

Our results indicate that IOS could be useful for evaluating disease severity in patients with NTM infection, although the cut-off values of inspiratory f_{res} might be different between the NTM and non-NTM subgroups. McDonnell *et al.* [28] reported that patients with right middle-lobe and lingular predominant bronchiectasis have a higher incidence of NTM and a lower BSI and FACED score, suggesting a milder phenotype of bronchiectasis. Moreover, women have additional risk factors for this phenotype, which is attributable to the pulmonary restriction caused by breast tissue or pregnancy [28, 29]. Given the large population with *Mycobacterium avium* complex (MAC), the relatively focal distribution of bronchiectasis on HRCT might have affected the lower cut-off values of inspiratory f_{res} in the NTM subgroup. Further studies to validate the hypothesis and improve the clinical usefulness of IOS in bronchiectasis would be desirable.

The present study had some limitations. First, it was a single-centre investigation, and some selection bias might thus have affected the findings. Second, this study mainly included patients with MAC in the NTM subgroup, and the number of patients with other types of NTM infection was small. Hence, a larger study population would be required to validate the results. Finally, the IOS device (*i.e.* Mostgraph-01), might have affected respiratory impedance, and it is unclear whether the findings of the present study are applicable to other IOS devices.

In conclusion, this study assessed the correlation of IOS parameters with hospital admissions, mortality and the disease severity indices. Inspiratory f_{res} measured by IOS could be useful for estimating the disease severity of bronchiectasis both with and without NTM infection, although the cut-off values might be different in patients with NTM infection. Further investigations of bronchiectasis with and without NTM infection are needed.

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