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BRONCHIECTASIS AND NON-TUBERCULOUS MYCOBACTERIAL INFECTION

Radiologic Characteristics of Non-tuberculous Mycobacteria Infection in Patients with Bronchiectasis

Iya Eisenberg[1] · Alaa Yasin[2] · Leonardo Fuks[3,4,5] · Nili Stein[6] · Walid Saliba[2,6] · Mordechai R. Kramer[4,5] · Yochai Adir[2,7] · Michal Shteinberg[2,7]

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Abstract

Introduction Non-tuberculous mycobacteria pulmonary disease (NTM-pd) commonly complicates bronchiectasis. However, clinical and radiological features of NTM-pd and bronchiectasis are very similar. We aimed to develop a radiologic prediction tool for bronchiectasis to identify NTM-pd.

Methods We reviewed clinical, laboratory and radiological data in patients with bronchiectasis. Radiologic features on CT scans and the individual components of the Bhalla scoring system were compared between people with and without NTM-pd. Logistic regression and receiver-operating curve (ROC) analysis were performed to predict NTM-pd.

Results People with NTM-pd had more pulmonary segments with bronchiectasis (13 ± 5 vs. 11 ± 5, $p = 0.03$), presence of mucus plugging (47% vs. 19%, $p < 0.0001$) and tree in bud infiltrates (53% vs. 28%, $p = 0.004$). The total modified- Bhalla score was worse among people with NTM-pd (median [IQR] 11[9,13] vs. 9[8,12], $p = 0.03$). Logistic regression identified the number of pulmonary segments involved, presence of bullae, consolidations, and a total score of 10 or more to be independently associated with presence of NTM-pd. ROC analysis with radiographic variables only identified an AUC of 0.706 (95% CI 0.644–0.762). When people with chronic *Pseudomonas* infection were excluded from the ROC analysis, prediction for NTM was improved: AUC = 0.87 (95% CI 0.796–0.945).

Discussion and Conclusions Radiological features together with advanced age and female gender may predict NTM-pd among people with bronchiectasis. Infection with *Pseudomonas aeruginosa* may resemble NTM radiographically, and this prediction rule may better differentiate people with and without NTM-pd when *Pseudomonas* infection is not present.

Keywords Bronchiectasis · Non-tuberculous mycobacteria · Radiology

Introduction

One of the most prominent features of bronchiectasis is chronic bacterial infection. The common bacterial infections in patients with bronchiectasis are *Pseudomonas aeruginosa, Haemophilus influenzae*, and non-tuberculous mycobacteria (NTM) [1]. Prevalence studies showed significant differences in the prevalence of NTM infection depending

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✉ Michal Shteinberg
michalsh@technion.ac.il

[1] Department of Diagnostic Radiology, Carmel Medical Center, Haifa, Israel

[2] B. Rappaport Faculty of Medicine, Technion- Israel Institute of Technology, Haifa, Israel

[3] Faculty of Medicine, Rokach Lung Institute, Hebrew University of Jerusalem, Jerusalem, Israel

[4] Pulmonology Institute, Rabin Medical Center, Petach Tiqva, Israel

[5] Tel Aviv University, Tel Aviv, Israel

[6] Department of Community Medicine and Epidemiology, Carmel Medical Center, Haifa, Israel

[7] Pulmonary Institute and CF Center, Carmel Medical Center, 7 Michal St., 3436212 Haifa, Israel

on geographic location. In North America the prevalence of NTM infection is 30–37% in patients with bronchiectasis [1]. In contrast, European studies show much lower prevalence rates of between 2 and 10% [2–4]. According to established criteria for NTM pulmonary disease (NTM-pd), detection of NTM from a respiratory culture is not enough to establish disease. Microbiological, radiological, and clinical criteria are needed for diagnosis and decision to start therapy [5, 6]. However, the symptoms of NTM pulmonary disease are variable and nonspecific [7]. In bronchiectasis, it is a challenge to differentiate symptoms of NTM-pd from symptoms of bronchiectasis: chronic or recurrent cough, increased sputum production, dyspnea, hemoptysis, chest pain, wheezing, fever, and fatigue are common in bronchiectasis with or without NTM-pd [1].

Not only clinical features, but also radiologic manifestations of NTM-pd are often indistinguishable from those of bronchiectasis. NTM-pd has been associated with bronchiectasis, consolidation, and cavities, and peripheral mucus plugging [1, 8, 9]. However, these features may also be seen in CT scans of people with bronchiectasis and so the differences are not specific enough to differentiate NTM from non-NTM based on CT scan alone. In bronchiectasis, the Bhalla CT scoring system was employed on chest CT scans of people with bronchiectasis, and the baseline, as well as longitudinal changes in the score was determined. NTM infection was associated with a deterioration of the score over time, but not with initial severity of the score [10]. Among patients with cystic fibrosis (CF), NTM-pd was associated with more mucus plugging and consolidations [1] also when compared to an age- matched cohort without NTM-pd [1, 11]. A regression model identified these factors to be independently associated with NTM-pd, with a receiver-operator curve (ROC) analysis of the binary regression model showing an area under the curve of 0.89, $p < 0.0001$ [11]. Due to radiologic differences between CF and non-CF bronchiectasis [12, 13], whether these findings could be translated to non-CF bronchiectasis remains to be determined.

In this study we investigated clinical, laboratory and radiologic findings in a cohort of patients with bronchiectasis with and without pulmonary NTM-pd, in order to determine the diagnostic accuracy of HRCT for detecting NTM-pd among people with bronchiectasis.

Methods

Study Design and Subjects

We retrospectively reviewed all adult patients in two bronchiectasis centers (Carmel medical center, Haifa, and Rabin medical center, Petah Tiqva, Israel) who had complete clinical, laboratory and radiological data and available CT scans. Patients with CF, and with bronchiectasis secondary to lung fibrosis were excluded. The diagnosis of NTM-pd was made at the relevant time by the treating pulmonologist, according to established guidelines [5, 6]. We ascertained that NTM-pd was diagnosed by recording prescription of anti-mycobacterial medications (regardless of the length of treatment). The study protocol was approved by Carmel Helsinki committee.

High Resolution Computed Tomography

Acceptable CT images were those that were performed with a thin (1-mm) collimation computed tomography (CT) at 10-mm intervals from lung apices to bases during suspended full inspiration in the supine position. HRCT images were scored for the severity and extent of bronchiectasis by using a modification of the Bhalla score [10, 14] (Table 1). The items evaluated were: (a) the severity of bronchiectatic dilatation; (b) peribronchial thickening; (c) extent of bronchiectasis (number of lung segments involved); (d) extent of mucus plugs (number of lung segments); (e) abscesses or sacculations (number of lung segments); (f) generation of the bronchial division involved with either bronchiectasis or plugs; (g) number of bullae; (h) emphysema (number of lung segments); (i) presence of atelectasis/infiltrate (including tree in bud or consolidations). A total score was a modification of the original one in that it was formed by summing individual scores (without subtracting from a fixed number), so that the best possible score was 0 and the worst was 25. Apart from the Bhalla score, which was developed for people with CF, we individually scored additional HRCT findings: distribution of bronchiectasis in lung lobes, tree in bud infiltrates, and morphology of bronchiectasis.

Statistical Analysis

Data were performed using IBM statistics (SPSS) vs 24. The continuous variables are presented by mean and standard deviation or Median and interquartile range (IQR), as appropriate. The categorical variables are presented in percentages. Differences in Bhalla score and other characteristics between the non-NTM group and the NTM group were analyzed using independent-*t*-test or Mann–Whitney for the continuous variables and Chi square for the categorical variables. $p < 0.05$ was considered statistically significant.

Logistic regression analysis was performed for the variables found to be significantly associated with NTM-pd. A ROC analysis was performed on variables with a trend towards significant difference between NTM-pd and no NTM-pd.

Table 1 Modified Bhalla score

Category	0	1	2	3
Severity of bronchiectatic dilatation	Absent	Mild (diameter subtly greater than the adjacent vessel)	Moderate (diameter 2 to 3 times higher than the adjacent vessel)	Severe (diameter 3 times higher than the adjacent vessel)
Peribronchial thickening	Absent	Mild (thickening of the wall equal to the vessel)	Moderate (greater thickening/ doubling of the vessel)	Severe (thickening 2 times greater than the vessel)
Extent of the bronchiectasis (number of lung segments involved)	Absent	1–5	6–9	> 9
Extent of mucus plugs (number of lung segments involved)	Absent	1–5	6–9	> 9
Abscesses or sacculations (number of lung segments involved)	Absent	1–5	6–9	> 9
Generation of the bronchial division involved (bronchiectasis/plug)	Absent	Up to the 4th generation	4–5th generation	5–6th generation and distal
Number of bullae	Absent	Unilateral (none > 4)	Bilateral (none > 4)	> 4
Emphysema (number of lung segment)	Absent	1–5	> 5	
Atelectasis/infiltrate	Absent	Subsegmental	Segmental/lobar	

The individual components are added to produce a final score (range 0–25). Based on Ref. [14]

Results

A total of 242 patients with bronchiectasis (mean age, 66.5 years, 60% females) had CT scans performed between the years 2008–2018 that were available for review. 32 patients had NTM-pd and 210 patients did not have NTM-pd. The NTM strains were *M. simiae* (11 patients), *M. intracellulare* (8), *M. fortuitum* (7), *M. avium* (2), *M. chelonae* (2), *M. Kansasii* (2), *M. abscessus* (1), *M. xenopii* (1) and *M. gordonae* (1) (some patients had more than one strain). The mean (± SD) age of the NTM positive patients was 71.8 ± 12.4 years, and of NTM negative patients was 65.6 ± 16.9 years ($p = 0.034$). Female:male ratio was higher for people with NTM (75% females with NTM-pd vs. 58% females without NTM-pd), with a trend towards statistical significance ($p = 0.062$) (Table 2).

The number of lung segments involved with radiological bronchiectasis was significantly higher in patients with positive NTM. Tree in bud opacities in at least two pulmonary segments were more common among people with NTM-pd (53% vs. 28%, $p = 0.004$) as well as presence of mucous plugs (27.3% vs. 9.1%, $p = 0.001$) Fig. 1 shows an example of a CT image demonstrating bilateral middle (A) and lower (B)-lobe bronchiectasis with "tree-in-bud" opacities. The modified Bhalla score of patients with NTM-pd was 11 (IQR 9;13), and for patients without NTM-pd median 9 (IQR 8;12) $p < 0.03$ (Table 3).

A univariate model revealed a significant relationship between NTM-pd and radiological variables: The number of pulmonary segments with bronchiectasis, presence of bullae, consolidation or tree in bud opacities in at least two lung segments & presence of mucous plugs.

We next performed a multivariate logistic regression to identify factors independently associated with NTM-pd. The presence of mucous plugs (OR 2.89 [1.26–6.6], $p = 0.012$), presence of bullae (OR 2.8 [0.95–8.4], $p = 0.062$), and consolidation or tree in bud opacities in at least two lung segments (OR 2.59 [1.05–6.43], $p = 0.04$) were all independently associated with NTM-pd. The number of pulmonary segments with bronchiectasis (OR 1.04 [0.96–1.13], $p = 0.306$) was not found to be independently associated with NTM-pd. The logistic regression formula derived from the individual parameters, and the sensitivity, specificity, positive likelihood ratio, positive predictive value and negative predictive value are shown in Table 4. ROC analysis with radiographic variables only identified an AUC of 0.706 [95% CI 0.60–0.81], which was better than the ROC curve derived from components of the Bhalla score: AUC 0.618 (95% CI 0.72–0.515). When age & gender were added to the radiological variables, AUC was 0.764 95% CI (0.67–0.86) ($p < 0.001$, Fig. 2a). The coordinates of the curve are attached as a supplement, as well as a calculator for predicting the probability of NTM-pd given the individual radiologic parameters.

Due to a higher number (which was not statistically significant) of people with *Pseudomonas aeruginosa* infection among people with NTM-pd, we wanted to isolate the radiological features of NTM-pd from those of *Pseudomonas* infection. Mucous plugs were associated with the presence of *Pseudomonas* in people without NTM (28.8% of NTM negative, *Pseudomonas* positive had mucous plugs vs. 12.6% of

Table 2 Clinical and radiological characteristics of patients with and without NTM

	Total $N=242$	No NTM $N=210$	NTM-pd $N=32$	p-value
Age, years (mean ± std)	66.5 ± 16.5	65.6 ± 16.9	71.8 ± 12.4	**0.034**
Gender				0.062
Male *N* (%)	97 (40.2)	89 (42.4%)	8 (25.0%)	
Female *N* (%)	145 (59.9%)	121 (57.6%)	24 (75%)	
BMI (kg/m^2, mean ± SD)	25.7 ± 5.8	25.7 ± 5.6	26.1 ± 7.5	0.727
FEV_1 (% predicted, mean ± SD)	77.4 ± 25.8	77.6 ± 26.5	74.5 ± 18.8	0.562
Infection with *Pseudomonas aeruginosa N* (%)	88 (36.7%)	73 (35.1%)	15 (46.9%)	0.201
Number of segments, mean ± std	11.2 ± 5.1	10.9 ± 5.1	13.1 ± 4.8	**0.030**
Distribution of bronchiectasis[a]				
Upper lobes *N* (%)	113 (46.7)	94 (44.8)	19 (59.4)	0.123
Middle lobes *N* (%)	168 (69.4)	143 (68.1)	25 (78.1)	0.251
Lower lobes *N* (%)	218 (90.1)	190 (90.5)	28 (87.5)	0.611
Types of bronchiectasis: N (%)				
Tubular/cylindrical	184 (76.0)	158 (75.2)	26 (81.3)	0.458
Varicose	69 (28.5)	56 (26.7)	13 (40.6)	0.103
Cystic	71 (29.3)	65 (31.0)	6 (18.8)	0.158
Tree in bud opacities N (%)	76 (31)	59 (28)	17 (53)	**0.004**

[a]Distribution of bronchiectasis-percentages add to more than 100% as individuals may have bronchiectasis in several lung lobes. The lingula was considered as a "middle lobe"

NTM-pd non-tuberculous mycobacteria pulmonary disease

Bold values indicate $p<0.05$

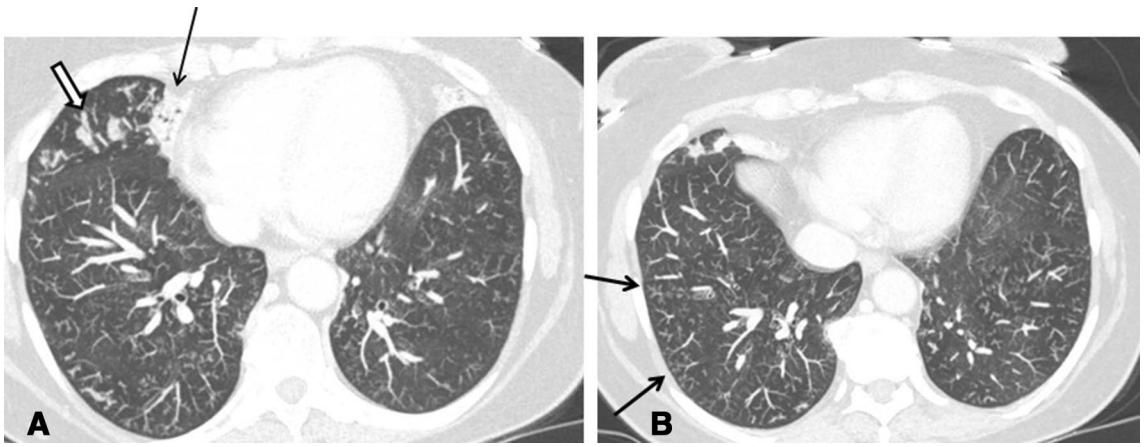

Fig. 1 CT scans of a patient with NTM showing: **a** atelectasis (thin arrow), mucous plugs (thick arrow); **b** tree in bud opacities (thin arrows)

NTM negative, *Pseudomonas* negative) ($p=0.023$) while the proportion was reverse amongst people with NTM-pd: (40% of people with NTM and *Pseudomonas* had mucous plugs vs. 52.9% of people with NTM-pd but without *Pseudomonas*). We therefore repeated the ROC analysis in people without *Pseudomonas* infection. Our cohort had 152 *Pseudomonas* negative patients, 17 with NTM-pd and 135 without NTM-pd. In this cohort, logistic regression identified bullae OR = 13.9, 95% CI (2.4–78.5), $p=0.003$, consolidation (including tree in bud) OR = 5.7, 95% CI (1.3–24.3), $p=0.019$, and mucous plugs OR = 5.4, 95% CI (1.3–21.9), $p=0.020$ to be independently associated with NTM-pd. ROC analysis was better than in the entire cohort: AUC = 0.87 95% CI (0.796–0.945) (Fig. 2b).

Discussion

High resolution computed tomography (HRCT) has proved to be a reliable and non-invasive method for the diagnosis of bronchiectasis. Several scoring systems exist and have been

Table 3 Components of the Bhalla scoring system in people with bronchiectasis with and without NTM-pd

	No NTM $N=210$	NTM-pd $N=32$	p-value
Bronchiectasis severity *N* (%)			0.352
0	1 (0.48%)	0 (0%)	
1	101 (48.3%)	19 (59.4%)	
2	62 (29.7%)	10 (31.2%)	
3	45 (21.5%)	3 (9.4%)	
Peribronchial thickening *N* (%)			0.27
0	24 (11.4%)	2 (6.3%)	
1	121 (57.6%)	16 (50.0%)	
2	60 (28.6%)	14 (43.8%)	
3	5 (2.4%)	0 (0.0%)	
Bronchiectasis extent (number of segments) *N* (%)			0.263
0	0 (0.0%)	0 (0.0%)	
1	43 (20.5%)	3 (9.4%)	
2	32 (15.2%)	4 (12.5%)	
v3	135 (64.3%)	25 (78.1%)	
Extent of mucoid impaction *N* (%)			**0.003**
0	170 (81.0%)	17 (53.1%)	
1	28 (13.3%)	8 (25.0%)	
2	9 (4.3%)	7 (21.9%)	
3	3 (1.4%)	0 (0.0%)	
Abcesses or sacculations *N* (%)			0.33
0	204 (97.1%)	30 (93.8%)	
1	5 (2.4%)	2 (6.3%)	
2	1 (0.5%)	0 (0.0%)	
3	0 (0.0%)	0 (0.0%)	
General aspects of bronchial zone involved *N* (%)			0.62
0	1 (0.5%)	0 (0.0%)	
1	17 (8.1%)	1 (3.1%)	
2	84 (40.2%)	12 (37.5%)	
3	107 (51.2%)	19 (59.4%)	
Number of Bullae *N* (%)			0.171
0	193 (92.3%)	26 (81.3%)	
1	13 (6.2%)	6 (18.8%)	
2	2 (1.0%)	0 (0%)	
3	1 (0.5%)	0 (0%)	
Emphysema *N* (%)			0.627
0	176 (83.8%)	29 (90.6%)	
1	19 (9.0%)	2 (6.3%)	
2	15 (7.1%)	1 (3.1%)	
Collapse/consolidation *N* (%)			**0.017**
0	72 (34.3%)	8 (25.0%)	
1	79 (37.6%)	7 (21.9%)	
2	59 (28.1%)	17 (53.1%)	
Modified Bhalla score	9 (8;12)	11 (9;13)	**0.03**

NTM-pd non-tuberculous mycobacteria pulmonary disease, *M-Bhalla* modified Bhalla score

Bold values indicate $p < 0.05$

Table 4 The sensitivity, specificity, positive likelihood ratio, positive predictive value and negative predictive value of several cutoffs of the logistic regression formula ($p = 1/1 + \exp - (-0.54 + \text{age}*0.025 + \text{sex}*1.029 + \text{presence of mucous plugs}*1.148 + \text{bullae}*1.063 + \text{lung segments with bronchiectasis}*0.0034 + \text{consolidation or atelectasis}*0.919)$)

Cutoff	Sensitivity	Specificity	Positive likelihood ratio	PPV	NPV
Above 0.05	90.6 (75.0–98.0)	27.3 (21.2–33.9)	1.25 (1.08–1.43)	16.0 (14.2–18.0)	95.0 (86.4–98.3)
Above 0.1	78.1 (60.0–90.7)	62.2 (55.2–68.8)	2.07 (1.61–2.66)	24.0 (19.7–29.0)	94.9 (90.5–97.3)
Above 0.15	65.6 (46.8–81.4)	76.1 (69.7–81.7)	2.74 (1.94–3.89)	29.6 (22.9–37.3)	93.5 (89.9–95.9)
Above 0.20	59.4 (40.6–76.3)	84.2 (78.6–88.9)	3.76 (2.46–5.75)	36.5 (27.4–46.8)	93.1 (89.9–95.4)
Above 0.25	43.8 (26.4–62.3)	89.5 (84.5–93.3)	4.16 (2.38–7.26)	38.9 (26.7–52.6)	91.2 (88.4–93.4)
Above 0.30	28.1 (13.8–46.8)	95.7 (92.0–98.0)	6.53 (2.8–15.2)	50.0 (30.0–70.0)	89.7 (81.8–91.5)
Above 0.35	25.0 (11.5–43.4)	97.1 (93.4–98.9)	8.7 (3.2–23.46)	57.1 (33.1–78.2)	89.4 (87.4–91.2)
Above 0.4	25.0 (11.5–43.4)	98.1 (95.2–99.5)	13.1 (4.17–40.9)	66.7 (39.0–86.2)	89.5 (87.5–91.3)

A calculator using these parameters is presented in Supplementary Material

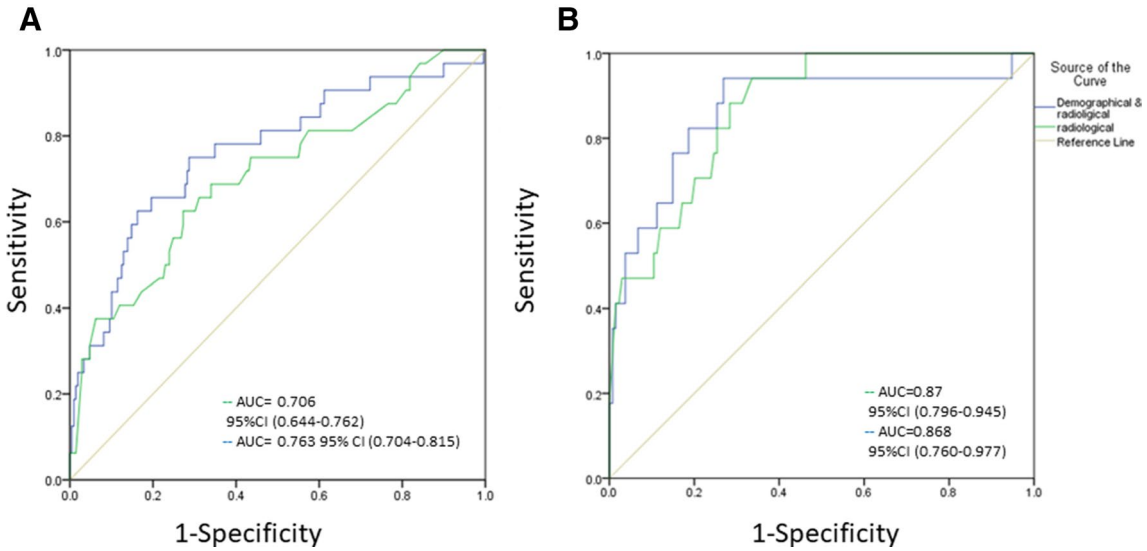

Fig. 2 Receiver operating curves for the whole cohort (**a**) and *Pseudomonas* negative (**b**)

correlated with disease severity and progression [10, 15]. However, the usefulness of radiological scoring systems to assess presence of NTM-pd in people with bronchiectasis were not assessed before to the best of our knowledge. The present study included patients with bronchiectasis from two bronchiectasis centers in Israel, with presence or absence of NTM-pd determined by the treating pulmonologists according to established criteria. We found significant clinical and radiologic differences between patients with and without NTM-pd, that, when used in a ROC model, allow to predict NTM-pd among patients with bronchiectasis, with a better prediction in people without co-infection with *Pseudomonas aeruginosa*.

We selected a modification of the Bhalla scoring system as a radiologic severity scoring system for positive NTM patients with bronchiectasis. This scoring system was developed for CF, and found to be correlated with disease severity in bronchiectasis [10, 15]. Moreover, findings of differences based on the Bhalla score in patients with CF with and without NTM-pd allowed to differentiate between these two groups [11]. In our study patients with NTM-pd had an increased Bhalla score, in comparison to patients without NTM-pd.

Our findings are similar to previous results in people with CF and NTM-pd, matched by age to people with CF and no NTM-pd [11]. A previous study by Park and colleagues which analyzed the CT scans of 155 people with bronchiectasis (69 with NTM colonization) did not find differences in the baseline Bhalla score among patients with and without NTM-pd. However, Park et al. found that the annual change in the CT score was greater (indicating accelerated progression) among patients with NTM infection. These differences between this and our study may result from the inclusion of a "single isolation" of NTM by Park and colleagues, which

may not necessarily indicate NTM pulmonary disease as per established guidelines. People with increased bronchiectasis severity may have more frequent isolation of NTM without NTM-pd and may deteriorate faster due to the bronchiectasis severity.

Several CT features distinguished people with NTM-pd from people with bronchiectasis without TNM-pd. Specifically, findings of parenchymal infiltrates, either consolidation or "tree in bud" opacities", were significantly more prevalent among people with NTM-pd (53%) than without NTM-pd (28%, $p=0.004$). Mucus plugging is another finding that distinguished NTM-pd from no NTM-pd: 49% vs. 19%, $p<0.0001$. These findings are similar to those found among people with CF [1, 11], while tree in bud opacities were found to be associated with NTM-pd among people with bronchiectasis [1, 16]. We did not find that the lobar distribution was different between people with and without NTM-pd in the setting of bronchiectasis. Older studies have found a predisposition of NTM-pd changes in the middle lobe and lingula [17, 18]; however, this distribution may not be unique to NTM-pd in the context of bronchiectasis [19]. Interestingly, sensitivity analysis of the NTM-pd associated findings in people without *Pseudomonas* infection did not change the results but improved the accuracy; it may be due to similar radiologic features, representing endobronchial inflammation, which are similar when either *Pseudomonas* or NTM are the infecting pathogen.

In our study patients with NTM-pd were significantly older than people without NTM-pd (mean 72 vs. 66 years). This finding is in contradiction to a previous finding by our group, which showed that the incidence of a new acquisition of NTM is decreased among the elderly (over 80 years old) [2]. Other studies examining prevalence of NTM isolation and NTM-pd have indeed found increasing age to be correlated with increased risk of NTM infection [3, 5, 20, 21]. These differences may indicate a "bimodal" pattern of NTM acquisition, with a peak in mid- age range and declining after 80 years of age. Another explanation may be that differences result from methodological differences: our previous study excluded people with existing NTM infection and tested risk for new NTM acquisition, while the present study and those of other groups tested characteristics of people with existing NTM-pd.

Despite finding significant clinical and radiological differences between people with bronchiectasis with and without NTM-pd, we as well as previous study did not any identifying radiological feature that is unique to people with NTM. However, a combination of several radiological findings (extent of bronchiectasis, mucous plugs, tree in bud infiltrates) may predict an increased likelihood of NTM-pd as demonstrated by the ROC analysis. Combing clinical features—age and female gender—with radiological features improved the prediction of NTM-pd. Interestingly, although radiological severity of bronchiectasis was increased among NTM-pd, we did not find that the severity of obstruction (FEV1) or colonization with *Pseudomonas* were associated with NTM-pd. This may suggest that the radiological differences may result from the NTM infection rather than merely reflect increased severity of bronchiectasis.

Our study has some limitations. First, a single radiologist scored the CT scans, which may risk inaccuracy. Second, due to the small number of people in our study and lack of access to an external dataset we were not able to validate the developed prediction model. Hence, the external validity of the prediction rule still needs to be determined before introducing it for use in the clinical setting.. Lastly, whether NTM-pd existed was determined by the treating physician, which may, in turn, have been influenced by CT findings as per published guidelines [5, 6]. However, as radiographic features alone are not enough to define NTM-pd, this cannot be the sole explanation to our findings. Our study is, to our knowledge, the first study that specifically scores both clinical and radiological features of NTM-pd in this population of people with bronchiectasis.

In conclusion, in people with bronchiectasis, radiologic and clinical features may accurately detect NTM-pd especially in people without *Pseudomonas* co-infection. The inclusion of HRCT among routine examinations may provide significant benefits in the management of patients.

Compliance with Ethical Standards

Conflict of interest Dr. Shteinberg reports grants, personal fees and non-financial support from GSK, grants and non-financial support from Novartis, grants and non-financial support from Trudell pharma, non-financial support from Actelion, personal fees from Boeringer Ingelheim, personal fees from Astra Zeneca, personal fees from Vertex pharmaceuticals, outside the submitted work. Dr. Adir reports grants and personal fees from Actelion, grants and personal fees from Boehringer Ingelheim, personal fees from TEVA, grants and personal fees from GSK, personal fees from Rafa, personal fees from Novartis, personal fees from Astra Zeneca, personal fees from Kamada, outside the submitted work. The rest of the authors declare no conflict of interest.

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