

RESEARCH ARTICLE

Body habitus in patients with and without bronchiectasis and non-tuberculous mycobacteria

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Abstract

Background

Female gender, tall stature, presence of bronchiectasis are associated with pulmonary non-tuberculous mycobacterial (NTM) infections. The biologic relationship between the body habitus and NTM infection is not well defined and the body habitus profile of the patients with NTM and concurrent bronchiectasis is completely unknown.

Methods

We conducted a case control study at the Miami VA Healthcare System and the University of Illinois Medical Center on patients with pulmonary NTM infections between 2010 and 2015. We compared pulmonary NTM subjects with and without bronchiectasis. NTM infection was confirmed by using the American Thoracic Society/ Infectious Disease Society of America criteria. Standard radiological criteria were used to define bronchiectasis in chest CT-scan.

Results

Two hundred twenty subjects with pulmonary NTM were enrolled in the study. Sixty six subjects (30%) had bronchiectasis on CT scan of the chest. Subjects in the bronchiectasis group included more women ($p = 0.002$) and were significantly older ($p = 0.005$). Those patients who had bronchiectasis tended to have a significantly lower weight (less than 50kg) and height ≤ 155 cm ($p < 0.0001$ and $p = 0.018$, respectively). Kaplan–Meier analysis confirmed that subjects who had bronchiectasis were shorter and weighed less, after adjusting for gender.

Conclusions

This study defines a new sub-phenotype of NTM subjects with bronchiectasis who tend to be short with lower body weight. Further studies are needed to better understand

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and define the body habitus profiles of this new sub-phenotype and their clinical implications.

Introduction

Bronchiectasis is defined as an abnormal dilation of the bronchi, usually irreversible, associated with airway obstruction, chronic productive cough and recurrent infections [1]. It typically begins with airway inflammation almost always after an infectious process [2], linking the release of toxins and immune mediators with the subsequent permanent damage to the respiratory tract anatomy. Moreover, these mechanisms lead to bacterial colonization and recurrent infections, enhancing tissue damage [3]. A broad variety of predisposing factors have been associated with the development of this condition, including infection, congenital defects, genetic predisposition and systemic inflammatory disorders [4]. Bronchiectasis can be further classified into two major groups; cystic fibrosis (CF), that typically occurs in childhood, and non-cystic fibrosis (non-CF) [5]. Previous studies have shown that adult-onset non-CF bronchiectasis usually involved middle aged to elderly women [6].

Non-tuberculous mycobacteria (NTM) are recently recognized as important etiology of pulmonary infections [7]. They are ubiquitous environmental organisms that are frequently isolated from soil and water [8]. Given that NTM infection is not reportable in the United States, it is difficult to determine the accurate prevalence of NTM [9]. It has been reported that the prevalence of NTM has increased in the last decades [10].

Interesting association between NTM and body habitus has been established earlier. In 1992, “Lady Windermere Syndrome” was reported in thin postmenopausal women of European American descent who presented with middle lobe and lingular bronchiectasis and NTM infection, commonly caused by *Mycobacterium avium* complex (MAC) [11].

Later, other studies found similar results and confirmed that tall stature, low body weight, female gender, and elderly were risk factors of NTM infection [12–14]. Among patients with pulmonary NTM, airway diseases including COPD and bronchiectasis are common findings [15].

In our previous work we reported that 37% of patients with NTM had bronchiectasis [15]. Bronchiectasis which is accompanied with small nodular opacities, and a tree-in-bud pattern on CT scan of the chest are associated with a greater probability of isolation of mycobacteria in sputum and bronchial alveolar lavage (BAL) [16]. MAC is the most common isolate in patients with bronchiectasis [15], although other species may be found too [17].

In 2014, our team reported an increased frequency of NTM infections in elderly, thin women [18], but we were unable to show if bronchiectasis was associated with gender, weight, and height in those with pulmonary NTM infections. To our knowledge, the relationship between body habitus and bronchiectasis in patients with NTM infection has not been reported previously.

We hypothesized that patients with bronchiectasis and concurrent NTM infection have different body habitus profile from patients with NTM but without bronchiectasis. We also sought to better understand the association of bronchiectasis with anthropometrics and mycobacterial species.

Methods

Study design and data collection

To delineate the body habitus of subjects with NTM and bronchiectasis, we analyzed medical records of patients with confirmed pulmonary NTM from the Miami Veterans Affairs (VA)

Healthcare System and University of Illinois at Chicago (UIC), in a retrospective case control study between the years 2010 and 2015. The study was reviewed and accepted by the ethics committee as reflected in the approval numbers 2006–0742 and 574.01. Consent was waived due to the retrospective nature of the study.

Anthropometrics data (age, sex, race, height, weight, and body mass index, BMI), date of onset of symptoms and date of NTM infection diagnosis, clinical symptoms including cough, sputum, hemoptysis, dyspnea, weight loss, smoking habits including current smoking status and number of packs smoked, comorbidities, family history of bronchiectasis, chest imaging findings, sputum microbiology results, history of bronchoscopy and treatment outcomes were collected.

Criteria and definitions

Subjects 18 years or older were screened if they have International Classification of Diseases ninth revision (ICD-9) code for pulmonary NTM (ICD-9: 031.0). Mycobacterial disease was confirmed if subjects met the clinical, radiologic and microbiologic criteria of American Thoracic Society/Infectious Disease Society of America guidelines for NTM infection [19]. Polymerase chain reaction (PCR) technology was used in both institutes for NTM speciation from respiratory secretion culture, as previously reported [20–22]. Diagnostic criteria for bronchiectasis in chest images included bronchial dilation, bronchial wall thickening, and cylindrical changes [23]. Double reading by radiologist and pulmonologist was used for assurance of accurate diagnosis of bronchiectasis in chest CT.

Outcome was classified as cured, incomplete or no treatment (no treatment offered by physicians). Cured subjects were those who continued antibiotic therapy at least twelve months after sputum conversion to negative. An incomplete outcome was recognized when subjects received at least 6 months treatment but lost to follow up or stopped therapy without physician order. No treatment was defined when physicians decided to not initiate treatment based on individual clinical judgment.

Statistical analysis

Categorical variables were described as counts and percentages and were tested by the Chi-square test or, if applicable, Fischer's exact test. Univariate analysis was used to compare differences in demographic and clinical variables between groups with and without bronchiectasis. Normality of distribution of continuous variables was tested by Shapiro-Wilk test. Mann-Whitney U test was used to compare continuous variables because of the majority of variables were not normally distributed.

The Kaplan-Meier estimate curve was used to determine the risk of bronchiectasis for weight and height while adjusting for gender. Curves were compared using the log-rank test. Multivariate logistic regression analysis was performed to identify independent variables that predict the diagnosis of bronchiectasis in subjects with NTM. The model included Anthropometric variables, including age, gender, weight, height and race. The goodness-of-fit of the model was examined by the Hosmer-Lemeshow test. Statistical analysis was performed using IBM SPSS 22.0 statistical software (Armonk, NY).

Two-tailed *p*-values were used and those <0.05 were considered to be statistically significant.

Results

Patient characteristics and demographics

Two hundred twenty (62 from Miami VA and 158 from UIC) subjects with pulmonary NTM infection were enrolled in the study. 11 subjects from Miami VA (16.7%) and 51 (33.1%) from

Table 1. Comparison of clinical characteristics of subjects with NTM infection at Miami VA and UIC.

Variable	Miami VA	UIC	p-value
	62 (28.1%)	158 (71.8%)	
Age > 65	24 (38%)	104 (65%)	<0.0001
Bronchiectasis	11 (16.7%)	51 (33.1%)	0.015
Emphysema	5 (8.1%)	31 (19.6%)	0.044
Female	5 (8.1%)	31 (19.6%)	0.044
Age Mean (SD) (years)	61.7 (±13)	67.1 (±14.2)	0.010
BMI	23.36 (±5.2)	24 (±7.3)	0.553
Height Mean (SD) (cm)	176.5 (±9.1)	164.9 (±8.8)	<0.0001
Weight Mean (SD) (kg)	73 (±17)	65.4 (±20.9)	0.015

NTM: non-tuberculous mycobacteria, Miami VA: Miami Veterans Affairs (VA) Healthcare System; UIC: University of Illinois at Chicago; COPD: chronic obstructive pulmonary disease; BMI: body mass index; (SD) standard deviation.

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UIC had the diagnosis of bronchiectasis. Patients from UIC were older and had more women when compared to patients from Miami VA. [Table 1](#) displays characteristics of enrolled subjects from Miami VA and UIC.

Subjects were grouped as those with bronchiectasis (n = 66, 30%) and without bronchiectasis (n = 154, 70%). The mean (± standard deviation) age of subjects was 69.3 (±13) and 64 (±14.3) years for the bronchiectasis and non-bronchiectasis groups, respectively, with a significant statistical difference between groups (p = 0.011).

Majority of subjects with bronchiectasis 66.7% were of European American origin, followed by 7.9% African Americans and 6.3% Asians. In the non-bronchiectasis group, European Americans comprised 60% of the subjects, followed by African Americans (21.2%) and Asians (2.6%). African American race was the only one that showed a significant statistical difference between the bronchiectasis and non-bronchiectasis group (p = 0.025).

The bronchiectasis group had more women (47, 71.2%) when compared to the non-bronchiectasis group (74, 48.1%), with a statistical significant difference (p = 0.002). 72% of the NTM and bronchiectasis group were 65 years or older when compared to 51.9% in the NTM without bronchiectasis group (p = 0.005).

Mean height was 165 cm (±10) and 170 cm (±10) in the bronchiectasis and non-bronchiectasis group, respectively. When subcategorizing subjects according to height less than 155cm, the bronchiectasis group tended to be shorter than those in the non-bronchiectasis group (9, 18% versus 7, 5.8%, respectively) with a significant statistical difference (p = 0.018).

The mean weight of subjects with bronchiectasis was 61.9 kg (±18.5) versus 69.9 kg (±20.5) in those without bronchiectasis (p = 0.008). Furthermore, weight less than 50 kg, was found in 21 (32.3%) subjects in the bronchiectasis group in contrast to 16 (11%) in the non-bronchiectasis group (p <0.0001).

Comparison of characteristics of subjects with NTM and with or without bronchiectasis is listed in [Table 2](#).

ICD-9 codes accuracy

A total of 96 subjects were coded for NTM according to ICD-9 codes in the Miami VA cohort. Our review revealed that out of 96 subjects, 17 (22.3%) were wrongly diagnosed or classified, 4 (5.2%) were actually latent tuberculosis patients, and 13 (17.1%) had no microbiological data

Table 2. Clinical characteristics of subjects with NTM infection with and without bronchiectasis at Miami VA and UIC.

Variable	NTM with bronchiectasis	NTM without bronchiectasis	p-value
Age Mean (SD) (years)	69.3 (±13)	64 (±14.3)	0.011
Age > 65 years	48 (72%)	80 (51.9%)	0.005
African American	5 (7.9%)	32 (21.2%)	0.025 ^a
Asian	4 (6.3%)	4 (2.6%)	0.207
Cancer	11 (16.7%)	28 (18.2%)	0.787
Cerebrovascular disease	1 (1.5%)	9 (5.8%)	0.288
Chronic renal failure	0 (0%)	5 (3.3%)	0.326
COPD	26 (42.6%)	41 (28.9%)	0.56
Current smoker	7 (17.5%)	34 (31.5%)	0.091
Diabetes	2 (3.1%)	11 (7.6%)	0.21
Dyspnea	23 (37.1%)	40 (28.4%)	0.216
European American	44 (66.7%)	93 (60%)	0.094
Ex-smoker	22 (59.5%)	68 (67.3%)	0.39
Female gender	47(71.2%)	74 (48.1%)	0.002
Fever	5 (8.1%)	22 (15.7%)	0.141
Heart failure	6 (9.2%)	13 (8.9%)	0.939
Height < 155cm	9 (18%)	7 (5.8%)	0.018
Hemoptysis	20 (32.8%)	33 (23.6%)	0.173
Hispanic	1 (1.6%)	13 (8.6%)	0.92
HIV	0 (0%)	14 (9.6%)	0.007 ^a
Immunosuppressive therapy (including steroids)	5 (7.7%)	28 (18.2%)	0.055
Liver disease	1 (1.5%)	9 (6.2%)	0.18 ^a
Neurologic disorders	2 (3%)	15 (9.7%)	0.104
New onset of cough	61 (96.8%)	89 (64.5%)	<0.0001
Night sweats	13 (21%)	20 (14.4%)	0.245
Sputum production	54 (85.7%)	76 (55.9%)	<0.0001
Weight < 50kg	21 (32.3%)	16 (11%)	<0.0001
Weight 10% or below ideal body weight at time of diagnosis	4 (6.1%)	11 (7.2)	0.077
Weight loss	12 (19%)	21 (14%)	0.398
Weight Mean (SD) (kg)	61.99 (±18.5)	69.9 (±20.5)	0.008

NTM: non-tuberculous mycobacteria; COPD: chronic obstructive disease; HIV: human immunodeficiency virus.

^aFisher's exact test.

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to support the diagnoses. The accuracy of ICD-9 codes for pulmonary NTM in the Miami VA healthcare system was calculated as low as 65%.

Microbiological results

Bronchoalveolar lavage (BAL) was performed in 24 (36.4%) and 46 (31.8%) of subjects with and without bronchiectasis, respectively. *Mycobacterium avium* complex was the most commonly isolated species in both groups and significantly higher percentage in the bronchiectasis group (37, 58.7% and 59, 30.9%, $p = 0.013$). *Mycobacterium abscessus* was also isolated in significantly higher number of subjects in bronchiectasis group (17, 27% vs. 19, 12%, $p = 0.014$). *Mycobacterium kansasii* was isolated from 4 (6.3%) and 26 (17.6%) ($p = 0.03$) of NTM subjects with and without bronchiectasis, respectively. *Mycobacterium fortuitum* was isolated from 4 (6.3%) and 25 (16.9%) ($p = 0.049$) of NTM subjects with and without bronchiectasis

Table 3. Isolated mycobacteria species in subjects with and without bronchiectasis at Miami VA and UIC.

NTM isolate	NTM with bronchiectasis 66 (30%)	NTM without bronchiectasis 154 (70%)	p-value
MAC	37 (58.7)	59 (30.9)	0.013
<i>M. abscessus</i>	17 (27)	19 (12)	0.014
<i>M. chelonae</i>	18 (28.6)	27 (18)	0.096
<i>M. fortuitum</i>	4 (6.3)	25 (16.9)	0.049^a
<i>M. gordonae</i>	6 (9.6)	16 (10.8)	0.780 ^a
<i>M. kansasii</i>	4 (6.3)	26 (17.6)	0.03^a
<i>M. simiae</i>	3 (4.8)	4 (2.7)	0.451 ^a

NTM: non-tuberculous mycobacteria; Miami VA: Miami Veterans Affairs (VA) Healthcare System; UIC: University of Illinois at Chicago; MAC: *Mycobacterium avium* complex.

^aFisher’s exact test.

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respectively. Other species, such as *M. chelonae*, *M. gordonae*, and *M. simiae* were isolated without any significant difference between the two groups. More details are shown in Table 3.

Comorbidities and clinical characteristics

Cough and sputum production were the most common symptoms in subjects with bronchiectasis (61, 96.8% and 54, 85.7% respectively) compare to those without bronchiectasis (89, 64.5% and 76, 55.9% respectively) ($p < 0.0001$). The presence of comorbidities, including COPD, diabetes mellitus, congestive heart failure, renal disease, chronic liver disease, neurologic disorders and malignancy were not significantly different between the two groups, except for HIV which was significantly higher in those without bronchiectasis (0, 0% and 14, 9.6% $p = 0.01$ in bronchiectasis vs. non-bronchiectasis groups respectively). Table 4 displays chest CT imaging findings of patients with and without bronchiectasis. Of note, all patients had new nodular opacity, but other findings such as emphysema, cavitory lesions, mediastinal lymphadenopathy and pleural effusion were analyzed with no significant differences between bronchiectasis and non-bronchiectasis groups.

The probability of bronchiectasis in NTM subjects was significantly higher in shorter and lower weighing subjects after adjusting for gender as shown in Figs 1 and 2, respectively.

The multivariable logistic regression model for bronchiectasis in patients with NTM is depicted in Table 5. Among anthropometric variables, age greater than 65 years, weight and African American race were significantly associated with finding bronchiectasis in the chest CT of subjects with confirmed pulmonary NTM.

Table 4. Chest CT imaging findings of patients with and without bronchiectasis at Miami VA and UIC.

NTM isolate	NTM with bronchiectasis 66 (30%)	NTM without bronchiectasis 154 (70%)	p-value
Emphysema	8 (12)	28 (18)	0.269
Cavitory lesion	8 (17.4)	16 (23.9)	0.409
Lymphadenopathy	14 (31.8)	16 (18)	0.076
Pleural effusion	2 (4.2)	2 (2.8)	0.690

CT: computed tomography; NTM: non-tuberculous mycobacteria, Miami VA: Miami Veterans Affairs (VA) Healthcare System; UIC: University of Illinois at Chicago.

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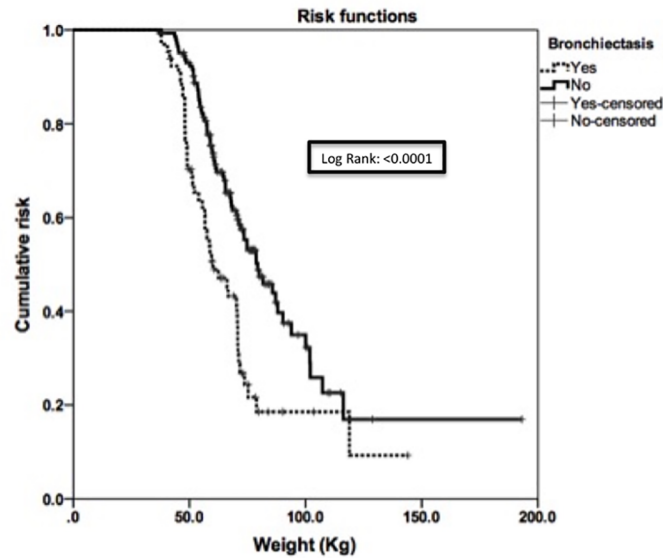


Fig 1. The Kaplan-Meier estimate curve for the cumulative risk according to weight and bronchiectasis, while adjusting for gender.

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Clinical outcome

Clinical outcome was found for 12 out of 66 subjects with bronchiectasis. Out of 12, 3 (25%) were cured, 4 (33.33%) had an incomplete outcome, and 5 (41.66%) had no treatment offered by physicians. Clinical outcome was found in 45 out of 154 subjects in non-bronchiectasis group. 14 (31.11%) had a satisfactory outcome, considered them as cured, 25 (55.55%) defined as incomplete outcome, and 6 (13.33%) had no treatment offered by physicians.

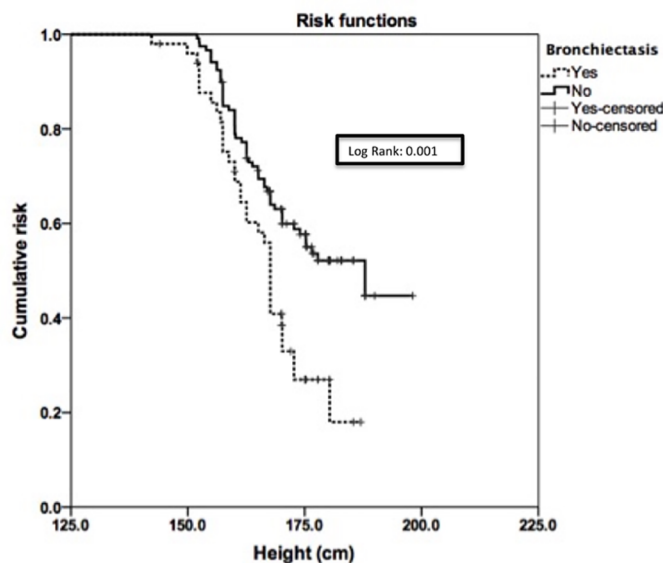


Fig 2. The Kaplan-Meier estimate curve for the cumulative risk according to height and bronchiectasis, while adjusting for gender.

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Table 5. Clinical and bacteriological features of subjects with dual NTM infection and bronchiectasis at Miami VA and UIC on multivariate analysis.

Variable	p-value, OR (95% CI)
Age >65 years	0.006, 3.1 (1.37–6.90)
African American race	0.076, 0.335 (0.10–1.12)
Female	0.170, 1.8 (0.77–4.12)
Height	0.57, 1.02 (0.97–1.07)
Weight	0.005, 1.04 (1.01–1.07)

NTM: non-tuberculous mycobacteria; Miami VA: Miami Veterans Affairs (VA) Healthcare System; UIC: University of Illinois at Chicago; OR: odds ratio; CI: confidence interval.

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Discussion

Our study reaffirms the close relationship between NTM and bronchiectasis. Bronchiectasis was more frequent in elderly women (age >65 years) with pulmonary NTM as previously reported [24]. *Mycobacterium avium* complex was the most common species isolated from bronchiectasis group. In the US, MAC has been repeatedly reported as the most common bacteria associated with pulmonary NTM [25, 26]. We found significantly higher frequency of MAC in subjects with bronchiectasis in the univariate analysis.

Although the relationship between NTM and bronchiectasis is well established, many questions on this association remained unanswered. Does bronchiectasis increase susceptibility to NTM? Does NTM contribute to the pathogenesis of bronchiectasis? Our study suggests that both scenarios could be true. We, and others, have previously shown that NTM susceptibility increases in elderly women with bronchiectasis [24]. The reasons for the association are not clearly defined but have been speculated. It has been postulated that it might be due to breakdown of the bronchial epithelium in bronchiectasis that subsequently allows NTM to take up residence, grow, and enhance the structural deformities of bronchiectasis. The molecular mechanisms and the sequence remain to be discovered.

Another unsolved puzzle is the reason for high prevalence of NTM in elderly females. It has been suggested that estrogen plays a protective role in NTM infection [27]. It is possible that in menopause women, estrogen protection effect disappears and consequently the risk for NTM increases [27]. Another plausible explanation for higher susceptibility to NTM in aged women might be because of decreased serum concentration of macrophage colony-stimulating factor and consequently the low macrophage activity [28]. Probably there are several other factors may play a role in gender susceptibility to NTM that will be uncovered with further investigations [24].

COPD was the most common comorbidity in bronchiectasis and non-bronchiectasis groups. No other comorbidity, except for HIV, demonstrated any association between pulmonary NTM and bronchiectasis. Interestingly, none of the HIV subjects had concurrent bronchiectasis in our study.

The presence of bronchiectasis was higher in shorter and thinner individuals. To our best knowledge, this finding has not been reported previously. Chen and Iseman reported that slender, older women are more susceptible to NTM, however, they did not separate out the presence of bronchiectasis in their review [13].

A common feature of bronchiectasis is malnutrition [29]. Malnutrition causes short height for the age, secondary to slowing skeletal growth, as well as low weight in children [30]. In adults, malnutrition is often related to low weight, sparing any effect in the height. In our study,

the multivariate logistic regression analysis identified the weight (not height) as an independent risk factor for finding bronchiectasis in chest image, suggesting a relationship between adulthood malnutrition with bronchiectasis in subjects with NTM infection. In particular, it would be interesting to determine if this is related to Vitamin D deficiency. We would suggest further investigation on association of malnutrition and bronchiectasis in adults.

In our study, the proportion of NTM subjects without bronchiectasis was greater than reported in other studies. Kim *et al* [12] found that 95% of subjected referred to their clinic were females and > 90% had concurrent bronchiectasis. Our data might be skewed due to reviewing Veterans population, which has dominantly men and high incidence of COPD [31, 32]. Other limitation of our analysis includes its retrospective nature and ICD-9 accuracy, as discussed earlier.

In conclusion, this study demonstrates that subjects with bronchiectasis and pulmonary NTM infections have a specific body habitus. Whether these associations are causal or result of the disease will need further investigation. Future studies are also needed to determine if there are association between some genetic polymorphisms in immune genes and increased susceptibility to NTM in this body habitus, or environmental factors such as malnutrition and vitamin deficiency paly a role in this susceptibility.

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