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MAJOR ARTICLE

Prevalence of Latent Tuberculous Infection in Patients With Nontuberculous Mycobacterial Lung Disease and Colonization: A Prospective Study in an Intermediate Tuberculosis Burden Country

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Background. Controlling latent tuberculosis infection (LTBI) is important in eliminating tuberculosis (TB); however, the prevalence of LTBI has rarely been studied in patients with nontuberculous mycobacterial (NTM) lung disease (LD) and colonization (LC).

Methods. We prospectively recruited subjects with NTM isolated from sputum mycobacterial cultures from December 2011 to June 2019. NTM-LD and NTM-LC were defined according to the American Thoracic Society guidelines. Patients with negative cultures were recruited as controls. Patients with a history of active TB or positive TB cultures were excluded. LTBI was confirmed using a QuantiFERON-TB Gold In-tube test. The prevalence and factors associated with LTBI were analyzed.

Results. A total of 406 participants were enrolled, including 171 in the NTM-LD group, 153 in the NTM-LC group, and 82 in the control group. The prevalence of LTBI was higher in the NTM-LD and NTM-LC groups than in the controls (21.6%, 20.9%, and 6.1%; $P = .006$). Multivariable analysis showed that old age (adjusted odds ratio [aOR], 1.021, per year increment; $P = .042$), NTM-LD (aOR, 4.030; $P = .005$), NTM-LC (aOR, 3.610; $P = .011$, compared with the controls), and pulmonary cavitary lesions (aOR, 3.393; $P = .034$) were independently associated with LTBI.

Conclusions. The prevalence of LTBI was higher in the patients with NTM-LD and NTM-LC than in the controls. Old age, pulmonary cavitation, and NTM isolated from sputum were associated with a higher risk of LTBI.

Keywords. latent tuberculosis infection; nontuberculous mycobacterial lung colonization; nontuberculous mycobacterial lung disease; tuberculosis; QuantiFERON test.

Tuberculosis (TB) remains an important infectious disease worldwide. Although the incidence of TB has decreased in the past decade [1], there were still around 10 million new cases of active TB and nearly 1.2 million deaths in 2019, and TB is still a major public health problem in some countries [2]. The World Health Organization estimated that 24.8% of the global population has latent *Mycobacterium tuberculosis* infection [3]. In addition to optimized treatment for active TB disease, interventions for latent tuberculosis infection (LTBI) are also important to control TB [4]. LTBI screening is recommended for individuals with active TB exposure and close contact, and also for high-risk populations including patients on dialysis, those with immunodeficiency, and those using biological agents [3].

Notably, patients with chronic respiratory diseases are not included in the targeted population for LTBI screening, even though there is a significant association between chronic respiratory diseases and the development of active TB [5]. Chronic respiratory diseases such as chronic obstructive pulmonary disease and bronchiectasis are also associated with nontuberculous mycobacterial lung disease (NTM-LD) [6].

The incidence of NTM-LD has increased in recent decades [6, 7]. A >10-fold increased risk of pulmonary TB has been reported in patients with previous NTM disease [7]. Even though NTM-LD may be associated with LTBI, few studies have investigated this issue. Furuuchi et al used the QuantiFERON-TB test to detect LTBI in Japan, a country with

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a low prevalence of TB, and reported a positive rate of 8% in patients with NTM-LD and 31% in those with nontuberculous mycobacterial lung colonization (NTM-LC) [8]. However, the number of patients in their study was small (N = 112), and there was no control group of patients without NTM isolated from sputum cultures.

To the best of our knowledge, no other study has focused on the association between LTBI and NTM-LD or NTM-LC. This issue is particularly important due to the increasing number of patients with NTM-LD, and to help prevent TB in these patients. Therefore, we conducted this prospective study to investigate the prevalence and characteristics of LTBI in patients with NTM-LD and NTM-LC compared to a control group without NTM in Taiwan, a country with an intermediate TB burden.

METHODS

Participant Enrollment

We prospectively recruited patients who were ≥20 years old with positive NTM sputum cultures from December 2011 to June 2019 at National Taiwan University Hospital (NTUH). The Research Ethics Committee of NTUH approved this study (institutional review board number: 201108022RC, 20142032RINC, and 201705087RINA). The exclusion criteria were patients (1) with human immunodeficiency virus infection; (2) receiving chemotherapy; (3) with a concomitant bacterial pulmonary infection; or (4) with prior active TB disease proven by a positive culture for *M tuberculosis* or compatible pathology or radiological findings. In addition, cultures with *Mycobacterium kansasii*, *Mycobacterium szulgai*, *and Mycobacterium marinum* were excluded, because these NTM species are associated with false-positive QuantiFERON-TB Gold In-tube (QFT-GIT; Qiagen, Germany) test results. All participants signed informed consent before enrollment into this study.

Participant Group Classification

NTM-LD was diagnosed according to the diagnostic guidelines recommended by the American Thoracic Society (ATS) [6]. In brief, NTM-LD was diagnosed if all of the following criteria were met: (1) 2 or more sputum culture-positive specimens for the same NTM species; (2) chest images (radiography or computed tomography) demonstrating lesions compatible with NTM-LD (ie, fibrocavitary lesions or nodular bronchiectasis); (3) presence of respiratory symptoms; and (4) no obvious alternative diagnosis at that time. Patients who had positive sputum cultures for NTM but did not fulfil the ATS diagnostic criteria for NTM-LD were classified into the NTM-LC group. We recruited a control group from our clinics, all of whom had negative chest radiograph findings or negative sputum mycobacterial cultures. TB and NTM-LD or NTM-LC were excluded during clinical workup. Mycobacterial cultures and the identification of NTM species were performed as in our previous report [9].

Investigation of Pulmonary Radiograph

Pulmonary radiographic images of the participants were examined by pulmonologists and classified into different patterns, including fibrocavitary, nodular bronchiectasis, and cavitation. Although different patterns could be present in 1 pulmonary radiograph, the predominant pattern was used for analysis. Radiographic scores were calculated systematically [9]. The lung field was divided into upper, middle, and lower parts in both lung fields, for a total of 6 areas. The scores were calculated as follows: a normal appearance in an area, 0 points; if the lung infiltration involved less than one-third of the area, 1 point; if one-thirds to two-thirds of the area was involved, 2 points; and if the area was almost totally involved, 3 points. The scores were summed, and the total score ranged from 0 to 18.

Definition of LTBI With the QFT-GIT Test and Exclusion of Active TB

Every participant underwent a QFT-GIT test after enrollment to determine LTBI status. The QFT-GIT tests (Qiagen) were performed according to the manufacturer's instructions with a 3-tube system including an *M tuberculosis* antigen tube, positive control tube, and negative control tube. We incubated the participants' blood in the 3 tubes for 16–24 hours, and then isolated the reaction supernatants and examined the concentration of interferon-gamma (IFN-γ) in the tubes.

If the IFN-γ concentration in the antigen tube minus that in the negative control tube (QFT-GIT response) was ≥0.35 IU/mL, the result was defined as being positive; if the QFT-GIT response was <0.35 IU/mL, the result was defined as being negative. If the QFT-GIT response was <0.35 IU/mL and the concentration of IFN-γ in the positive control tube was <0.5 IU/mL or the concentration of IFN-γ in the negative tube was ≥8.0 IU/mL, the QFT-GIT result was defined as being indeterminate. We defined the participants with a positive QFT-GIT test result in whom active TB disease had been excluded as having LTBI. Participants with negative or indeterminate results were classified into the non-LTBI group.

Statistical Analysis

The prevalence rates of LTBI in the control, NTM-LD, and NTM-LC groups were compared using the χ^2 test. Data were analyzed using the Student *t* test and χ^2 test for continuous and categorized variables. The risk factors for LTBI were analyzed using logistic regression analysis. In the multivariable logistic regression analysis of the risk factors for LTBI, all factors with a P value < 0.15 in the χ^2 test were included in forward stepwise regression. All statistical analyses were performed with IBM SPSS version 24.0 software. A P value < .05 was considered to be statistically significant.

RESULTS

Participant Demographics

A total of 406 participants were enrolled, of whom 171 were classified into the NTM-LD group, 153 into the NTM-LC

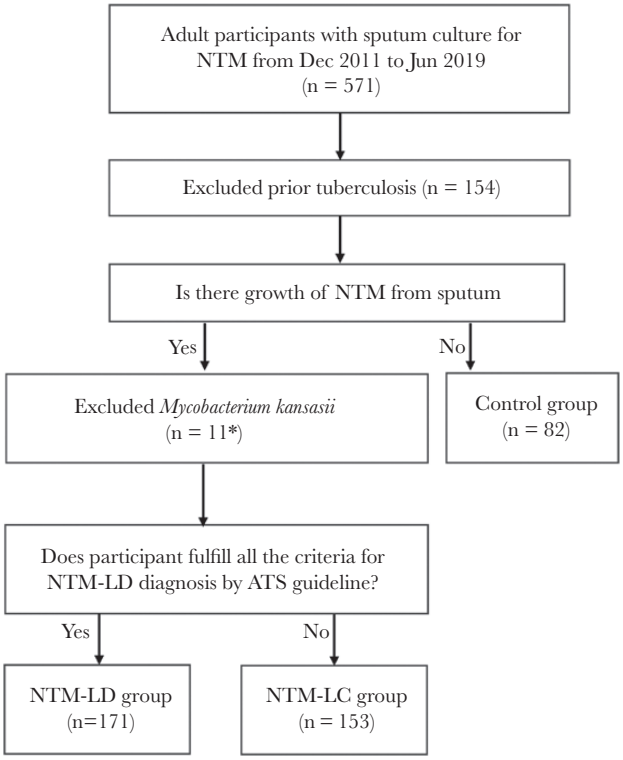

Figure 1. Flowchart of patient enrollment. *None of the patients had *Mycobacterium szulgai* or *Mycobacterium marinum* isolated in sputum cultures. Abbreviations: ATS, American Thoracic Society; NTM, nontuberculous mycobacteria; NTM-LC, nontuberculous mycobacterial lung colonization; NTM-LD, nontuberculous mycobacterial lung disease.

group, and 82 into the control group (Figure 1). Control group participants were younger than the NTM-LD and NTM-LC groups (mean age ± standard deviation [SD]: 57.7 ± 16.7 vs 61.8 ± 13.6 vs 65.1 ± 12.9 years, respectively; $P < .001$). There were fewer males (NTM-LD, 35.7%; control, 53.7%; and NTM-LC, 49.7%; $P = .007$) and the body mass index was lower in the NTM-LD group compared to the control and NTM-LC groups (mean ± SD: 21.0 ± 3.5, 23.5 ± 3.7, and 22.6 ± 3.8 kg/m^2, respectively; $P < .001$) (Table 1).

Clinical, Microbiology, and Radiographic Patterns

With regards to the clinical symptoms, there were significantly higher rates of cough, hemoptysis, and constitutional symptoms in the NTM-LD and NTM-LC groups than in the controls; however, there was no significant difference between the NTM-LD and NTM-LC groups. There were no significant differences among the 3 groups in underlying diseases or comorbidities. Acid-fast stain positivity was significantly higher in the NTM-LD group than in the NTM-LC group. In the NTM-LC group, 98.7% of the acid-fast stain results were negative, and only 0.7% reported grade 1+, and 0.7% reported grade 2+. With regards to the mycobacterial cultures, *Mycobacterium avium* complex (NTM-LD group, 71.3%; NTM-LC group, 66.0%) and *Mycobacterium abscessus* complex (NTM-LD group, 25.1%; NTM-LC group, 23.5%) were the leading pathogens, accounting for 96.4% of the cultures in the NTM-LD group and 89.5% of the cultures in the NTM-LC group. In the lung patterns on chest radiographs, fibrocavitary disease, presence of cavitation, and increased radiographic scores were significantly higher in the NTM-LD group than in the NTM-LC group. Nodular bronchiectasis was the most common pattern, and there was no significant difference between the NTM-LD and NTM-LC groups.

LTBI Status in the NTM-LD and NTM-LC Groups and the Associated Factors

The prevalence of LTBI was significantly higher in the NTM-LD and NTM-LC groups than in the controls (21.6%, 20.9%, and 6.1%, respectively; $P = .006$). Age, status of NTM lung infection, and cavitation on pulmonary radiograph were associated with LTBI (Supplementary Table 1). For the QFT-GIT test, 36 cases (8.87% of all participants) had indeterminate results, including 5 cases (6.1%) in the control group, 12 cases (7.8%) in the NTM-LC group, and 19 cases (11.1%) in the NTM-LD group.

Univariable logistic regression analysis for LTBI-associated factors showed that age (odds ratio [OR], 1.023 [95% CI, 1.004–1.043]; $P = .017$), NTM lung infection status (control group as the reference; NTM-LD group: OR, 4.252 [95% CI, 1.604–11.274], $P = .004$; and NTM-LC group: OR, 4.073 [95% CI, 1.521–10.905], $P = .005$), and cavitation pattern (OR, 3.574 [95% CI, 1.201–10.632], $P = .022$) were significantly associated with LTBI (Table 2). In forward stepwise multivariable logistic regression, age (adjusted odds ratio [aOR], 1.021 [95% CI, 1.001–1.041]; $P = .042$), NTM lung infection status (control group as the reference; NTM-LD group: aOR, 4.030 [95% CI, 1.514–10.727]; $P = .005$; NTM-LC group: aOR, 3.610 [95% CI, 1.338–9.737]; $P = .011$), and cavitation pattern (aOR, 3.393 [95% CI, 1.097–10.499]; $P = .034$) were independently associated with LTBI.

The positive percentage of QFT-GIT tests in different subgroups are shown in Figure 2. Both the NTM-LD and NTM-LC groups had significantly higher positive QFT-GIT test results than the control group. Regarding age and the presence of radiographic cavitation, patients aged >65 years and those with cavitation had a trend of higher QFT-GIT positivity compared with the corresponding counterpart groups. Regarding QFT-GIT values, the NTM-LD and NTM-LC groups had significantly higher QFT-GIT values than the controls (Supplementary Figure 1).

In the NTM-LD group, there was no difference in LTBI among those with different NTM subspecies ($P = .564$, χ^2 test) (Supplementary Table 2). In contrast, in the NTM-LC group, the incidence of LTBI was higher in those with rapidly growing mycobacteria other than *M abscessus*, whereas the incidence of LTBI was lower in those with *M abscessus* and other slowly growing mycobacteria ($P = .015$, χ^2 test) (Supplementary Table 3).

Table 1. Demographics According to Different Nontuberculous Mycobacterial Infection Status

Characteristic	Control (n = 82)	NTM-LD (n = 171)	NTM-LC (n = 153)	*P* Value[a]
Age, y, mean ± SD	57.7 ± 16.7	61.8 ± 13.6[b]	65.1 ± 12.9[c,d]	.001
Male sex	44 (53.7%)	61 (35.7%)[b]	76 (49.7%)[d]	.007
Current smoker	5 (6.1%)	2 (1.2%)	5 (3.3%)	.140
Ex-smoker	11 (13.4%)	21 (12.3%)	27 (17.6%)	
BMI	23.5 ± 3.7	21.0 ± 3.5[b]	22.6 ± 3.8[d]	<.001
Symptoms				
Cough	41 (50%)	121 (70.8%)[b]	96 (62.7%)	.006
Dyspnea	19 (23.2%)	41 (24.0%)	38 (24.8%)	.958
Hemoptysis	2 (2.4%)	41 (24.0%)[b]	33 (21.6%)[c]	<.001
Chest pain	6 (7.3%)	11 (6.4%)	6 (3.9%)	.478
Constitutional symptoms	5 (6.1%)	34 (19.9%)[b]	19 (12.4%)	.010
Underlying diseases				
ESRD	1 (1.2%)	1 (0.6%)	3 (2.0%)	.533
Malignancy	5 (6.1%)	24 (14.0%)	24 (15.7%)[c]	.102
Cirrhosis of liver	0 (0%)	2 (1.2%)	1 (0.7%)	.589
Diabetes mellitus	9 (11.0%)	10 (5.8%)	21 (13.7%)[d]	.055
GERD	5 (6.1%)	14 (8.2%)	12 (7.8%)	.836
Sinusitis	3 (3.7%)	6 (3.5%)	3 (2.0%)	.653
COPD	7 (8.5%)	14 (8.2%)	17 (11.1%)	.639
Asthma	12 (14.6%)	16 (9.4%)	19 (12.4%)	.432
Autoimmune disease	3 (3.7%)	14 (8.2%)	14 (9.2%)	.300
Transplant status	0 (0%)	2 (1.2%)	3 (2.0%)	.428
Mycobacteriology				
AFS positive	0	73 (42.7%)[b]	2 (1.4%)[d]	<.001
NTM culture				
No growth	82 (100%)	0 (0%)[b]	0 (0%)[c]	<.001
MAC	0	122 (71.3%)[b]	101 (66.0%)[c]	
M abscessus	0	43 (25.1%)[b]	36 (23.5%)[c]	
RGM other than *M abscessus*		3 (1.8%)[b]	3 (2.0%)[c]	
SGM other than MAC		0 (0%)[b]	2 (1.3%)[c]	
Mixed		3 (1.8%)[b,e]	11 (7.2%)[c,f]	
QFT-GIT result				
Positive	5 (6.1%)	37 (21.6%)[b]	32 (20.9%)[c]	.009
Negative	72 (87.8%)	115 (67.3%)[b]	109 (71.2%)[c]	
Indeterminate	5 (6.1%)	19 (11.1%)[b]	12 (7.8%)[c]	
Radiographic pattern				
FC	0 (0%)	21 (12.3%)[b]	5 (3.3%)[d]	<.001
NB	28 (34.1%)	131 (76.6%)[b]	108 (70.6%)[c]	<.001
Cavitation	0 (0%)	12 (7.0%)[b]	2 (1.3%)[d]	.003
Radiographic score	1.9 ± 2.1	4.6 ± 2.9[b]	3.7 ± 2.8[c,d]	<.001

Data are presented as No. (%) unless otherwise indicated. Nominal variables were analyzed using the χ^2 test, including sex, smoking status, symptoms, underlying diseases, mycobacteriology, QFT-GIT result, and radiographic patterns. Numerical variables were analyzed using the Student *t* test, including age and BMI.

Abbreviations: AFS, acid-fast stain; BMI, body mass index; COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease; FC, fibrocavitary; GERD, gastroesophageal reflux disease; MAC, *Mycobacterium avium* complex; NB, nodular bronchiectasis; NTM, nontuberculous mycobacteria; NTM-LC, nontuberculous mycobacterial lung colonization; NTM-LD, nontuberculous mycobacterial lung disease; QFT-GIT, QuantiFERON-TB Gold In-tube; RGM, rapid-growing mycobacteria; SD, standard deviation; SGM, slow-growing mycobacteria.

[a]Comparison among the 3 groups using 1-way analysis of variance.

[b]Significant difference between the control and NTM-LD groups using the Student *t* test or χ^2 test as appropriate.

[c]Significant difference between the control and NTM-LC groups using the Student *t* test or χ^2 test as appropriate.

[d]Significant difference between the NTM-LD and NTM-LC groups using the Student *t* test or χ^2 test as appropriate.

[e]Mixed NTM species in culture in the NTM-LD group: MAC and *M abscessus* in 2 participants; MAC and *Mycobacterium fortuitum* in 1 participant.

[f]Mixed NTM species in culture in the NTM-LC group: MAC and *M abscessus* in 4 participants; MAC and *M fortuitum* in 4 participants; MAC, *M abscessus*, and *M fortuitum* in 1 participant; MAC and unidentified NTM in 1 participant; unidentified species in 1 participant.

Follow-up of the TB Status of the Cohort

None of the LTBI cases in this study received treatment for LTBI. We followed their status for ≥2 years, during which 6 patients were diagnosed with new active TB, including 3 (2%) in the NTM-LC group, 2 (1.2%) in the NTM-LD group, and 1 (1.2%) in the control group ($P = .821$, χ^2 test). Of these 6 patients, 3 (1.0%) had a negative QFT-GIT status, 2 (2.7%) had a positive status, and 1 (2.8%) had an indeterminate status ($P = .445$, χ^2 test).

Table 2. Univariable and Multivariable Logistic Regression for Factors Associated With Latent Tuberculosis Infection in All Participants

	Univariable Regression		Multivariable[a]	
Variables	Crude OR (95% CI)	*P* Value	Adjusted OR (95% CI)	*P* Value
Age (years), per 1 year	1.023 (1.004–1.043)	.017	1.021 (1.001–1.041)	.042
Sex (male)	1.395 (.842–2.312)	.196	…	
Autoimmune disease	0.290 (.068–1.244)	.096	…	
NTM infection status				
Controls	Ref	.012	Ref	.019
NTM-LD	4.252 (1.604–11.274)	.004	4.030 (1.514–10.727)	.005
NTM-LC	4.073 (1.521–10.905)	.005	3.610 (1.338–9.737)	.011
Cavitation	3.574 (1.201–10.632)	.022	3.393 (1.097–10.499)	.034

[a]Demographic factors with $P < .15$ between those with and without latent tuberculosis infection (Supplementary Table 1) were included for analysis. Forward stepwise selection was used in multivariable logistic regression.

Abbreviations: CI, confidence interval; NTM, nontuberculous mycobacteria; NTM-LC, nontuberculous mycobacterial lung colonization; NTM-LD, nontuberculous mycobacterial lung disease; OR, odds ratio.

DISCUSSION

In this prospective study, the prevalence of LTBI was significantly higher in the patients with NTM-LD and NTM-LC than in the controls. There was no significant difference in the prevalence of LTBI between the NTM-LD and NTM-LC groups. In addition, old age, NTM-LD or NTM-LC status, and the presence of a cavitary pattern were associated with LTBI. The risk of LTBI in the NTM-LD group was not related to any specific species of NTM; however, since most of the enrolled NTM cases were caused by *M avium* complex and *M abscessus*, we can only conclude that the prevalence of LTBI was similar between NTM infections caused by *M avium* complex and *M abscessus*.

Previous studies of LTBI in high-risk populations in Taiwan have reported a prevalence rate of 25% in patients with end-stage renal disease [10], 20% in kidney transplant recipients [11], 28.2% in patients with diabetes mellitus [12], and 16.8% in residents and workers in long-term care facilities with a mean age of 70 years [13]. In our study, the prevalence of LTBI was around 20% in patients with NTM lung infection, compatible with other LTBI high-risk groups. This may suggest that patients with NTM-LD and NTM-LC are associated with a higher risk of *M tuberculosis* infection.

Although patients with prior TB disease were excluded in this study, we still found a higher prevalence of LTBI in the NTM-LD and NTM-LC groups. Due to the cross-sectional design of this study, we could not confirm whether *M tuberculosis* and NTM were concurrent infections or if there was a causal relationship. Nevertheless, this study is the largest to investigate LTBI in patients with NTM-LD and NTM-LC at present, and it provides important evidence for LTBI interventions.

NTM-LC is defined as patients with airway colonization by NTM but no evidence of active infection who do not usually require NTM treatment [6]. In this study, the NTM-LC group had fewer symptoms, lower NTM bacilli load, less pulmonary radiographic extent, and lower proportion of cavitation

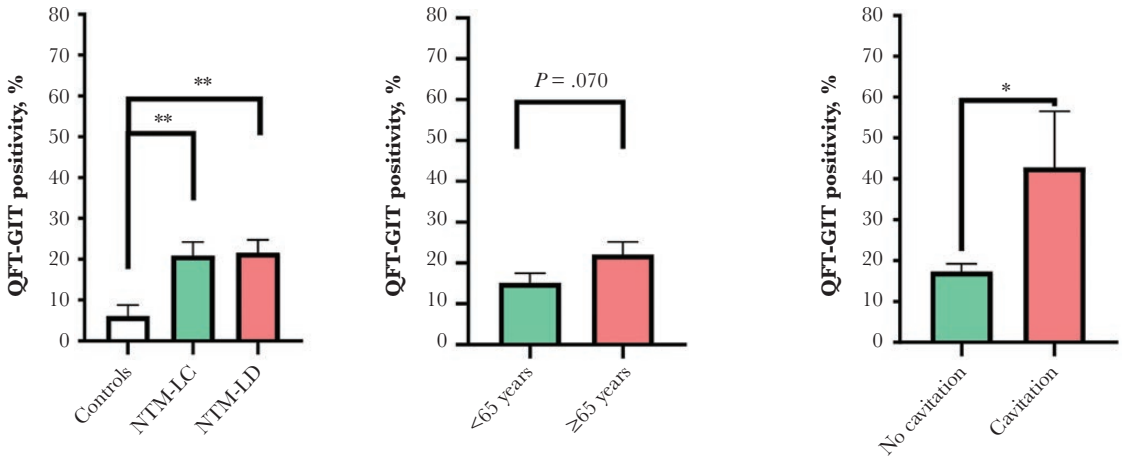

Figure 2. The association between the risk factors for latent tuberculosis infection and positive percentage of QuantiFERON-TB Gold In-tube tests. $*P < .05$; $**P < .01$. Comparisons were performed using χ^2 test. Abbreviations: NTM-LC, nontuberculous mycobacterial lung colonization; NTM-LD, nontuberculous mycobacterial lung disease; QFT-GIT, QuantiFERON Gold In-tube.

compared to the NTM-LD group. Although the patients with NTM-LC had a higher incidence of hemoptysis, a more nodular bronchiectasis pattern on imaging, and a higher radiographic score of disease extent than the control group, there were no significant differences in NTM bacilli burden and fibrocavitary pattern. The NTM-LC group were also older and had a higher percentage of malignancy than the control group. Therefore, the higher prevalence of LTBI in the NTM-LC group may be due to preexisting pulmonary structural changes, especially given the nodular bronchiectasis pattern, and underlying host factors (old age and more malignancy; Table 1).

Previous LTBI studies have reported that old age is an important risk factor for LTBI [10, 14]. The risk of LTBI in the elderly may increase with exposure and contact with TB patients as supported by previous studies of healthcare workers and household contacts [14, 15]. In addition, the adverse effect of aging on immune cells such as macrophages, neutrophils, and dendritic cells may cause T cells to dysfunction, consequently making the host more susceptible to *M tuberculosis* infection [16]. The trend of a decrease in the prevalence of TB in recent decades has also reduced the exposure of younger people to patients with TB [2]. These findings are consistent with our study and may explain the relationship between age and LTBI.

In the present study, lung cavitation was associated with LTBI in multivariable analysis. Although the reason for this association is not clear, it is possible that cavitation is a sign of previous active TB disease that resolved without treatment. The differential diagnosis for pulmonary cavitation includes TB disease (post–primary TB), NTM infection, bacterial pneumonia with abscess and aspergillosis, and noninfectious causes such as cancer, autoimmune diseases, and vascular lesions [17]. The presence of pulmonary cavitary lesions may imply a high risk of *M tuberculosis* infection in patients with cancer or autoimmune disease [18, 19].

The QFT-GIT test examines IFN-γ release in response to TB-specific peptides according to the white blood cells in the patients' blood [20]. Immunocompromised status and prior active TB as well as some NTM species (*M kansasii*, *M szulgai*, and *M marinum*) can lead to false-negative and false-positive results, respectively, in the QFT-GIT test. We thus excluded patients with previous TB and the specific NTM species related to lung infection and colonization. Thirty-six cases (8.87% of all participants) had indeterminate QFT-GIT test results in this study, and the incidence increased with the severity of NTM infection status (from the controls [6.1%] to the NTM-LC group [7.8%] to the NTM-LD group [11.1%]). Previous studies have reported associations between NTM-LD and an immunocompromised status [21], poor nutrition, and other poor clinical conditions [22, 23], which are all risk factors for an indeterminate QFT-GIT test result [20, 24].

There were some limitations to this study. First, the patients' baseline characteristics including age and sex were not exactly matched among the 3 groups. Although we adjusted for these factors in the multivariable regression analysis, selection bias is possible. Second, the pulmonary radiographic patterns were mostly assessed using plain film images as not all patients received chest computed tomography; therefore, the radiographic lesions and scores may be underestimated. Third, patients with prior TB and active TB disease were excluded by clinical history and examinations; however, some patients may still have had spontaneously resolved TB disease without a definite diagnosis or treatment. Fourth, the number of cases is too small to analyze the incidence of active TB disease. Finally, we focused on patients with NTM-LD and NTM-LC and compared them with a control group; however, the prevalence of LTBI in the general population is unknown and requires further investigations.

In conclusions, LTBI was highly prevalent in both the NTM-LD and NTM-LC patients in this study. Old age, pulmonary cavitation, NTM-LD, and NTM-LC were associated with LTBI. Further studies are needed to clarify the association between LTBI and NTM lung infection. Whether screening for LTBI is needed in populations with NTM lung infection to control TB requires further validation.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. C.-C. S. conceived and conducted the study. H.-S. L., Y.-F. W., P.-H. W., C.-Y. C., S.-W. P., C.-C. S., and Y.-J. T. were involved in data interpretation and analysis. C.-C. S., H.-S. L., and Y.-F. W. were responsible for manuscript preparation.

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Ethics approval. The Research Ethics Committee of National Taiwan University Hospital approved this study (institutional review board number: 201108022RC, 20142032RINC, and 201705087RINA). Written informed consent was obtained from each participant at the time of enrollment.

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Potential conflicts of interest. Qiagen provided tubes of QuantiFERON-G plus for 200 tests to C.-C. S. for another study. All other authors report no potential conflicts of interest.

References

1. Wejse C. Tuberculosis elimination in the post millennium development goals era. Int J Infect Dis **2015**; 32:152–5.
2. World Health Organization. Global tuberculosis report 2020. Geneva, Switzerland: WHO; **2020**. https://www.who.int/publications/i/item/9789240013131. Accessed 26 July 2021.
3. Getahun H, Matteelli A, Abubakar I, et al. Management of latent mycobacterium tuberculosis infection: WHO guidelines for low tuberculosis burden countries. Eur Respir J **2015**; 46:1563–76.
4. Lonnroth K, Migliori GB, Abubakar I, et al. Towards tuberculosis elimination: an action framework for low-incidence countries. Eur Respir J **2015**; 45:928–52.

5. Byrne AL, Marais BJ, Mitnick CD, Lecca L, Marks GB. Tuberculosis and chronic respiratory disease: a systematic review. Int J Infect Dis **2015**; 32:138–46.
6. Griffith DE, Aksamit T, Brown-Elliott BA, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med **2007**; 175:367–416.
7. Hsing SC, Weng SF, Cheng KC, et al. Increased risk of pulmonary tuberculosis in patients with previous non-tuberculous mycobacterial disease. Int J Tuberc Lung Dis **2013**; 17:928–33.
8. Furuuchi K, Morimoto K, Yoshiyama T, et al. Interrelational changes in the epidemiology and clinical features of nontuberculous mycobacterial pulmonary disease and tuberculosis in a referral hospital in Japan. Respir Med **2019**; 152:74–80.
9. Pan SW, Shu CC, Feng JY, et al. Microbiological persistence in patients with *Mycobacterium avium* complex lung disease: the predictors and the impact on radiographic progression. Clin Infect Dis **2017**; 65:927–34.
10. Shu CC, Hsu CL, Lee CY, et al. Comparison of the prevalence of latent tuberculosis infection among non-dialysis patients with severe chronic kidney disease, patients receiving dialysis, and the dialysis-unit staff: a cross-sectional study. PLoS One **2015**; 10:e0124104.
11. Shu CC, Tsai MK, Lin SW, Wang JY, Yu CJ, Lee CY. Latent tuberculosis infection increases in kidney transplantation recipients compared with transplantation candidates: a neglected perspective in tuberculosis control. Clin Infect Dis **2020**; 71:914–23.
12. Leow MK, Dalan R, Chee CB, et al. Latent tuberculosis in patients with diabetes mellitus: prevalence, progression and public health implications. Exp Clin Endocrinol Diabetes **2014**; 122:528–32.
13. Chiu T-F, Yen M-Y, Shie Y-H, Huang H-L, Chen C-C, Yen Y-F. Determinants of latent tuberculosis infection and treatment interruption in long-term care facilities: a retrospective cohort study in Taiwan [manuscript published online ahead of print 11 October 2021]. J Microbiol Immunol Infect **2021**. doi:10.1016/j.jmii.2021.09.013.
14. Yeon JH, Seong H, Hur H, et al. Prevalence and risk factors of latent tuberculosis among Korean healthcare workers using whole-blood interferon-gamma release assay. Sci Rep **2018**; 8:10113.
15. Middelkoop K, Bekker LG, Morrow C, Lee N, Wood R. Decreasing household contribution to TB transmission with age: a retrospective geographic analysis of young people in a South African township. BMC Infect Dis **2014**; 14:221.
16. Salam N, Rane S, Das R, et al. T cell ageing: effects of age on development, survival and function. Indian J Med Res **2013**; 138:595–608.
17. Nin CS, de Souza VVS, Alves GRT, et al. Solitary lung cavities: CT findings in malignant and non-malignant disease. Clin Radiol **2016**; 71:1132–6.
18. Hong S, Mok Y, Jeon C, Jee SH, Samet JM. Tuberculosis, smoking and risk for lung cancer incidence and mortality. Int J Cancer **2016**; 139:2447–55.
19. Bonfiglioli KR, Ribeiro AC, Moraes JC, et al. LTBI screening in rheumatoid arthritis patients prior to anti-TNF treatment in an endemic area. Int J Tuberc Lung Dis **2014**; 18:905–11.
20. Pai M, Zwerling A, Menzies D. Systematic review: T-cell-based assays for the diagnosis of latent tuberculosis infection: an update. Ann Intern Med **2008**; 149:177–84.
21. Shu CC, Wang JY, Wu MF, et al. Attenuation of lymphocyte immune responses during *Mycobacterium avium* complex–induced lung disease due to increasing expression of programmed death-1 on lymphocytes. Sci Rep **2017**; 7:42004.
22. Oh J, Park HD, Kim SY, Koh WJ, Lee SY. Assessment of vitamin status in patients with nontuberculous mycobacterial pulmonary disease: potential role of vitamin a as a risk factor. Nutrients **2019**; 11:343.
23. Faverio P, De Giacomi F, Bodini BD, et al. Nontuberculous mycobacterial pulmonary disease: an integrated approach beyond antibiotics. ERJ Open Res **2021**; 7:00574-2020.
24. Shu CC, Wu VC, Yang FJ, et al. Predictors and prevalence of latent tuberculosis infection in patients receiving long-term hemodialysis and peritoneal dialysis. PLoS One **2012**; 7:e42592.