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Original Article

Association of pulmonary nontuberculous mycobacteria with the outcomes of patients with lung cancer: A retrospective matched cohort study with a special emphasis on the impact of chemotherapy

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KEYWORDS
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Abstract *Introduction:* Nontuberculous mycobacteria (NTM) may be present in the respiratory tract of patients with lung cancer. We investigated the association of pulmonary NTM with the clinical features and outcomes of patients with lung cancer.
Methods: Between 2015 and 2019, the data of patients diagnosed with lung cancer at a medical center in northern Taiwan were analyzed. Patients whose respiratory specimens were culture-positive for NTM were identified (NTM group). For each patient in the NTM group, a matched control was selected (control group). The survival of the two groups was compared using the Kaplan–Meier method and Cox proportional hazards regression analysis.
Results: Among 8718 patients with lung cancer, 5418 (62.1%) underwent a sputum mycobacterial culture. At least one NTM species was isolated from 138 (2.5%) patients. The median age was 72 years (range: 64–80). In the NTM group, 19.8% fulfilled both the microbiological and radiographic criteria for the diagnosis of NTM lung disease. Compared with the control group, the NTM group exhibited a lower body mass index (22.4 vs. 23.6, $p = 0.025$) and a higher prevalence of structural lung disease (38.9% vs. 22.2%, $p = 0.004$). The two-year survival was not significantly different between the two groups (hazard ratio [HR]: 1.110; 95% confidence interval [CI]: 0.702–1.754, $p = 0.656$). In patients receiving chemotherapy, pulmonary NTM was associated with worse survival (HR: 2.497, 95% CI: 1.262–4.943, $p = 0.009$).

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Conclusions: Except in patients receiving chemotherapy, pulmonary NTM may not be clinically relevant in patients with lung cancer.

Introduction

Nontuberculous mycobacteria (NTM) are mycobacterial species other than *Mycobacterium tuberculosis* complex and *Mycobacterium leprosy*. In the past decade, both the incidence and prevalence of NTM lung disease have increased worldwide.[1] A cross-sectional study on mycobacteria isolated from respiratory specimens collected in northern Taiwan indicated that the annual incidence of NTM infection and colonization significantly increased during the study period.[2,3] NTM lung disease occurs primarily in four groups of patients: those with structural lung disease (e.g., bronchiectasis and chronic obstructive pulmonary disease), those with immunologic or genetic disorders (e.g., cystic fibrosis, primary ciliary dyskinesia, and common variable immunodeficiency), those with immunosuppressive agent use (e.g., an inhaled corticosteroid and anti-TNF-a therapy), and those with no known overt lung or immunologic abnormalities.[4,5] Structural lung disease is also associated with the development of lung cancer, either due to chronic inflammation or sharing risk factors.[6,7] Therefore, patients with lung cancer may sometimes have NTM isolated from their respiratory specimens. As a consequence, NTM lung disease has been detected in 1.4%—25% of patients with lung cancer.[8—11]

Studies on the clinical features and prognosis of patients with lung cancer in the presence of pulmonary NTM, however, remain limited, and the results are controversial. A small retrospective study conducted in Japan revealed that NTM coexistence did not alter the prognosis of patients with lung cancer.[8] Another retrospective study on 63 patients with lung cancer and the presence of pulmonary NTM revealed that 60% of patients were not treated for NTM lung disease and remained asymptomatic for a median follow-up period of more than one year.[12] Some of these patients received chemotherapy, and regular follow-up without treatment was suggested.[12] Another retrospective study on 29 patients with lung cancer and the presence of pulmonary NTM revealed that 28.5% of patients experienced deterioration of NTM lung disease during chemotherapy.[13] Therefore, this retrospective matched cohort study investigated the association of pulmonary NTM and the clinical features and outcomes of patients with lung cancer, with an emphasis on those receiving chemotherapy.

Methods

Patients and study design

The study was conducted at a medical center in northern Taiwan and was approved by the institutional research ethics committee (202008058RINB). Informed consent was deemed unnecessary due to the retrospective nature of the study. Adult patients (age >20) with lung cancer diagnosed between 1 January 2015 and 31 December 2019 were selected. The lung cancer diagnosis was confirmed using histopathological or cytological methods. Among them, those who underwent a mycobacterial culture for respiratory specimens before or while diagnosed as having lung cancer were identified. Of them, those with presence of pulmonary NTM, defined as respiratory specimens being culture-positive for NTM, were selected for further study (NTM group). Presence of congenital or acquired immunodeficiency was not an exclusion criterion. For each patient in the NTM group, a patient with lung cancer whose respiratory specimen was culture-negative for NTM and who matched in age (within five years), sex, respiratory specimen type, histology type, stage, and initial treatment was selected (control group).

In this hospital, bronchial washing for mycobacterial culture was performed routinely before or after transbronchial lung biopsy. Tissue culture and sputum culture were performed if the primary care physician deemed necessary. Each respiratory specimen was cultured in Mycobacteria Growth Indicator Tube (liquid medium) and Löwenstein—Jensen medium (solid medium). NTM lung disease and NTM lung colonization was diagnosed according to the current guidelines.[14]

We reviewed patient's images and histology reports and re-staged with the American Joint Committee on Cancer (AJCC) stage classification for lung cancer, eighth edition.[15] Histological types of lung cancer included adenocarcinoma, squamous cell carcinoma, and small cell lung cancer. Cancers were dichotomized into early and locally advanced lung cancer (Stage I, II, and IIIA) and advanced lung cancer (Stage IIIB, IIIC, and IV). The four types of initial treatment included definitive radiation, radical surgery, or concurrent chemoradiotherapy; chemotherapy combined with palliative radiotherapy or immunotherapy; a tyrosine kinase inhibitor; and palliative treatment.

Data collection

We used a prespecified case record form and collected the data regarding demographics, comorbidities, the Charlson comorbidity index,[16] histology types, cancer stage,[15] initial treatments, respiratory specimen types, NTM species, NTM lung disease status, and survival from the medical records. NTM lung disease status was assessed as per current NTM guidelines.[14]

Outcomes

Each patient was followed up for two years after the diagnosis of lung cancer was confirmed, loss of follow-up, or death, whichever occurred first. Two-year survival was the primary endpoint.

Statistical analysis

Data were presented as number (percentage) or median (interquartile range [IQR]) as appropriate. Mann—Whitney U test, chi-square test, and Fisher's exact test were used for intergroup comparisons. Moreover, the effects of NTM and covariates, with a significant difference between the NTM and control groups, were investigated using the multivariate Cox proportional hazards regression analysis. We reported hazard ratios (HRs) and the corresponding 95% confidence intervals (CIs) and used the Kaplan—Meier estimator to generate survival curves. *P* values less than 0.05 were considered statistically significant, and statistical analyses were performed using the IBM SPSS Version 25 software.

In the subpopulation analyses, the following subgroups were selected and analyzed: non-small cell lung cancer, early and locally advanced lung cancer, advanced lung cancer, receiving chemotherapy, receiving tyrosine kinase inhibitor, NTM lung disease, and NTM colonization. Patients receiving chemotherapy included those who received concurrent chemoradiotherapy and chemotherapy combined with or without palliative radiotherapy and immunotherapy.

Results

Patient selection and demographics

Among the 8718 patients who received a diagnosis of lung cancer between January 2015 and December 2019 (Fig. 1), 3300 (37.9%) did not undergo a mycobacterial culture for respiratory specimens. The remaining 5418 (62.1%) patients underwent a mycobacterial culture for sputum, bronchoscopic, or surgical specimens before lung cancer diagnosis. At least one NTM isolate was reported for 138 (2.5%) patients. Twelve patients were excluded because we could not identify matched controls, leaving 126 patients in the NTM group and 126 matched patients in the control group. All were diagnosed from histopathology, except one 82-years-old man with stage IIIA adenocarcinoma being diagnosed by bronchial brushing cytology. Because of old age and poor performance status, he received definitive radiotherapy without systemic treatment. Among the 252 patients, 141 (56.0%) patients were followed up for two years, 77 (30.6%) died within 2 years, and 34 (13.5%) were lost to follow-up.

The median age was 72 years (64—80) in the NTM group and 73 years (63—78) in the control group; 64.2% of patients were men (Table 1). The median Charlson comorbidity index was 4 (2—5) in both the NTM and control groups.

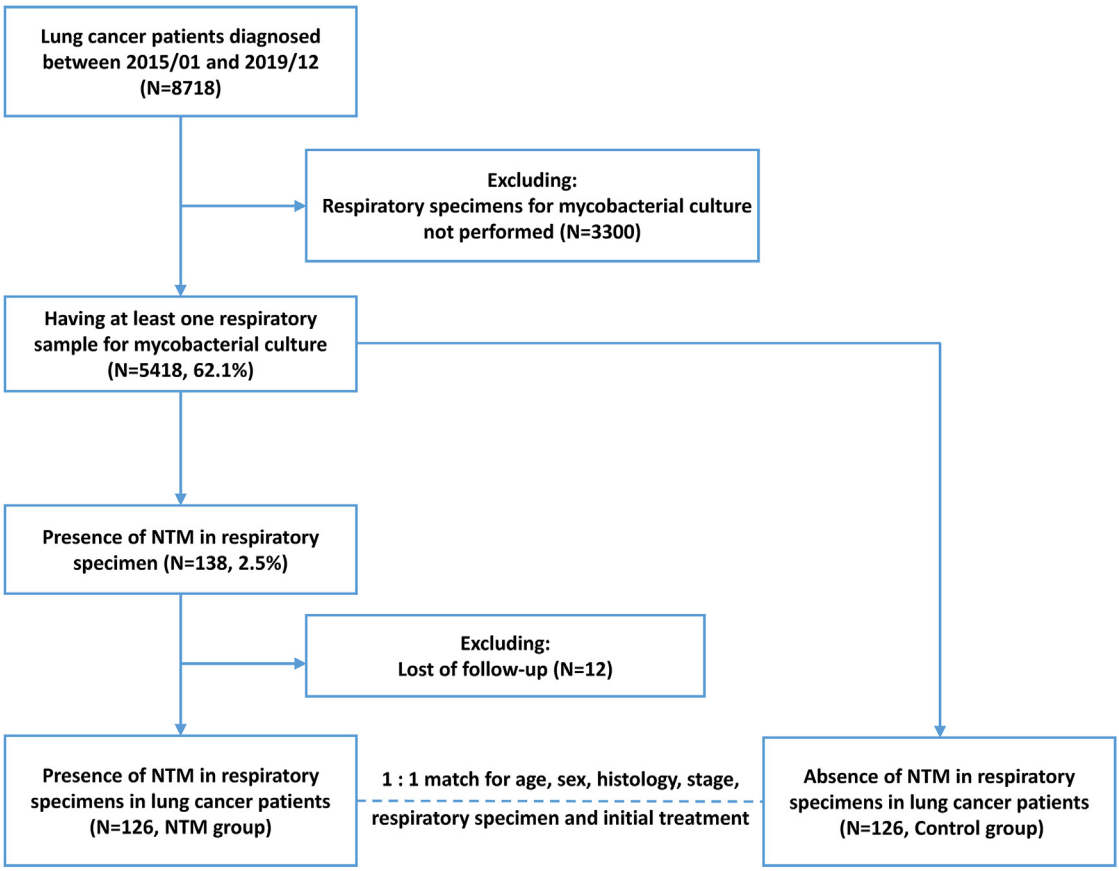

Fig. 1. Patient selection process (NTM, nontuberculous mycobacteria).

Table 1 Baseline characteristics of patients.

	NTM group (n = 126)	Control group (n = 126)	*p*-value
Age, year	72 [64–80]	73 [63–78]	0.517
Male	81 (64.2)	81 (64.2)	>0.999
Histology			
Adenocarcinoma	87 (69.0)	87 (69.0)	>0.999
Squamous cell carcinoma	21 (16.7)	21 (16.7)	>0.999
Small cell lung cancer	9 (7.1)	9 (7.1)	>0.999
Others	9 (7.1)	9 (7.1)	>0.999
Staging			
I, II, IIIA	54 (42.9)	54 (42.9)	>0.999
IIIB, IIIC, IV	72 (57.1)	72 (57.1)	>0.999
Brain metastasis	13 (10.3%)	13 (10.3%)	>0.999
Initial lung cancer treatment			
Radical surgery, definite RT, or CCRT	55 (43.7)[a]	55 (43.7)[a]	>0.999
CT ± palliative RT ± IT	37 (29.4)	37 (29.4)	>0.999
Tyrosine-kinase inhibitors	23 (18.3)	23 (18.3)	>0.999
Palliative treatment	11 (8.7)	11 (8.7)	>0.999
BMI, kg/m2	22.4 [19.8–24.5]	23.6 [21.3–25.7]	0.025
Current smoker	67 (53.2)	70 (55.6)	0.704
ECOG 0 or 1	102 (81.0%)	97 (77.0%)	0.651
Comorbidities			
Charlson comorbidity index	4 [2–5]	3 [2–5]	0.579
Hypertension	60 (47.6)	64 (50.8)	0.614
Structural lung disease[b]	49 (38.9)	28 (22.2)	0.004
Diabetes mellitus	20 (15.9)	26 (20.6)	0.328
Cardiovascular disease[c]	22 (17.5)	17 (13.5)	0.384
Other malignancy	13 (10.3)	16 (12.7)	0.554
Chronic kidney disease	11 (8.7)	9 (7.1)	0.641
Heart failure	4 (3.1)	3 (2.4)	>0.999
Autoimmune disease	4 (3.1)	5 (4.0)	>0.999
Hematologic malignancy	3 (2.4)	3 (2.4)	>0.999
Dialysis	2 (1.6)	2 (1.6)	>0.999
Asthma	1 (0.8)	3 (2.4)	0.622
Cirrhosis of liver	1 (0.8)	2 (1.6)	>0.999
Interstitial lung disease	1 (0.8)	1 (0.8)	>0.999
HIV infection	0	0	

[a] Three patients received concurrent chemoradiotherapy.
[b] Including chronic obstructive pulmonary disease, a history of pulmonary tuberculosis, and bronchiectasis.
[c] Including coronary artery disease, peripheral arterial occlusive disease, and stroke.
Abbreviations: RT, radiotherapy; CCRT, concurrent chemoradiotherapy; CT, chemotherapy; IT, immunotherapy.
Data are expressed as number (%) or median (interquartile range).

Table 2 Nontuberculous mycobacteria (NTM) species of clinical isolates.

	No. Of patients	Culture-positive specimen		
		Sputum	Bronchial washing	Lung issue
M. avium complex	57 (45.2)	52	7[a]	1[b]
M. abscessus complex	21 (16.7)	20	2	0
M. fortuitum	18 (14.3)	18	0	0
M. gordonae	13 (10.3)	13	0	0
M. kansasii	11 (8.7)	8	3	1
M. chelonae	2 (1.6)	2	0	0
Other species	24 (19.0)	23	1	0

[a] Two patients in the group received anti-NTM treatment.
[b] One patient in the group received anti-NTM treatment.
Data are expressed as numbers (%).

Table 3 Causes of death.

	NTM group		Control group	
	All (n = 126)	CT (n = 40)	All (n = 126)	CT (n = 40)
Overall	41 (32.5)	25 (62.5)	36 (28.6)	18 (45.0)
Bacterial pneumonia	25 (19.8)	17 (42.5)	13 (10.3)	7 (17.5)
Klebsiella pneumoniae	6 (4.8)		2 (1.6)	
Pseudomonas aeruginosa	2 (1.6)		2 (1.6)	
Acinetobacter baumannii	3 (2.4)		2 (1.6)	
Staphylococcus aureus	2 (1.6)		0	
Others	12 (9.5)[a]		7 (5.6)[b]	
Lung cancer progression	8 (6.3)	4 (10)	15 (11.9)	6 (15.0)
Others	5 (4.0)	3 (7.5)	8 (6.3)	4 (10)
Unknown	3 (2.4)	1 (2.5)	1 (2.4)	1 (2.5)

[a] The causal microorganism was *Acinetobacter nosocomialis* in 3 patients, *Enterobacter cloacae* in 2 patients, *Burkholderia cepacia* complex in 2 patients, *Ralstonia mannitolilytica* in 2 patients, *Fusobacterium necrophorum* in 1 patient, and not identified in 2 patients.
[b] The causal microorganism was *Serratia marcescens* in 1 patient, *Enterobacter aerogenes* in 1 patient, *Pseudomonas mendocina* in 1 patient, and not identified in 4 patients.
Data are expressed as number (%).
Abbreviation: CT, chemotherapy.

Adenocarcinoma (69%) was the most common form of lung cancer, followed by squamous cell carcinoma (16.7%), small cell lung cancer (7.1%), and other forms (7.1%). Among all carcinomas, 57.1% were in the advanced stage. The initial treatment was radical surgery, definitive radiotherapy, or concurrent chemoradiotherapy in 43.7% of patients, chemotherapy combined with palliative radiotherapy or immunotherapy in 29.4% of patients, and tyrosine kinase inhibitors in 18.3% of patients. None received immunotherapy alone. Compared with the control group, the NTM group exhibited a lower body-mass index (BMI; 22.4 vs. 23.6, $p = 0.025$) and a higher prevalence of structural lung disease (38.9% vs. 22.2%, $p = 0.004$). The most commonly isolated NTM species was *Mycobacterium avium* complex (45.2%), followed by *Mycobacterium abscessus* complex (16.7%; Table 2).

In the NTM group, 112 patients had NTM isolated only from sputum, two from lung tissue, and 12 from bronchoscopic specimens. Among them, 48 (38.0%) and 34 (27.0%) patients fulfilled the microbiological and radiographic criteria for the diagnosis of NTM lung disease, respectively.[14] 25 (19.8%) fulfilled both criteria, and it included 8 (20%) of 40 who received chemotherapy. Three patients, who did not receive chemotherapy, received anti-NTM treatment during the follow-up period (Table 2). One of them had NTM isolated from lung tissue and the remaining two from bronchoscopic specimens. After the three patients were diagnosed as having stage I adenocarcinoma and concomitant bronchiectasis, they received lobectomy plus lymph node resection and were alive at the 2-year follow-up.

Causes of death

In the NTM group, 41 (32.5%) patients died within two years. The most common cause of death was bacterial pneumonia complicated by respiratory failure, followed by lung cancer progression (Table 3). Among the 25 patients who died of bacterial pneumonia, one had *Mycobacterium kansasii* isolated from lung tissue. The *M. kansasii* infection was not treated, and the patient died of aspiration pneumonia with septic shock. Culture from pleural effusion yielded *Fusobacterium necrophorum*. The patient was diagnosed as having stage IIIC small cell lung cancer and had received concurrent chemoradiotherapy. In the control group, 36 (28.6%) patients died within two years. The most common cause of death was lung cancer progression, followed by bacterial pneumonia complicated by respiratory failure (Table 3).

Among patients who received chemotherapy with or without other treatment modalities, 25 (62.5%) patients died within two years in the NTM group, with 17 (42.5%) dying of bacterial pneumonia complicated by respiratory failure. In the control group, 18 (45%) patients died within 2 years. Among them, seven (17.5%) patients died of bacterial pneumonia complicated by respiratory failure and six (15.0%) died of cancer progression (Table 3).

Survival analysis and subpopulation analyses

The Kaplan–Meier survival analysis (Fig. 2A) and multivariate Cox proportional hazards regression analysis revealed no difference in two-year survival between the NTM and control groups (HR: 1.110; 95%, CI: 0.702–1.754; $p = 0.656$). However, BMI was an independent prognostic factor for two-year survival (HR: 0.914, 95% CI: 0.865–0.965; $p = 0.001$) (Supplementary Table S1).

The subpopulation analysis revealed no difference in the two-year survival among patients with non-small cell lung cancer, NTM lung disease, early and locally advanced cancer, advanced cancer, and receiving tyrosine kinase inhibitors (Table 4 and Fig. 2B–E). The two-year survival was also not different between patients with NTM lung disease and those with NTM lung colonization in the multivariate Cox proportional hazards regression analysis (HR: 0.524; 95% CI: 0.211–1.301; p = 0.164) (Supplementary Table S2).

However, in the subpopulation receiving chemotherapy, pulmonary NTM was associated with shorter survival (HR: 2.497; 95% CI: 1.262–4.943; $p = 0.009$; Fig. 2F).

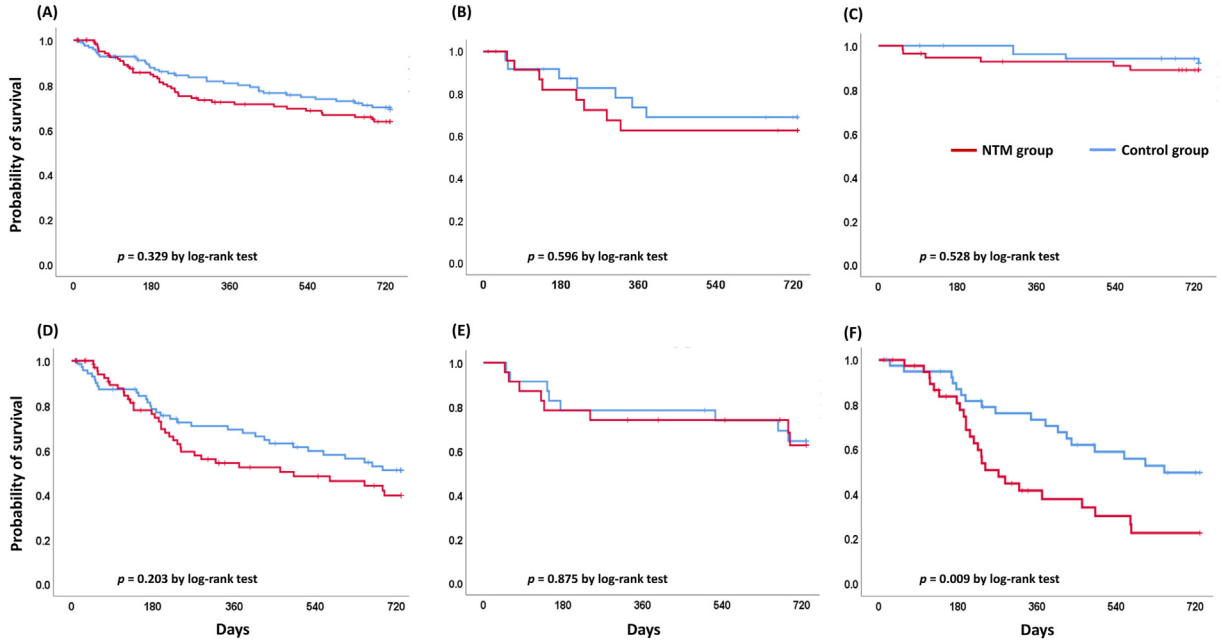

Fig. 2. Kaplan–Meier plot and log-rank test for 2-year survival of the NTM and control groups in overall study population (A) and in different subpopulations, including NTM lung disease (B), early or locally advanced stage (C), advanced stage (D), receiving tyrosine kinase inhibitors (E), and receiving chemotherapy (F).

Discussion

This retrospective matched cohort study on patients with lung cancer and the presence of pulmonary NTM revealed two major findings. First, 2.5% of patients with lung cancer exhibited the presence of NTM in their respiratory tract. Second, although with no clinical relevance, pulmonary NTM was associated with worse two-year survival in patients receiving chemotherapy. To the best of our knowledge, this is the first study investigating the effect of pulmonary NTM on the survival of patients with lung cancer.

Table 4 Multivariate stratified Cox proportional hazards regression analysis for the effect of pulmonary non-tuberculous mycobacteria (NTM) on the 2-year survival of different subpopulations.

	Hazard ratio	95% confidence interval	*p*-value
Overall study population	1.110	0.702–1.754	0.656
Sub-population			
Non-small cell lung cancer	1.105	0.678–1.803	0.689
NTM lung disease	1.415	0.393–5.096	0.595
Early stage	1.179	0.313–4.439	0.808
Advanced stage	1.206	0.731–1.988	0.463
Chemotherapy[a]	2.497	1.262–4.943	0.009
Tyrosine-kinase inhibitor	1.091	0.403–2.955	0.863

[a] Chemotherapy included concurrent chemoradiotherapy and chemotherapy combined with or without palliative radiotherapy and immunotherapy.
The analyses were adjusted for the Charlson comorbidity index, body mass index, and structural lung disease.

The prevalence of pulmonary NTM in patients with lung cancer in the literature varies widely, partly due to the small number of cases. The prevalence reported in this study (2.5%) is comparable with that of a previous report (1.4%).[8] However, Lande L. et al. Reported that 62 of 249 (25%) patients with lung cancer had *M. avium* complex isolated from their respiratory specimens.[10] Although the coexistence of lung cancer and pulmonary NTM is not rare, the prognostic effect of NTM in patients with lung cancer remains controversial. The overlapping symptoms and radiological findings of NTM lung disease and lung cancer progression pose difficulties in disease differentiation. Therefore, investigating the clinical relevance of pulmonary NTM in patients with lung cancer is not easy. Although this study has a retrospective design, it is the first and largest longitudinal study to provide the best estimate of the prevalence of pulmonary NTM in patients with lung cancer.

The finding revealing the association of a worse two-year survival with pulmonary NTM in patients with lung cancer receiving chemotherapy is both novel and practically important. In the NTM group, the most common cause of death in patients receiving chemotherapy was bacterial pneumonia complicated by respiratory failure and not NTM lung disease or lung cancer progression. This finding may have two possible explanations. First, pulmonary NTM can

cause airway inflammation and lead to epithelial damage and scarring over time, which in turn compromises airway mucus clearance and increases the risk of pneumonia.[17,18] Second, pulmonary NTM might be associated with structural changes in the lungs and impaired local immunity.[19] Because chemotherapy directly inhibits effector cells or indirectly induces immune paralysis,[20] it can further compromise the local defense mechanism[13] and increase the susceptibility to bacterial infections.[21] Therefore, as indicated by this study, bacteriological tests should be performed to detect pulmonary NTM in patients with lung cancer before chemotherapy initiation. Furthermore, during chemotherapy, pulmonary NTM should increase the clinicians' suspicion of bacterial infection of the lungs in patients with lung cancer.

In this study, anti-NTM treatment was not initiated in the patients who met both the microbiological and radiographic criteria of NTM lung disease[14] and received chemotherapy, probably because of three reasons. First, the clinical course of NTM lung disease is variable, and there is no consensus regarding the optimal timing to initiate treatment.[14] Second, NTM lung disease requires a prolonged treatment (usually longer than 12 months) with multiple toxic drugs (adverse effects include gastrointestinal upset, nephrotoxicity, hepatotoxicity, and hearing impairment)[18] that are usually intolerable for patients with cancer. Third, antimycobacterial drugs, especially rifampin, have clinically significant drug—drug interaction with chemotherapeutic agents.[13,18] For example, rifampin may enhance paclitaxel metabolism, resulting in decreased paclitaxel plasma concentrations.[22]

The current study did not specifically investigate the impact of NTM lung disease on the survival of lung cancer patients. In study like this, clear differentiation between NTM lung disease and colonization was always difficult. The number of sputum samples in this retrospective study varied. Some may have typical radiographical manifestations of NTM lung disease but failed to fulfill every component of the diagnostic criteria because more sputum samples were not collected. On the other hand, radiographical pattern may be not typical for NTM lung disease due to the coexistence of lung cancer. However, no significant difference in two-year survival was noted between patients with NTM lung disease and those with NTM lung colonization.

This study has some limitations. First, bias in case selection is likely because mycobacterial culture was not routinely performed for every patient with lung cancer. Furthermore, the prevalence of pulmonary NTM may be overestimated because those who underwent mycobacterial cultures for respiratory specimens may indeed have some symptoms suggestive of pulmonary infection. Second, the small sample size and single-center retrospective design may bias the results because of no standard protocol for the evaluation and management of NTM lung disease in patients with lung cancer. Moreover, treatment for lung cancer is complicated, and pulmonary NTM may itself alter the cancer treatment plan. Third, BMI has a J-shaped association with all-cause mortality.[23] Worse outcome appears at either side out of the healthy range. However, we treated the BMI as a continuous variable because the point of most benefit of BMI in this study population is currently unknown. Fourth, though presence of structural lung disease was included in the regression model, the impact of its severity was not addressed in this study. Fifth, the effect of anti-NTM treatment was not investigated. Last, NTM subspecies identification was not performed. This is crucial because the survival of patients is associated with the type of subspecies.[24]

Conclusion

Pulmonary NTM was detected in approximately 2.5% of patients with lung cancer and was not associated with worse survival, except in those receiving chemotherapy. Although routine mycobacterial culture for respiratory specimens is not helpful for all patients with lung cancer, it should be considered before chemotherapy.

Abbreviations

BMI	body-mass index
CI	confidence interval
HR	hazard ratio
IQR	interquartile range
NTM	nontuberculous mycobacteria

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Consent for publication

Not applicable.

Declaration of competing interest

None.

References

1. Johnson MM, Odell JA. Nontuberculous mycobacterial pulmonary infections. *J Thorac Dis* 2014 Mar;**6**(3):210—20.
2. Chien JY, Lai CC, Sheng WH, Yu CJ, Hsueh PR. Pulmonary infection and colonization with nontuberculous mycobacteria, Taiwan, 2000-2012. *Emerg Infect Dis* 2014 Aug;**20**(8):1382—5.
3. Lee MR, Chang LY, Ko JC, Wang HC, Huang YW. Nontuberculous mycobacterial lung disease epidemiology in Taiwan: a systematic review. *J Formos Med Assoc* 2020 Jun;**119**(Suppl 1): S4—12.
4. Honda JR, Knight V, Chan ED. Pathogenesis and risk factors for nontuberculous mycobacterial lung disease. *Clin Chest Med* 2015 Mar;**36**(1):1—11.
5. Shu CC, Wu MF, Pan SW, Wu TS, Lai HC, Lin MC. Host immune response against environmental nontuberculous mycobacteria and the risk populations of nontuberculous mycobacterial lung disease. *J Formos Med Assoc* 2020 Jun;**119**(Suppl 1):S13—22.

6. Chung WS, Lin CL, Hsu WH, Kao CH. Increased risk of lung cancer among patients with bronchiectasis: a nationwide cohort study. *QJM* 2016 Jan;**109**(1):17—25.
7. Kusumoto T, Asakura T, Suzuki S, Okamori S, Namkoong H, Fujiwara H, et al. Development of lung cancer in patients with nontuberculous mycobacterial lung disease. *Respir Investig* 2019 Mar;**57**(2):157—64.
8. Tamura A, Hebisawa A, Sagara Y, Suzuki J, Masuda K, Baba M, et al. [Pulmonary nontuberculous mycobacteriosis in patients with lung cancer]. *Kekkaku* 2004 Jun;**79**(6):367—73.
9. Winthrop KL, McNelley E, Kendall B, Marshall-Olson A, Morris C, Cassidy M, et al. Pulmonary nontuberculous mycobacterial disease prevalence and clinical features: an emerging public health disease. *Am J Respir Crit Care Med* 2010 Oct 1;**182**(7): 977—82.
10. Lande L, Peterson DD, Gogoi R, Daum G, Stampler K, Kwait R, et al. Association between pulmonary mycobacterium avium complex infection and lung cancer. *J Thorac Oncol* 2012 Sep; **7**(9):1345—51.
11. Tamura A, Hebisawa A, Kusaka K, Hirose T, Suzuki J, Yamane A, et al. Relationship between lung cancer and Mycobacterium avium complex isolated using bronchoscopy. *Open Respir Med J* 2016;**10**:20—8.
12. Desai D, Adachi JA, Asymptomatic Rolston K. *Non-tuberculous Mycobacterial (NTM) lung infections in cancer patients*. Texas: MD Anderson Experience Houston; 2012.
13. Tsuji T, Tsuyuguchi K, Tachibana K, Kimura Y, Kobayashi T, Minomo S, et al. Analysis of the impact of lung cancer treatment on nontuberculous mycobacterial lung diseases. *Respir Investig* 2017 Jan;**55**(1):45—50.
14. Daley CL, Iaccarino JM, Lange C, Cambau E, Wallace RJ, Andrejak C, et al. Treatment of nontuberculous mycobacterial pulmonary disease: an official ATS/ERS/ESCMID/IDSA clinical practice guideline: executive summary. *Clin Infect Dis* 2020 Aug 14;**71**(4):e1—36.
15. Detterbeck FC, Boffa DJ, Kim AW, Tanoue LT. The eighth edition lung cancer stage classification. *Chest* 2017 Jan;**151**(1): 193—203.
16. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chron Dis* 1987;**40**(5):373—83.
17. Park TY, Chong S, Jung JW, Park IW, Choi BW, Lim C, et al. Natural course of the nodular bronchiectatic form of Mycobacterium Avium complex lung disease: long-term radiologic change without treatment. *PLoS One* 2017;**12**(10):e0185774.
18. Velagapudi M, Sanley MJ, Ased S, Destache C, Malesker MA. Pharmacotherapy for nontuberculous mycobacterial pulmonary disease. *Am J Health Syst Pharm* 2022 Mar 7;**79**(6): 437—45.
19. Feng JY, Chen WC, Chen YY, Su WJ. Clinical relevance and diagnosis of nontuberculous mycobacterial pulmonary disease in populations at risk. *J Formos Med Assoc* 2020 Jun;**119**(Suppl 1):S23—31.
20. Zitvogel L, Apetoh L, Ghiringhelli F, Kroemer G. Immunological aspects of cancer chemotherapy. *Nat Rev Immunol* 2008 Jan; **8**(1):59—73.
21. Torres A, Peetermans WE, Viegi G, Blasi F. Risk factors for community-acquired pneumonia in adults in Europe: a literature review. *Thorax* 2013 Nov;**68**(11):1057—65.
22. Nagashima A, Matsumoto Y, Ohsawa M, Sumi T. Treatment of advanced ovarian carcinoma coexistent with peritoneal tuberculosis. *Mol Clin Oncol* 2013 Nov;**1**(6):1084—6.
23. Bhaskaran K, Dos-Santos-Silva I, Leon DA, Douglas IJ, Smeeth L. Association of BMI with overall and cause-specific mortality: a population-based cohort study of 3.6 million adults in the UK. *Lancet Diabetes Endocrinol* 2018 Dec;**6**(12):944—53.
24. Hoefsloot W, van Ingen J, Andrejak C, Angeby K, Bauriaud R, Bemer P, et al. The geographic diversity of nontuberculous mycobacteria isolated from pulmonary samples: an NTM-NET collaborative study. *Eur Respir J* 2013 Dec;**42**(6):1604—13.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2022.11.003.