Prevalence and risk factors of non-tuberculous mycobacterial pulmonary isolates and infection in interstitial lung disease associated with systemic autoimmune disease

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Abstract

Objective

Non-tuberculous mycobacterial (NTM) lung disease (NTM-LD) prevalence is increasing worldwide. In this study, we aimed to evaluate the clinical significance of NTM pulmonary isolates (NTM-PI) and NTM-LD in patients with systemic autoimmune disease (SAD) who had a concurrent interstitial lung disease (ILD) diagnosis.

Methods

We retrospectively identified patients with SAD who had a concurrent ILD diagnosis (SAD-ILD) and from whom clinically indicated sputum specimens were collected for NTM culture between 2003 and 2018 at a tertiary referral hospital. We analysed the prevalence and risk factors of NTM pulmonary isolates (NTM-PI; ≥1 positive culture) and NTM-LD (≥2 positive cultures).

Results

This study included 258 patients. Rheumatoid arthritis and Sjögren's syndrome were the most common SADs (32.2% and 26.7%, respectively). The NTM-negative subgroup had 204 patients (79.1%) and the NTM-PI subgroup had 54 patients (20.9%). In the NTM-PI subgroup, 33 patients had one NTM positive set of specimens (NTM 1+, 12.8% of the entire sample) and 21 had NTM-LD (8.1% of the entire sample). In a multivariable analysis, chronic kidney disease (CKD; adjusted odds ratio [aOR]: 3.10 [1.53, 6.29]) and chronic obstructive pulmonary disease (COPD; aOR: 2.59 [1.16, 5.78]) were significantly associated with NTM-PI. For NTM-LD, CKD (aOR: 2.79 [1.00, 7.76]) and COPD (aOR: 3.70 [1.23, 10.72]) remained significant risk factors.

Conclusion

In patients with SAD-ILD, the NTM-PI and NTM-LD prevalence rates were 20.9% and 8.1%, respectively. COPD and CKD were independent risk factors of both NTM-PI and NTM-LD. Previous use of biological agents was associated with NTM-PI.

Key words

Non-tuberculous mycobacterial lung disease, autoimmune disease, interstitial lung disease, prevalence, risk factor

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Introduction

Non-tuberculous mycobacterial (NTM) lung disease (NTM-LD) has increased in prevalence worldwide over the last 20 years and has become a major public health problem. NTM-LD is especially problematic for patients with structural lung disease or an immunosuppressive disease other than human immunodeficiency virus infection (1, 2). The five-year mortality of the population with NTM-LD is approximately 25% (3-5), which is even higher than that of the population that is immunocompromised; therefore, comprehensive clinical research is required to improve our understanding of the epidemiological profiles of NTM-LD in susceptible groups (6).

Notably, systemic autoimmune disease (SAD) has been recognised as a key contributor to the development of NTM-LD (7, 8). For instance, a report from Canada found that patients with rheumatoid arthritis (RA) had higher odds of NTM-LD (odds ratio [OR]: 2.07) (9). In Taiwan, the risk was estimated to be 6.24-fold higher in a group with RA than in a control group (10). In addition, in Taiwan, patients with Sjögren's syndrome have a higher incidence of NTM-LD than the general population (hazard ratio: 17.77) (11). The specific mechanisms that predispose patients with autoimmune diseases to NTM-LD remain to be fully elucidated. The use of immunosuppressive agents, disease-specific immune dysfunctions, and local pathophysiological characteristics of lung structures due to autoimmune diseases are associated with an increased risk of NTM-LD (7, 8). In fact, approximately 2–71% of patients with SAD have interstitial lung disease (ILD) (12), which can cause bronchiolitis and bronchiectasis and serves as a precursor of NTM-LD (13). However, few studies have systematically evaluated the clinical significance of NTM pulmonary infection in patients with SAD-ILD (14-16). To fill this clinical gap, we characterised patients with SAD-ILD from whom clinically indicated sputum specimens were collected for an NTM culture to investigate the prevalence of and risk factors associated with NTM pulmonary isolates (NTM-PI) and NTM-LD.

Materials and methods

Study population

For this retrospective case–control study, we obtained data from the Clinical Research Data Repository (CRDR) of China Medical University Hospital (CMUH). The CRDR contains the electronic medical records of 2,873,887 patients who sought care at CMUH between January 1, 2003 and December 31, 2018. It includes administrative and demographic information and data on diagnoses, medical and surgical procedures, prescriptions, laboratory measurements, pathology reports, imaging reports, physiological monitoring, hospitalisation, and catastrophic illness status as well as National Death Registry data and has been carefully verified (17-19).

The study population consisted of patients with SAD who had a concurrent ILD diagnosis and from whom clinically indicated sputum specimens were collected for an NTM culture at CMUH at any time between 2003 and 2018. From the CRDR, we first identified patients with any SAD defined by the Catastrophic Illness Database (*i.e.* polymyositis, dermatomyositis, RA, Sjögren's syndrome, systemic lupus erythematosus, systemic sclerosis, and vasculitis syndrome; Supplementary Table S1) and who received a chest computed tomography (CT) examination for persistent unexplained respiratory symptoms or standard of care for systemic sclerosis and idiopathic inflammatory myopathies due to their higher risk of developing ILD associated with these conditions. A rheumatologist (PCW) and pulmonologist (CCS) reviewed the CT image characteristics from the CT reports to verify patients with ILD. The radiographic features of ILD were categorised into three patterns: airway-related (bronchiectasis, bronchiolectasis, bronchial wall thickening, bronchiolitis, or bronchitis); interstitial (honeycombing, usual interstitial pneumonia, reticulation, septal thickening, or interstitial pneumonia); and alveolar (consolidation, organising pneumonia, mosaic attenuation, or centrilobular or ground-glass opacities). We excluded patients (1) from whom clinically indicated sputum specimens were not collected for an

NTM culture within one year prior to the chest CT examination date and before the end of 2018, or (2) who had a positive NTM culture one year prior to the chest CT examination date.

The index date for patients without a positive NTM culture was the earliest culture date during the survey window; the index date for patients with a positive NTM culture was the first positive culture date (if having only one positive culture) or the second positive culture date (if having at least two positive cultures). The detailed selection process and the definitions of the study population and index date are summarised in Figures 1 and 2. This study was approved by the Big Data Center of CMUH and the Research Ethics Committee/Institutional Review Board of CMUH, which waived the need for informed consent (CMUH105-REC3-068).

Outcome definition

The outcome of interest was NTM positivity (Fig. 1), defined as (1) NTM-PI: the presence of ≥1 positive culture results; or (2) NTM-LD: the presence of ≥2 positive culture results, hence satisfying the corresponding microbiological criteria for NTM-LD (6). Since CMUH is a tertiary referral hospital, some patients might have had positive culture results from the previous hospital. To avoid misclassification, patients with only one set of positive culture results were considered to have NTM-LD if they also satisfied one of the following conditions: (1) they had an International Classification of Diseases (ICD) diagnosis of NTM infection (ICD 9: 031; ICD 10: A31) and received azithromycin or clarithromycin for 60 cumulative days within any 90-day period during the survey window; (2) they received azithromycin or clarithromycin for 60 cumulative days within any 90-day period and received amikacin, imipenem, tigecycline, cefoxitin, or isoniazid for 30 cumulative days within any 60-day period; or (3) they were treated with isoniazid, rifampicin, or ethambutol for 30 days before and after the positive NTM culture date but without a diagnosis of tuberculosis (ICD 9: 011–018; ICD 10: A15–A18).

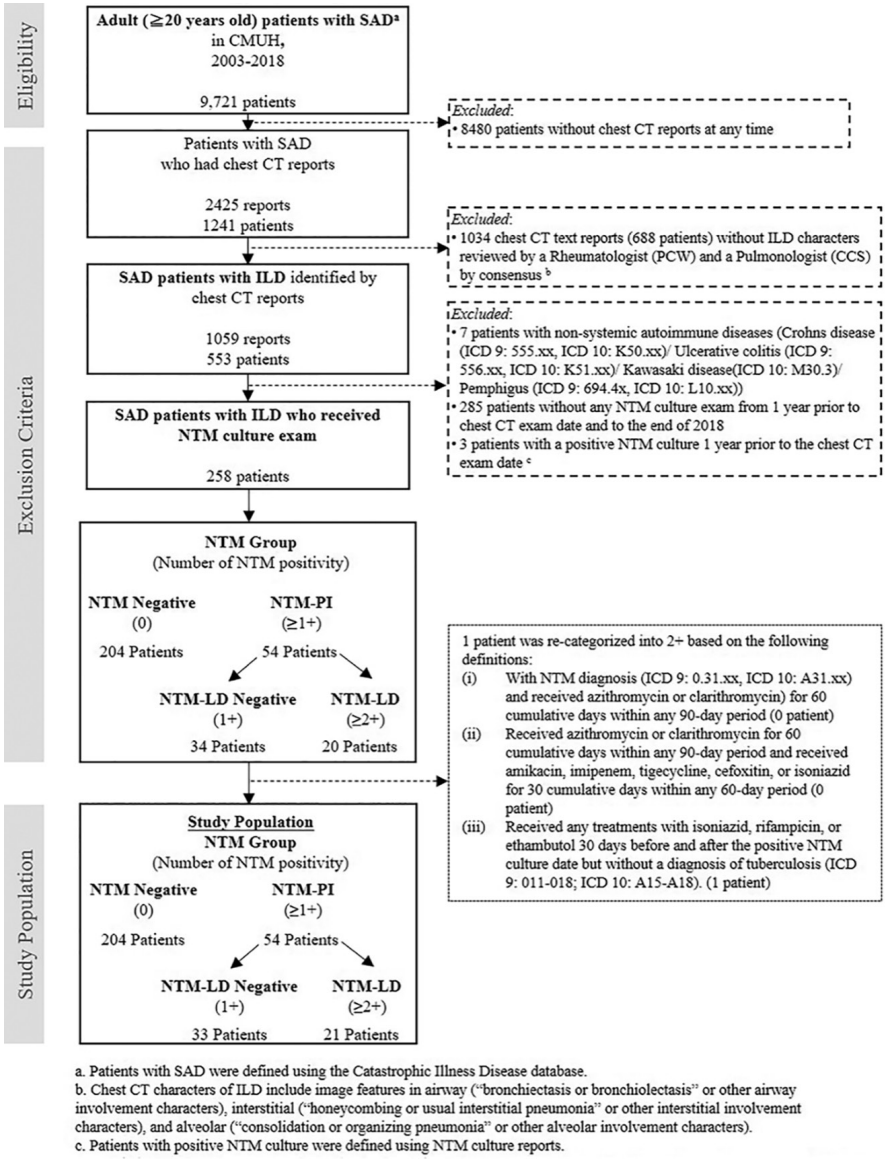
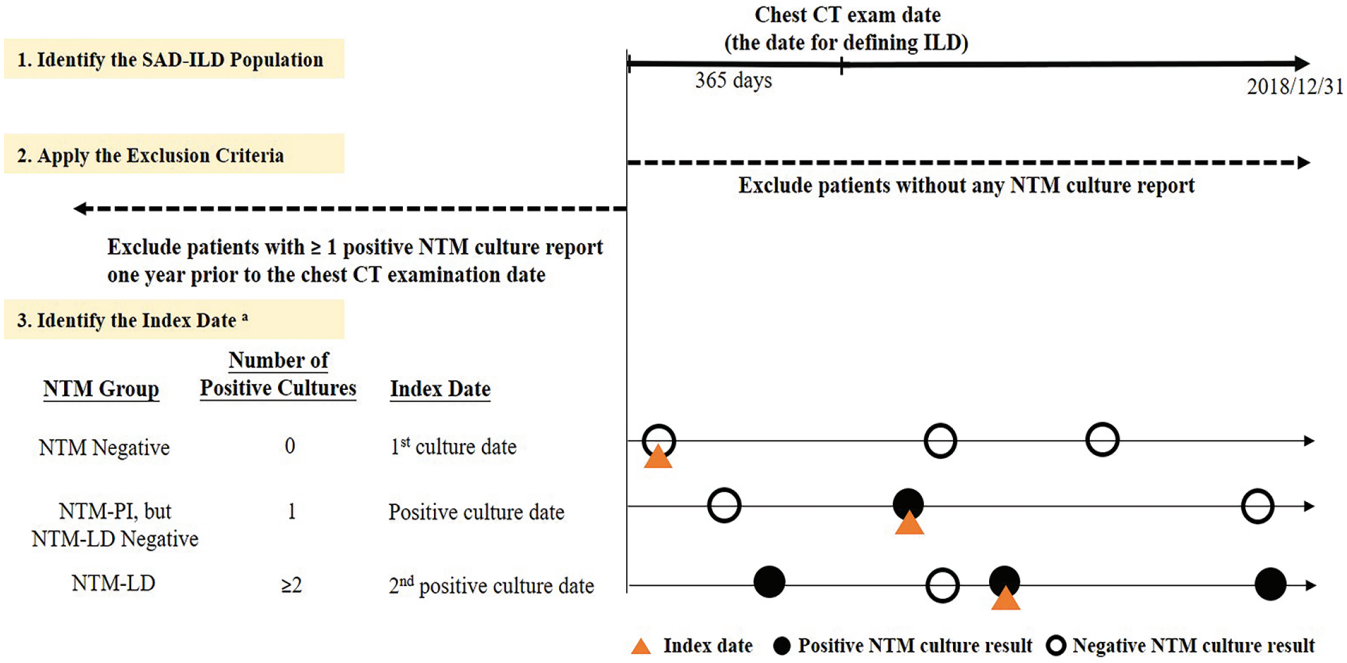


Fig. 1. The recruitment process.
CMUH: China Medical University Hospital; CT: computed tomography; ILD: interstitial lung disease; LD: lung disease; NTM: non-tuberculous mycobacterium; PI: pulmonary isolates; SAD: systemic autoimmune disease.

Covariables

Data on demographic characteristics, baseline comorbidities, chest CT reports, and medication history were retrieved from the CRDR (19). Baseline comorbidities were those in the ICD that were diagnosed within one year prior to the index date; baseline diabetes and hypertension were defined as an ICD diagnosis with medication within one year prior to the index date. Baseline medication profiles were taken within one year prior to the index date. SAD was diagnosed if a catastrophic illness certificate of SAD was issued by the Bureau of Taiwan National Health Insurance at any time during the study period. We further examined baseline steroid use over 30 days or 90 days prior to the index date. We standardised the steroid dose with a steroid-equivalent dose of prednisolone (5 mg) and calculated the cumulative steroid dosages within the period (20). In addition to corticosteroids, the following drugs were considered: conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), including hydroxychloroquine, sulfasalazine, methotrexate, and leflunomide; biological DMARDs (bDMARDs), including anti-TNF (golimumab, adalimumab,



a. The index date for patients without positive NTM culture was the earliest culture date within 1 year before chest CT. The index date for patients with positive NTM culture results was the first positive culture date (for only 1 positive) or the second positive culture date (for having at least 2 positive).

Fig. 2. Definitions of study population and index date.
CT: computed tomography; ILD: interstitial lung disease; LD: lung disease; NTM: non-tuberculous mycobacterium; PI: pulmonary isolates.

Table I. Baseline demographic and clinical characteristics of the study population.

Characteristics	Overall	NTM Group for NTM-PI (Number of NTM positive cultures)			NTM Group for NTM-LD (Number of NTM positive cultures)		
		NTM Negative (0)	NTM-PI (≥1)	*p*-value [b]	NTM-negative or NTM 1+ (0-1)	**NTM-LD** (≥2)	*p*-value [b]
N (%)	258 (100.0)	204 (79.1)	54 (20.9)		237 (91.9)	21 (8.1)	
Demographic, median (IQR)							
Age	63 (53, 72)	63 (52, 72)	65 (58, 72)	0.169	63 (52, 72)	64 (62, 70)	0.331
≥ 65 years old	119 (46.1)	92 (45.1)	27 (50)	0.521	109 (46)	10 (47.6)	0.886
Male, n (%)	73 (28.3)	57 (27.9)	16 (29.6)	0.807	68 (28.7)	5 (23.8)	0.634
Total no of NTM report	0 (0, 0)	0 (0, 0)	1 (1, 2)	**<0.001**	0 (0, 0)	2 (2, 3)	**<0.001**
Total no of culture report	3 (3, 7)	3 (2, 6)	5 (3, 11)	**<0.001**	3 (3, 6)	7 (3, 12)	**0.001**
Systemic autoimmune diseases [c], n (%)							
Polymyositis or dermatomyositis	35 (13.6)	32 (15.7)	3 (5.6)	0.053	33 (13.9)	2 (9.5)	0.748
Rheumatoid arthritis	83 (32.2)	62 (30.4)	21 (38.9)	0.235	72 (30.4)	11 (52.4)	**0.039**
Primary Sjögren's syndrome	69 (26.7)	53 (26.0)	16 (29.6)	0.590	65 (27.4)	4 (19.0)	0.406
Systemic lupus erythematosus	17 (6.6)	14 (6.9)	3 (5.6)	0.731	16 (6.8)	1 (4.8)	1.000
Systemic sclerosis	18 (7.0)	17 (8.3)	1 (1.9)	0.133	18 (7.6)	0 (0.0)	0.376
Vasculitis	9 (3.5)	6 (2.9)	3 (5.6)	0.401	9 (3.8)	0 (0.0)	0.999
Image features [d], n (%)							
1.Airway							
Bronchiectasis or bronchiolectasis	97 (37.6)	72 (35.3)	25 (46.3)	0.138	88 (37.1)	9 (42.9)	0.604
Other airway involvement characters	26 (10.1)	17 (8.3)	9 (16.7)	0.070	23 (9.7)	3 (14.3)	0.454
2.Interstitial							
Honeycombing or usual interstitial pneumonia	30 (11.6)	25 (12.3)	5 (9.3)	0.541	29 (12.2)	1 (4.8)	0.484
Other interstitial involvement characters	55 (21.3)	47 (23.0)	8 (14.8)	0.189	53 (22.4)	2 (9.5)	0.265
3.Alveolar							
Consolidation or organising pneumonia	62 (24)	52 (25.5)	10 (18.5)	0.286	56 (23.6)	6 (28.6)	0.611
Other alveolar involvement characters	83 (32.2)	65 (31.9)	18 (33.3)	0.837	78 (32.9)	5 (23.8)	0.392

Characteristics	Overall	NTM Group for NTM-PI (Number of NTM positive cultures)			NTM Group for NTM-LD (Number of NTM positive cultures)		
		NTM Negative (0)	NTM-PI (≥1)	*p*-value [b]	NTM-negative or NTM 1+ (0-1)	**NTM-LD** (≥2)	*p*-value [b]
Baseline comorbidities [e], n (%)							
Diabetes mellitus	37 (14.3)	28 (13.7)	9 (16.7)	0.583	34 (14.3)	3 (14.3)	0.999
Hypertension	58 (22.5)	43 (21.1)	15 (27.8)	0.294	52 (21.9)	6 (28.6)	0.585
Cardiovascular disease	45 (17.4)	36 (17.6)	9 (16.7)	0.866	41 (17.3)	4 (19.0)	0.769
Chronic kidney disease (eGFR<60 ml/min/1.73 m^2)	56 (23.1)	36 (18.8)	20 (40.0)	**0.002**	48 (21.6)	8 (40.0)	0.092
Liver cirrhosis	5 (1.9)	4 (2.0)	1 (1.9)	0.999	5 (2.1)	0 (0.0)	0.999
Chronic obstructive pulmonary disease	42 (16.3)	28 (13.7)	14 (25.9)	**0.031**	35 (14.8)	7 (33.3)	0.056
Cystic fibrosis	63 (24.4)	49 (24.0)	14 (25.9)	0.772	56 (23.6)	7 (33.3)	0.321
Asthma	21 (8.1)	18 (8.8)	3 (5.6)	0.581	20 (8.4)	1 (4.8)	0.999
Cancer	39 (15.1)	33 (16.2)	6 (11.1)	0.355	36 (15.2)	3 (14.3)	0.999
Prior medication use [e], n (%)							
Immune modulation therapy [f]	152 (58.9)	117 (57.4)	35 (64.8)	0.322	137 (57.8)	15 (71.4)	0.224
Conventional synthetic DMARDs (csDMARDs)	134 (51.9)	104 (51)	30 (55.6)	0.550	121 (51.1)	13 (61.9)	0.340
Biological DMARDs (bDMARDs)	27 (10.5)	16 (7.8)	11 (20.4)	**0.007**	22 (9.3)	5 (23.8)	0.053
Anti-TNF	14 (5.4)	11 (5.4)	3 (5.6)	0.999	11 (4.6)	3 (14.3)	0.094
Non-anti-TNF	15 (5.8)	6 (2.9)	9 (16.7)	**0.001**	12 (5.1)	3 (14.3)	0.112
Targeted synthetic DMARDs (tsDMARDs)	3 (1.2)	2 (1)	1 (1.9)	0.507	2 (0.8)	1 (4.8)	0.226
Immunosuppressants (except glucocorticoids)	51 (19.8)	41 (20.1)	10 (18.5)	0.796	49 (20.7)	2 (9.5)	0.388
Steroid	196 (76)	159 (77.9)	37 (68.5)	0.150	181 (76.4)	15 (71.4)	0.611
Methylprednisolone	80 (31)	62 (30.4)	18 (33.3)	0.678	73 (30.8)	7 (33.3)	0.810
Prednisolone	174 (67.4)	139 (68.1)	35 (64.8)	0.643	161 (67.9)	13 (61.9)	0.572
Dexamethasone	48 (18.6)	42 (20.6)	6 (11.1)	0.112	46 (19.4)	2 (9.5)	0.384
Other	90 (34.9)	75 (36.8)	15 (27.8)	0.218	85 (35.9)	5 (23.8)	0.267
Steroid used within 30 days prior to the index date	162 (62.8)	130 (63.7)	32 (59.3)	0.546	152 (64.1)	10 (47.6)	0.133
Methylprednisolone	50 (19.4)	39 (19.1)	11 (20.4)	0.836	45 (19.0)	5 (23.8)	0.570
Prednisolone	126 (48.8)	101 (49.5)	25 (46.3)	0.674	119 (50.2)	7 (33.3)	0.138
Dexamethasone	16 (6.2)	16 (7.8)	0 (0.0)	**0.028**	16 (6.8)	0 (0.0)	0.377
Cumulative steroid dosage [g], median (IQR)	26.5 (0, 87)	25.5 (0, 90.5)	28 (0, 69.5)	0.356	28 (0, 88)	0 (0, 70)	0.174
Steroid used within 90 days prior to the index date	169 (65.5)	135 (66.2)	34 (63)	0.659	157 (66.2)	12 (57.1)	0.400
Methylprednisolone	58 (22.5)	43 (21.1)	15 (27.8)	0.294	52 (21.9)	6 (28.6)	0.585
Prednisolone	133 (51.6)	106 (52)	27 (50)	0.798	125 (52.7)	8 (38.1)	0.198
Dexamethasone	27 (10.5)	26 (12.7)	1 (1.9)	**0.020**	27 (11.4)	0 (0.0)	0.142
Cumulative steroid dosage [g], median (IQR)	44 (0, 138.9)	42 (0, 144.8)	47.5 (0, 114.2)	0.832	44 (0, 143)	42 (0, 87)	0.389
Outcome (follow-up to 2018/12/31), n (%)							
All-cause mortality	108 (41.9)	84 (41.2)	24 (44.4)	0.665	99 (41.8)	9 (42.9)	0.923
Time to death, year, median (IQR)	1.2 (0.2, 3.6)	1 (0.2, 3.8)	1.8 (0.6, 3)	0.177	1.1 (0.2, 3.5)	1.7 (0.7, 5.8)	0.274
1 year	51 (19.8)	42 (20.6)	9 (16.7)	0.520	48 (20.3)	3 (14.3)	0.775
3 year	78 (30.2)	60 (29.4)	18 (33.3)	0.577	72 (30.4)	6 (28.6)	0.863
5 year	90 (34.9)	71 (34.8)	19 (35.2)	0.958	84 (35.4)	6 (28.6)	0.527
Lung cancer [h]	7 (2.7)	6 (3.0)	1 (1.9)	0.999	7 (3.0)	0 (0.0)	0.999

[a.] Categorical variables are presented as frequency (%) and continuous variables are presented as median (IQR), if not otherwise specified.
[b.] *p*-values are calculated by Wilcoxon rank sum test for continuous variables and chi-square test for categorical variables.
[c.] Systemic autoimmune diseases were defined by catastrophic illness disease any time within study period.
[d.] Rheumatologists scanned chest CT reports to defined ILD and identified image characters. Other airway involvement characters include bronchial wall thickening, bronchiolitis, and bronchitis; other interstitial involvement characters include interstitial pneumonia, reticular, reticulation, and septal thickening; and other alveolar involvement characters include mosaic attenuation, centrilobular, and 4 ground glass opacities (opacity).
[e.] Baseline comorbidities were defined by ICD diagnoses within 1 year before the index date, baseline diabetes mellitus or hypertension were further defined by the use of glucose-lowering or anti-hypertensive agents, respectively; baseline chronic kidney disease were defined by biochemical data of eGFR and 242 (93.8%) patients were available in eGFR. Prior medication use was indicated when medication was prescribed within 1 year prior to the index date.
[f.] Conventional synthetic DMARDs (csDMARDs) includes hydroxychloroquine, sulfasalazine, methotrexate, and leflunomide; biological DMARDs (bDMARDs) contains anti-TNF (golimumab, adalimumab, etanercept, certolizumab) and non-anti-TNF (tocilizumab, abatacept, rituximab, secukinumab, ixekizumab, ustekinumab, guselkumab, dupilumab, omalizumab); targeted synthetic DMARDs (tsDMARDs) includes tofacitinib and baricitinib; and immunosuppressants (except glucocorticoids) includes azathioprine, cyclophosphamide, cyclosporin, and mycophenolate mofetil.
[g.] We converted steroid by replace steroid equivalent dosage to prednisolone (5mg), and calculate the cumulative steroid dosages within the period.
[h.] The denominator for the lung cancer outcome was 257 patients because one patient who had lung cancer before index date was excluded.
eGFR, estimated glomerular filtration rate; IQR, interquartile range; LD, lung disease; NTM, non-tuberculous mycobacterium; PI, pulmonary isolates.

etanercept, and certolizumab) and non-anti-TNF (tocilizumab, abatacept, rituximab, secukinumab, ixekizumab, ustekinumab, guselkumab, dupilumab, and omalizumab) drugs; targeted synthetic DMARDs (tsDMARDs), including tofacitinib and baricitinib; and immunosuppressants (except glucocorticoids), including azathioprine, cyclophosphamide, cyclosporin, and mycophenolate mofetil.

Statistical analyses

Continuous variables are presented as medians and interquartile ranges (IQRs) and were compared using the Wilcoxon rank-sum test. Categorical variables were expressed as frequencies and percentages and were compared using the chi-square test or Fisher's exact test. Three multivariable logistic regression models were constructed to investigate the relationship between the risk factors of NTM-PI and NTM-LD. All statistical analyses were performed using SAS v. 9.4 (SAS Institute, Cary, NC, USA) and R v. 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set as a two-sided α value of 0.05.

Results

Description of the overall population

Of the 9721 patients who received a diagnosis of an autoimmune disorder at CMUH between 2003 and 2018, we excluded 8480 patients who had not received a chest CT examination, 688 patients who received a chest CT examination but did not receive a diagnosis of ILD, 285 patients without an NTM culture within the period of one year prior to the chest CT examination to the end of 2018, 7 patients without SAD, and 3 patients with a positive NTM culture dated earlier than one year prior to the chest CT examination. This study included 258 patients (47% of 553 patients) in the final sample with SAD, ILD, and a suitably dated NTM culture (Fig. 1).

The most prevalent autoimmune diseases were RA (32.2%), Sjögren's syndrome (26.7%), polymyositis or dermatomyositis (13.6%), and systemic lupus erythematosus (6.6%). The airway, interstitial, and alveolar radiographic patterns of ILD were present in 47.7%, 32.9%, and 56.2% of the study sample, respectively. RA was significantly more prevalent in the NTM-LD subgroup (52.4%) than in the NTM-negative and NTM 1+ subgroup combination (30.4%; p=0.039). The prevalence of various autoimmune diseases and the radiographic features of ILD were similar between the NTM-negative and NTM-PI subgroups and between the NTM-negative and NTM 1+ subgroup combination and the NTM-LD subgroup. For example, the final NTM-PI was only three and NTM-LD was only one among systemic lupus erythematosus (SLE)-ILD.

The study population was segmented by NTM positivity. The NTM-negative subgroup had 204 patients (79.1%), and the NTM-PI subgroup had 54 patients (20.9%). In the NTM-PI subgroup, 33 patients had one NTM-positive set (NTM 1+, 12.8% of the entire sample) and 21 had NTM-LD (8.1% of the entire sample).

Clinical characteristics of NTM infection

The distributions of age (63 *vs*. 65 years old), gender (45.1% *vs*. 50.0%), and SADs were similar between the NTM-negative and NTM-PI subgroups (Table I). The distributions of age (63 *vs*. 64 years old), gender (46% *vs*. 47.6%), and SADs were also similar between the NTM-negative and NTM 1+ subgroup combination and the NTM-LD subgroup (Table I).

Rheumatoid arthritis was significantly more prevalent in the NTM-LD subgroup (52.4%) than in the NTM-negative and NTM 1+ subgroup combination (30.4%; p=0.039). The prevalence of various autoimmune diseases and the radiographic features of ILD were similar between the NTM-negative and NTM-PI subgroups and between the NTM-negative and NTM 1+ subgroup combination and the NTM-LD subgroup.

The prevalence of chronic kidney disease (CKD; 40.0% *vs*. 18.8%; p=.002) and chronic obstructive pulmonary disease (COPD; 25.9% *vs*. 13.7%; p=.031) was higher in the NTM-PI subgroup than in the NTM-negative subgroup. By contrast, the prevalence rates of CKD and COPD were only slightly higher (p=.092 and .056, respectively) in the NTM-LD subgroup than in the NTM-negative and NTM 1+ subgroup combination. The prevalence of other comorbidities, such as hypertension, diabetes mellitus, cardiovascular disease, cirrhosis, asthma, and cancer, was similar between the subgroups.

The NTM-PI subgroup was more likely than the NTM-negative subgroup to use bDMARDs at any time prior to the index date (20.4% *vs*. 7.8%; p=0.007) and was less likely to use dexamethasone within 30 days prior to the index date (0% *vs*. 7.8%; p=0.028) or within 90 days prior to the index date (1.9% *vs*. 12.7%; p=0.02). However, the cumulative steroid dosage taken within 30 or 90 days prior to the index date was similar between the three groups. The median cumulative steroid-equivalent dose of prednisone taken within 30 or 90 days prior to the index date was 26.5 mg and 44 mg, respectively. Previous medication use was similar between the NTM-LD group and the NTM-negative and NTM 1+ subgroup combination.

We also evaluated the outcomes, all-cause mortality and lung cancer (Table I). We found no difference in mortality between the NTM-PI subgroup (44.4%) and the NTM-negative subgroup (41.2%), as well as between the NTM-LD subgroup (42.9%) and the NTM-negative and NTM 1+ subgroup combination (41.8%). The proportion of lung cancer was also similar between the subgroups (1.9% *vs*. 3.0% and 0% *vs*. 3.0%, respectively).

Risk factors associated with NTM positivity in the logistic regression

In univariate analyses, CKD (crude OR=2.89, 95% confidence interval [CI]=1.48–5.66), COPD (OR=2.24, 95% CI=1.05–4.77) and bDMARDs (OR=3.10, 95% CI=1.34–7.20) were associated with NTM-PI. For NTM-LD, COPD (OR=3.20, 95% CI=1.19–8.62), bDMARDs (OR=3.03, 95% CI=1.01–9.14), and rheumatoid arthritis (OR=2.83, 95% CI=1.12–7.14) were significant factors in univariate analyses. In the fully adjusted multivariable logistic regression models (Table II;

Table II. Multivariable analysis of the risk factors associated with NTM positivity (n=242 patients) with adjustment bDMARD use.

A. NTM Group for NTM-PI (n. of cases = 50) [a]

Variables	Univariate		Model 1		Model 2		Model 3	
	OR (95% CI)	*p*-value	aOR (95% CI)	*p*-value	aOR (95% CI)	*p*-value	aOR (95% CI)	*p*-value
Chronic kidney disease	**2.89 (1.48, 5.66)**	**0.002**	**3.34 (1.66, 6.71)**	**<.001**	**3.30 (1.64, 6.65)**	**<.001**	**3.10 (1.53, 6.29)**	**0.002**
Chronic obstructive pulmonary disease	**2.24 (1.05, 4.77)**	**0.036**	**2.79 (1.27, 6.17)**	**0.011**	**2.76 (1.25, 6.11)**	**0.012**	**2.59 (1.16, 5.78)**	**0.020**
Rheumatoid arthritis	1.38 (0.72, 2.64)	0.328			1.31 (0.67, 2.56)	0.438	0.99 (0.47, 2.11)	0.986
Biological DMARDs (bDMARDs)	**3.10 (1.34, 7.20)**	**0.008**					2.51 (0.96, 6.58)	0.062
Akaike's Information Criteria (AIC)			237.23		238.63		237.27	

B. NTM Group for NTM-LD (n. of cases = 20) [a]

Variables	Univariate		Model 1		Model 2		Model 3	
	OR (95% CI)	*p*-value	aOR (95% CI)	*p*-value	aOR (95% CI)	*p*-value	aOR (95% CI)	*p*-value
Chronic kidney disease	2.42 (0.94, 6.25)	0.069	**2.99 (1.11, 8.10)**	**0.031**	**2.91 (1.06, 8.00)**	**0.038**	**2.79 (1.00, 7.76)**	**0.0498**
Chronic obstructive pulmonary disease	**3.20 (1.19, 8.62)**	**0.022**	**3.91 (1.39, 11.03)**	**0.010**	**3.84 (1.34, 11.02)**	**0.012**	**3.70 (1.28, 10.72)**	**0.016**
Rheumatoid arthritis	**2.83 (1.12, 7.14)**	**0.030**			**2.72 (1.05, 7.03)**	**0.039**	2.41 (0.85, 6.83)	0.098
Biological DMARDs (bDMARDs)	**3.03 (1.01, 9.14)**	**0.049**					1.47 (0.41, 5.23)	0.554
Akaike's Information Criteria (AIC)			134.91		132.65		134.31	

[a] Sixteen patients were not available in CKD status and 242 patients were left for analysis, of them, 192 (79.3%) were NTM negative and 50 (20.7%) were NTM-PI. Of NTM-PI patients, 20 [8.3%] were NTM-LD.
CI: confidence interval; aOR: adjusted odds ratio; LD, lung disease; NTM: non-tuberculous mycobacterium; PI: pulmonary isolates.

Model 3), the following factors were significantly associated with NTM-PI: CKD (adjusted OR [aOR]=3.10; 95% CI=1.53–6.29); and COPD (aOR=2.59; 95% CI=1.16–5.78). The prior use of bDMARDs (aOR=2.51; 95% CI=0.96–6.58) was not significantly associated with NTM-PI. CKD (aOR=2.79; 95% CI=1.00–7.76) and COPD (aOR= .70; 95% CI=1.23–10.72) were significantly associated with NTM-LD in the fully adjusted multivariable logistic regression models (Table II; Model 3). RA was significant in Model 2 (OR=2.72, 95% CI=1.05–7.03) and was borderline significant in Model 3 (OR=2.41, 95% CI=0.85–6.83).

Discussion

To the best of our knowledge, the present study is the first to investigate the prevalence and risk of superimposed NTM-LD in SAD-ILD. The prevalence of NTM-PI was approximately 20.9%, and that of NTM-LD was 8.1% in patients with SAD-ILD with clinical suspicion of mycobacterial infection. In multivariable analysis, COPD and CKD were independent factors associated with respiratory tract isolates of NTM (NTM-PI) and presumptive NTM-LD, whereas corticosteroids were not. The use of biological agents was significantly associated with NTM-PI but non-significantly associated with NTM-LD.

The key finding of this study was the 20.9% prevalence of NTM-PI and 8.1% prevalence of presumptive NTM-LD (using the microbiological criteria of ATS/IDSA guidelines) (6) in patients with SAD-ILD (Table I). Non-tuberculous mycobacteria are ubiquitous in the home environment, including in bathrooms and showerheads, and will thus inevitably find its way into the human body (21). A patient with SAD-ILD may be predisposed to NTM pulmonary infection that can further worsen their lung condition. Although NTM-PI and NTM-LD were not significantly associated with mortality and lung cancer occurrence in the present study, lung function and other short-term outcomes warrant investigation in future prospective studies.

The factors associated with NTM-PI and NTM-LD in patients with SAD-ILD were baseline CKD and COPD in SAD-ILD. COPD is a well-known risk factor of NTM-LD (22) due to both structural changes and the inhalation of corticosteroids (8). CKD is also a well-known risk factor of *Mycobacterium tuberculosis* infection (23, 24); however, whether it increases the risk of NTM-LD in SAD-ILD remains unaddressed. Our study demonstrates that CKD is a risk factor of NTM-LD in SAD. This finding is consistent with recent reports from Japan and Taiwan that CKD is one of the comorbidities of NTM-LD (25, 26). A possible explanation might be that patients with CKD have immune dysfunction encompassing all aspects of innate and adaptive immunity (27-30). In addition, the presence of COPD or CKD may indicate more extensive organ involvement and more severe autoimmune diseases, which further predispose patients to NTM-LD.

The association between NTM-LD and autoimmune diseases was non-significant, although most patients in the present study had RA–ILD (Table I). In addition, the association between NTM-LD development and specific radiographic features of ILD was non-significant. Although glucocorticoids are conventionally thought to be associated with an increased risk of mycobacterial diseases (31), we found no such association in our SAD-ILD cohort. The use of immunosuppressants, csDMARDs, or tsDMARDs did not increase the risk of NTM-LD. By contrast, bDMARDs were associated with NTM positivity and NTM-LD, although the association with NTM-

LD was no-significant after multivariable adjustment (Table II). Notably, non-anti-TNF agents might be correlated with NTM-PI, whereas anti-TNF agents showed a trend of being associated with NTM-LD in the present study. Our findings agree with those of previous studies showing that biological agents are a risk factor of NTM-LD (32-34). Therefore, bDMARDs should be used with caution when the risk of NTM pulmonary infection is high. Future studies should investigate the safety of bDMARDs in patients with SAD-ILD, particularly if they have COPD or CKD as a comorbidity.

This study has several limitations: 1. its retrospective observational database research design precluded causal inference and the patients' symptoms were not available as the database did not record them; 2. the lack of a standardised study protocol meant that confounding related to positive indication of NTM could not be completely excluded, especially with regard to the timing of sputum sampling; 3. NTM culture with lung tissue was not included; 4. the sample size was small, which reduced the statistical power of the results; and 5. residual confounding factors could not be completely eliminated – for example, data on histopathologic patterns and ILD severity grade were lacking for our SAD-ILD cohort; and (6) the findings may not be generalisable outside the Taiwanese population.

Conclusions

In conclusion, the prevalence of NTM-PI and NTM-LD in patients with SAD-ILD was 20.9% and 8.1%, respectively. The underlying comorbidities COPD and CKD were associated with NTM-PI and NTM-LD prevalence and the use of biological agents with NTM-PI prevalence. Sputum samples from patients with SAD-ILD, coexisting with COPD or CKD comorbidities, or those receiving biological agents should be monitored for the presence of non-tuberculous mycobacteria. Our findings provide a conceptual framework to guide the development of risk assessment tools for NTM-PI and NTM-LD in patients with SAD-ILD. More studies, especially those with larger samples, are warranted to verify our findings and evaluate potential interactions between underlying comorbidities and immunomodulatory agents.

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