BRITISH JOURNAL OF HOSPITAL MEDICINE

ARTICLE

The Influencing Factors of Extensive Lung Lesions and Cavities in Patients With Non-Tuberculous Mycobacterial Lung Disease

Xueqi Li[1], Zhisong Wu[1], Yao Zhang[1], Nanlan Ma[1,*]

[1]Department of Tuberculosis, The Second Hospital of Nanjing, Nanjing, Jiangsu, China
*Correspondence: xql890121@163.com (Nanlan Ma)

Abstract

Aims/Background The resolution of non-tuberculous mycobacterial (NTM) lung disease is associated with the extent of pulmonary lesions and the presence of lung cavities. This study aims to identify factors influencing the development of extensive lung lesions and cavities in patients with NTM lung disease, thereby generating valuable insights for the management and treatment of NTM lung disease.

Methods Retrospective analysis was conducted on clinical data from 198 hospitalized patients with NTM lung disease at the Department of Tuberculosis, The Second Hospital of Nanjing, between 2022 and 2023. Patient data like age, gender, past medical history, nutritional risk screening 2002 (NRS-2002) score, lymphocyte count, peripheral blood neutrophil-to-lymphocyte ratio (NLR), pulmonary computed tomography (CT) imaging findings (including extent of lung lesions and presence of cavities), and T cell subsets count were gathered through electronic medical records and hospital information system (HIS) system. Univariate and multivariate logistic regression analyses were carried out with extensive lung lesions and cavities as dependent variables and other factors as independent variables.

Results Among the 198 patients, 138 (69.7%) exhibited extensive lung lesions, while cavities were observed in 76 individuals (38.4%). Based on the results of logistic regression analysis, a high NLR (OR = 4.685 [1.176–18.663], $p = 0.029$) and an NRS-2002 score ≥ 3 (OR = 12.082 [3.726–39.183], $p < 0.001$) were identified as risk factors for the development of extensive lung lesions in patients with NTM lung disease. Furthermore, elevated NLR (OR = 3.454 [1.483–8.047], $p = 0.004$) was associated with an increased risk of cavities in patients with NTM lung disease.

Conclusion In patients with NTM lung disease, high NLR is the risk factor for extensive lung lesions and formation of pulmonary cavities, whereas malnutrition elevates the risk for prevalent lung lesions. Early intervention and active monitoring of these related indicators are necessary to prevent disease progression and enhance overall cure rates.

Key words: non-tuberculous mycobacterial; pulmonary lesions; cavities; influencing factors

Submitted: 19 November 2024 Revised: 2 January 2025 Accepted: 8 January 2025

How to cite this article:
Li X, Wu Z, Zhang Y, Ma N. The Influencing Factors of Extensive Lung Lesions and Cavities in Patients With Non-Tuberculous Mycobacterial Lung Disease. Br J Hosp Med. 2025. https://doi.org/10.12968/hmed.2024.0927

Introduction

Non-tuberculous mycobacterial (NTM) lung disease refers to a pulmonary infection caused by mycobacteria other than *Mycobacterium tuberculosis* complex and *Mycobacterium leprae*, leading to the development of pulmonary tissue lesions and presenting a range of symptoms including fatigue, weight loss, cough with expectoration, chest tightness, and asthma (Cowman et al, 2019; Kumar and Loebinger, 2022). Due to the overlapping clinical manifestations of NTM lung

disease with tuberculosis, bronchiectasis with infection, chronic obstructive pulmonary disease (COPD), and other diseases, as well as the co-occurrence with these conditions with a rather high frequency, accurate diagnosis of NTM lung disease poses a significant challenge (Hendrix et al, 2022; Ku et al, 2023). However, in recent years, the advancement of molecular biology technologies has led to an increased identification of NTM lung infections. Previous studies have demonstrated that the prevalence of NTM lung disease in the United States is approximately 8.6 cases per 100,000 individuals, while in Japan, it ranges from 33 to 65 cases per 100,000 individuals; both regions exhibit a gradual upward trend (Dahl et al, 2022; Morimoto et al, 2014; Prevots and Marras, 2015; Winthrop et al, 2010). Currently, there is a dearth of epidemiological data on NTM lung disease in China. But recent study has shown that the incidence of NTM lung disease in Mainland China is about 6% (Liu et al, 2021). NTM lung disease has become a major public health problem threatening human health. In the management of NTM lung disease, the extent of pulmonary lesions and the presence of cavities are pivotal determinants influencing its successful resolution (Hwang et al, 2023; Yagi et al, 2021). The number of lung fields involved in the lesion is an indicator to evaluate the extent of the lesion (Nguyen et al, 2024). Therefore, in this study, we consider lung lesions are extensive when the number of lesions involved was $\geq$3. Previous studies have proved that the range of lesions and the number of cavities affect the sputum turning negative; the severity of the lesion and the cavity affect the prognosis of the disease and are the risk factors leading to treatment failure. It has also been reported that both the NTM lung disease and tuberculosis share similar imaging features. Patients with diabetes are more vulnerable to the formation of pulmonary lesions and cavities, while patients with bronchiectasis are more likely to develop NTM infection (Gopalaswamy et al, 2020). The cavities caused by NTM lung disease are smaller, with thinner walls and more uniform sizes. A study has shown that concomitant bronchiectasis, COPD, and gastroesophageal reflux are risk factors for NTM lung disease (Tan et al, 2021) but studies on the risk factors causing extensive lung lesions and cavities in NTM lung disease remain scarce.

By analyzing the pertinent clinical data, this study aims to investigate the contributing factors associated with the development of extensive lung lesions and cavities in patients diagnosed with NTM lung disease. The findings from this research can serve as a valuable reference for the management and treatment of individuals affected by NTM lung disease, emphasizing the importance of early intervention and prompt medical care.

Methods

Study Participants

A retrospective study was conducted to collect the clinical data of patients with NTM lung disease who were hospitalized in the Department of Tuberculosis, The Second Hospital of Nanjing from January 2022 to December 2023 (Fig. 1).

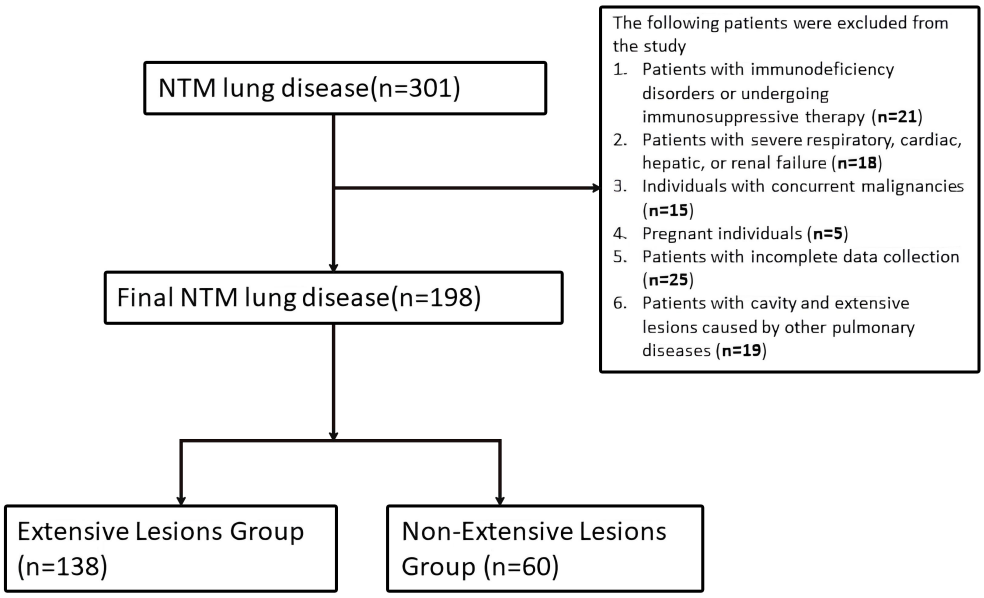

Fig. 1. Flowchart depicting the inclusion and exclusion of study participants. NTM, non-tuberculous mycobacterial.

Inclusion and Exclusion Criteria

Inclusion criteria of this study are as follows: (1) participants who fulfilled the diagnostic criteria for NTM lung disease, which are based on the 2020 clinical practice guideline for the treatment of non-tuberculous mycobacterial pulmonary disease (NTM-PD) by the American Thoracic Society (Lange et al, 2022); (2) participants who had not started any relevant treatment prior to admission; (3) participants who exhibited positive sputum or alveolar lavage fluid cultures with identification of NTM strains; and (4) participants aged ≥18 years old.

Individuals with the following conditions were excluded: (1) patients with immunodeficiency disorders or undergoing immunosuppressive therapy; (2) individuals complicated by severe respiratory, cardiac, hepatic, or renal failure; (3) individuals with concurrent malignancies; (4) pregnant individuals; (5) patients with incomplete data; and (6) patients with cavity and extensive lesions caused by other pulmonary diseases.

Study Methods

This retrospective study was carried out using the opt-out method for the case series in our hospital. The study was approved by the Medical Ethics Committee of The Second Hospital of Nanjing (number: 2024-LS-ky070) and was conducted in accordance with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

The clinical data of the subjects were collected while they were hospitalized through the electronic medical record and the hospital information management system. This comprehensive data set included age, gender, past medical history, and nutritional risk screening 2002 (NRS-2002) score. NRS-2002 is a nutritional

risk screening tool developed by the European Society for Nutrition and the European Society for Clinical Nutrition and Metabolism (Kondrup et al, 2003). The patients were scored by a professionally trained nurse at admission. The score, ranging from 0 to 10, factors in age, nutritional status, and disease severity. A score of $\geq$3 indicates nutritional risk in the tested patient. Lymphocyte count, peripheral blood neutrophil-to-lymphocyte ratio (NLR), pulmonary computed tomography (CT) imaging findings (including extent of lung lesions and presence of cavities), T cell subsets count, and nutritional status assessment (according to NRS-2002 score) were collected.

The subjects included were divided into groups according to extent of pulmonary lesions, which was determined according to the number of lung fields involved, and the presence of lung cavities. There were 138 patients in the group with pulmonary lesions $\geq$3 and 60 patients in the group with pulmonary lesions $<$3. On the other hand, there were 76 patients in the group with cavities and 122 patients in the group without cavities.

Statistical Analysis

The statistical analysis was performed using SPSS 20.0 software (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was employed to assess the normality of data distribution. For variables that followed a normal distribution, data are expressed as mean $\pm$ standard deviation, and group comparisons were conducted using independent sample *t*-tests. For non-normally distributed variables, data are presented as median (interquartile range), and the Mann-Whitney *U* test was used for comparisons. Categorical variables are expressed as counts and percentages, and group differences were analyzed using the chi-square test or Fisher's exact test as appropriate.

Receiver operating characteristic (ROC) curve analysis was utilized to evaluate the predictive performance of logistic regression models for the extent of lung lesions and cavity formation in patients. The area under the curve (AUC) was calculated to determine the discriminative ability of the models. Sensitivity (true positive rate) and specificity (true negative rate) were derived based on the optimal cut-off values determined using the Youden Index. Sensitivity was defined as the proportion of correctly identified positive cases (e.g., patients with extensive lung lesions or cavities), while specificity was the proportion of correctly identified negative cases (e.g., patients without extensive lesions or cavities). Additionally, the positive predictive value (PPV) and negative predictive value (NPV) were calculated to further assess model performance. The discriminative ability of the models was interpreted using the AUC as follows: 0.5 indicates no discrimination, 0.7–0.8 acceptable, 0.8–0.9 excellent, and $>$0.9 outstanding.

Results

Comparison of Clinical Characteristics

A total of 198 patients were enrolled, comprising 86 males (43.4%) and 112 females (56.6%). The age range was between 22 and 91 years, with a mean age of 62

years. There were 138 patients (69.7%) with extensive lesions and 76 patients with cavities (38.4%). The mean lymphocyte count of all patients was 1.43 $\times$ 10^9/L, the mean cluster of differentiation (CD) 4+ T cells was 538 cells/μL, and the mean CD8+ T cells was 376 cells/μL. Among them, there were 12 patients with diabetes, 112 patients with bronchiectasis, 41 patients had a history of tuberculosis, and 77 patients had a history of smoking. Tables 1,2 present the detailed characteristics of the study population. The comparison of the collected data revealed no statistically significant differences in gender, history of diabetes, history of tuberculosis, and bacterial type between patients with extensive lung lesions and non-extensive lung lesions (all $p > 0.05$, Table 1). However, significant differences were observed in age, lymphocyte count, CD4+ T cells, CD8+ T cells, NLR, CD4+/CD8+ ratio, smoking history, history of bronchiectasis, and nutritional risk screening score (all $p < 0.05$, Table 1). Similarly, there were no significant differences in age, history of diabetes, history of bronchiectasis, history of pulmonary tuberculosis, and bacterial type between the groups with and without cavities (all $p > 0.05$, Table 2). However, statistical differences were found in gender, lymphocyte count, CD4+ T cells, CD8+ T cells, NLR, CD4+/CD8+ ratio, smoking history, and nutritional risk screening scores (all $p < 0.05$, Table 2). Regarding the species composition, *Mycobacterium avium* intracellular complex constituted the predominant species type, accounting for 76.3% of the total isolates, followed by *Mycobacterium abscessus*, *Mycobacterium kansasii*, and *Mycobacterium chelonae*, representing proportions of 9.6%, 7.6%, and 4%, respectively. The remaining isolates belonged to rare species types.

Analysis of Influencing Factors

In the multivariate logistic regression analysis, variables that showed statistically significant differences in univariate analysis were used as independent variables to minimize the confounding effects of various clinical factors. The dependent variables were the extensiveness of lung lesions and the presence of cavities, while relevant clinical characteristics were assigned accordingly (Table 3).

Based on the results of univariate analysis, a multivariate logistic regression analysis was conducted on age, lymphocyte levels, CD4+ T cells, CD8+ T cells, NLR, CD4+/CD8+ ratio, presence of bronchiectasis, smoking history, and nutritional risk screening score to evaluate their contributions to the extensiveness of pulmonary lesions in patients with NLM lung disease. The final results showed that NLR (OR = 4.685 [1.176–18.663], $p = 0.029$) and nutritional risk screening score (OR = 12.082 [3.726–39.183], $p < 0.001$) were still statistically significant. Among them, NLR and NRS-2002 score $\geq$3 were risk factors for extensive lung lesions in patients with NTM lung disease (Table 4). In this study, ROC curve was used to judge the effectiveness of the model. The AUC (area under the ROC curve) of this model was 0.889 (95% CI: 0.844–0.933, $p < 0.001$), the cut-off value was 0.671, and the sensitivity and specificity were 0.804 and 0.917, respectively (Fig. 2).

Based on the results of the univariate analysis, a multivariate logistic regression analysis was conducted on gender, lymphocyte level, CD4+ T cells, CD8+ T

Table 1. Comparison of clinical characteristics between the group with extensive lung lesions and the group with non-extensive lung lesions.

Clinical characteristics	Pulmonary lesions ≥3 (n = 138)	Pulmonary lesions <3 (n = 60)	Test value	p-value
Age	66.20 ± 10.96	54.05 ± 14.60	t = 6.456	<0.001
<40	4 (2.9%)	12 (20.0%)	χ^2 = 26.871	<0.001
40–59	32 (23.2%)	24 (40.0%)		
≥60	102 (73.9%)	24 (40.0%)		
Gender			χ^2 = 2.493	0.114
Male	65 (47.1%)	21 (35.0%)		
Female	73 (52.9%)	39 (65.0%)		
Lymphocyte count			χ^2 = 12.094	<0.001
<1.1 × 10^9/L	61 (44.2%)	11 (18.3%)		
≥1.1 × 10^9/L	77 (55.8%)	49 (81.7%)		
NLR			χ^2 = 31.896	<0.001
≥3.13	67 (48.6%)	4 (6.7%)		
<3.13	71 (51.4%)	56 (93.3%)		
CD4+ T cells	418.50 (283.25, 608.00)	646.50 (510.25, 804.25)	Z = –5.778	<0.001
CD8+ T cells	315.00 (197.00, 424.50)	366.50 (284.50, 474.00)	Z = –2.584	0.01
CD4+/CD8+			χ^2 = 13.539	<0.001
<1	39 (28.3%)	3 (5.0%)		
≥1	99 (71.7%)	57 (95.0%)		
Smoking history			χ^2 = 5.411	0.020
Yes	61 (44.2%)	16 (26.7%)		
No	77 (55.8%)	44 (73.3%)		
NRS-2002			χ^2 = 72.412	<0.001
≥3	102 (73.9%)	5 (8.3%)		
<3	36 (26.1%)	55 (91.7%)		
Diabetes			χ^2 = 1.917*	0.166*
Yes	11 (8.0%)	1 (1.7%)		
No	127 (92.0%)	59 (98.3%)		
Bronchiectasis			χ^2 = 11.648	<0.001
Yes	89 (64.5%)	23 (38.3%)		
No	49 (35.5%)	37 (61.7%)		
History of tuberculosis			χ^2 = 2.851	0.091
Yes	33 (23.9%)	8 (13.3%)		
No	105 (76.1%)	52 (86.7%)		
Strain type			χ^2 = 1.004	0.316
MAC	108 (78.3%)	43 (71.7%)		
Other types	30 (21.7%)	17 (28.3%)		

*Tested with continuous correction.

Abbreviations: NLR, neutrophil-to-lymphocyte ratio; MAC, *Mycobacterium avium* intracellular complex; NRS, nutritional risk screening.

Table 2. Comparison of clinical characteristics between the group with cavities and the group without cavities.

Clinical characteristics	With cavities (n = 76)	Without cavities (n = 122)	Test value	p-value
Age	63.72 ± 14.45	61.77 ± 12.65	t = 1.000	0.391
<40	7 (9.2%)	9 (7.4%)	χ^2 = 4.446	0.108
40–59	15 (19.7%)	41 (33.6%)		
≥60	54 (71.1%)	72 (59.0%)		
Gender			χ^2 = 12.495	<0.001
Male	45 (59.2%)	41 (33.6%)		
Female	31 (40.8%)	81 (66.4%)		
Lymphocyte count			χ^2 = 11.917	<0.001
$<1.1 \times 10^9$/L	39 (51.3%)	33 (27.0%)		
$\geq 1.1 \times 10^9$/L	37 (48.7%)	89 (73.0%)		
NLR			χ^2 = 36.206	<0.001
≥3.13	47 (61.8%)	24 (19.7%)		
<3.13	29 (38.2%)	98 (80.3%)		
CD4+ T cells	380.50 (256.50, 565.50)	564.00 (429.00, 743.25)	Z = –4.826	<0.001
CD8+ T cells	301.50 (174.75, 416.75)	353.50 (259.25, 452.00)	Z = –2.404	0.016
CD4+/CD8+			χ^2 = 6.046	0.014
<1	23 (30.3%)	19 (15.6%)		
≥1	53 (69.7%)	103 (84.4%)		
Smoking history			χ^2 = 13.915	<0.001
Yes	42 (55.3%)	35 (28.7%)		
No	34 (44.7%)	87 (71.3%)		
NRS-2002			χ^2 = 24.642	<0.001
≥3	58 (76.3%)	49 (40.2%)		
<3	18 (23.7%)	73 (59.8%)		
Diabetes			χ^2 = 0.300*	0.584*
Yes	6 (7.9%)	6 (4.9%)		
No	70 (92.1%)	116 (95.1%)		
Bronchiectasis			χ^2 = 3.140	0.076
Yes	49 (64.5%)	63 (51.6%)		
No	27 (35.5%)	59 (48.4%)		
Tuberculosis			χ^2 = 2.363	0.124
Yes	20 (26.3%)	21 (17.2%)		
No	56 (73.7%)	101 (82.8%)		
Strain type			χ^2 = 0.109	0.742
MAC	57 (75.0%)	94 (77.0%)		
Other types	19 (25.0%)	28 (23.0%)		

*Tested with continuous correction.

cells, NLR, CD4+/CD8+, smoking history, and nutritional risk screening score to evaluate their contributions to cavity formation in patients with NLM lung disease. The multivariate analysis showed that NLR (OR = 3.454 [1.483–8.047], p = 0.004) remained statistically significant afterwards, suggesting that elevated NLR is a risk

Table 3. Assignment table of various factors.

Factors	Method of assignment
Age	<40 years = 1, 40–59 years = 2, ≥60 years = 3
Gender	Female = 0, male = 1
Lymphocyte levels	Lymphocyte count $<1.1 \times 10^9$/L = 0, lymphocyte count $\geq 1.1 \times 10^9$/L = 1
CD4+ T cells	CD4+ T cells <450/μL = 0, CD4+ T cells ≥450/μL = 1
CD8+ T cells	CD8+ T cells <320/μL = 0, CD8+ T cells ≥320/μL = 1
CD4+/CD8+	CD4+/CD8+ <1 = 0, CD4+/CD8+ ≥1 = 1
NLR	NLR <3.13 = 0, NLR ≥3.13 = 1
Nutrition score	NRS-2002 ≥3 = 1, NRS-2002 <3 = 0
Presence of bronchiectasis	With bronchiectasis = 1, without bronchiectasis = 0
History of smoking	History of smoking = 1, no history of smoking = 0

Table 4. Multivariate logistic regression analysis of the factors affecting the extent of lung lesions in patients with NTM lung disease.

Independent variables	β	S.E.	Wald	p	OR (95% CI)
Age(1)*	1.428	0.808	3.119	0.077	4.169 (0.855–20.328)
Age(2)**	1.423	0.838	2.883	0.090	4.151 (0.803–21.462)
Lymphocyte levels	0.968	0.694	1.942	0.163	2.632 (0.675–10.263)
CD4+ T cells	–1.213	0.838	2.092	0.148	0.297 (0.058–1.538)
CD8+ T cells	0.008	0.483	<0.001	0.986	1.008 (0.392–2.597)
NLR	1.544	0.705	4.794	0.029	4.685 (1.176–18.663)
Nutritional risk screening score	2.492	0.600	17.231	<0.001	12.082 (3.726– 39.183)
CD4+/CD8+	–1.669	0.859	3.775	0.052	0.188 (0.035–1.015)
History of smoking	0.185	0.493	0.142	0.707	1.204 (0.458–3.162)
History of bronchiectasis	0.628	0.435	2.083	0.149	1.875 (0.799–4.401)

*The group of 40–59 years compared to the group of <40 years; **The group of ≥60 years compared to the group of <40 years.

factor for the formation of cavities in patients with NTM lung disease (Table 5). In this study, ROC curve was used to assess the effectiveness of the model. The AUC (area under the ROC curve) of this model was 0.790 (95% CI: 0.727–0.854, $p < 0.001$), the cut-off value was 0.476, and the sensitivity and specificity were 0.658 and 0.820, respectively (Fig. 3).

Discussion

The prognosis of NTM lung disease is related to the extent of pulmonary lesions and cavities. Therefore, it is believed that the findings from risk factor investigation will offer invaluable insights into early intervention, cure rate improvement, and disease prognosis improvement (Jhun et al, 2020; Moon et al, 2019). Due to the atypical clinical manifestations resembling pulmonary tuberculosis and bronchiectasis, the diagnostic significance of NTM lung disease is often overlooked, leading to delayed diagnosis and extensive lung involvement upon detection (Xu and Xu,

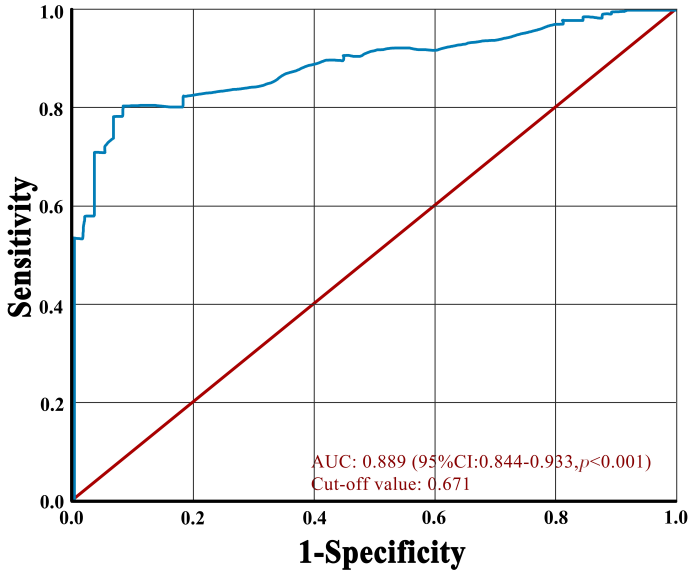

Fig. 2. ROC curve of the factors affecting the extent of lung lesions in patients with NTM lung disease. ROC, receiver operating characteristic; AUC, area under the curve.

Table 5. Multivariate logistic regression analysis of factors affecting cavity formation in patients with NTM lung disease.

Independent variables	β	S.E.	Wald	p	OR (95% CI)
NLR	1.240	0.431	8.255	0.004	3.454 (1.483–8.047)
CD4+ T cells	–0.628	0.495	1.611	0.204	0.534 (0.202– 1.407)
CD8+ T cells	–0.330	0.429	0.592	0.442	0.719 (0.310–1.666)
Gender	0.483	0.557	0.751	0.386	1.621 (0.544–4.831)
Smoking history	0.376	0.562	0.448	0.503	1.457 (0.484–4.382)
Lymphocyte levels	0.377	0.483	0.608	0.435	1.457 (0.566–3.754)
Nutritional risk screening score	0.541	0.420	1.661	0.197	1.718 (0.754– 3.912)
CD4+/CD8+	–0.508	0.475	1.144	0.285	0.602 (0.237–1.526)

2022). A study by Xu and Xu (2022) reported that at the time of diagnosis, lesions distributed throughout all three lobes and above were observed in approximately 70% of patients. In this study, approximately 69.7% (138/198) of the patients exhibited lesions on more than three lung fields at the time of initial diagnosis, consistent with findings from previous investigations. It has also been reported that the presence of a lung cavity is associated with prolonged treatment duration, reduced efficacy in eradicating sputum bacteria, and heightened therapeutic complexity (Matsuyama et al, 2023; Miura et al, 2020).

In this study, nutritional level was an independent factor affecting the extent of lung lesions in patients with NTM lung disease. The NRS-2002 is a widely employed clinical nutritional risk screening tool in medical practice, enabling early identification of patients at risk of malnutrition and facilitating prompt intervention (Neelemaat et al, 2011). Nutritional status is intricately linked to cellular immune function, as malnutrition can induce immunosuppression and subsequently

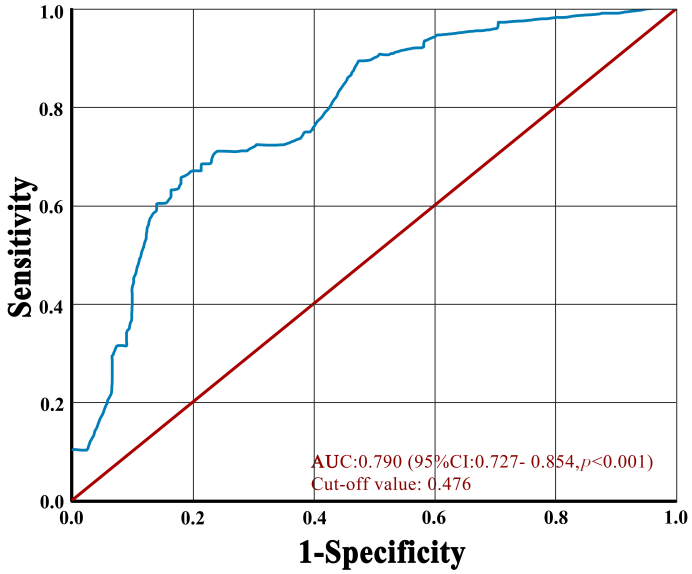

Fig. 3. ROC curve of the factors affecting cavity formation in patients with NTM lung disease.

increase the susceptibility to infectious diseases (Alwarawrah et al, 2018; Nguyen et al, 2024). Previous study has also utilized nutritional index and body mass index (BMI) as prognostic indicators for mortality attributed to NTM lung disease, revealing that patients with diminished nutritional index and BMI exhibit an elevated risk of fatality (Hachisu et al, 2020). Therefore, timely nutritional risk screening and provision of nutritional support are imperative for patients diagnosed with NTM lung disease in order to mitigate the progression of NTM lesions.

In univariate analysis, lymphocyte level, CD4+ T cells, CD8+ T cells and CD4+/CD8+ were influencing factors of the extent of pulmonary lesions and cavities in NTM lung disease, while in subsequent multivariate analysis, these factors were not identified as independent factors affecting these pathological conditions in NTM lung disease. This outcome does not align with our initial expectations. The reason for such discrepancy may be attributed to a discernible correlation among these factors. However, according to the results of univariate analysis, these factors are significantly different among different groups. Lymphocytes play a pivotal role as crucial immune cells within the human immune system. The quantification of lymphocytes in peripheral blood is closely associated with the immunological functionality of the human body. In patients with NTM lung disease, lymphocytes play a pivotal role as the primary effector cells in orchestrating the immune response against non-tuberculous mycobacteria, which is associated with lesion dissemination and cavity formation (Gramegna et al, 2022). CD4+ T cells possess the capability to secrete a diverse array of cytokines, thereby facilitating the activation of macrophages and orchestrating various immune cell activities through both direct and indirect mechanisms. CD8+T cells perform cytotoxic functions by secreting granulysin and releasing cytokines (Amelio et al, 2019; Henkle and Winthrop, 2015). Therefore, CD4+ T cells and CD8+ T cells can reflect the immune status of the body. The CD4+/CD8+ ratio is frequently employed as an indicator for assessing immune function, and its association with the morbidity and mortality

of numerous diseases has been well-established (Salih et al, 2022; Triplette et al, 2017; Vassallo et al, 2015). In this study, patients exhibiting inverted CD4+/CD8+ ratio demonstrated a higher susceptibility to developing extensive lesions, which was attributed to the patient's declining immune function. In patients with NTM lung disease, monitoring the lymphocyte levels is of utmost importance. Patients exhibiting low lymphocyte counts, particularly in CD4+ T cells, are more prone to experiencing lesion dissemination.

NLR, a widely used inflammatory marker in the management and prediction of various chronic diseases, primarily serves as an indicator of the body's inflammatory response. Previous research has established associations between NLR and conditions such as tumors, systemic lupus erythematosus, tuberculosis, pneumonia, among others (Abakay et al, 2015; Diem et al, 2017; Qin et al, 2016; Yang et al, 2020). At present, there is no unified conclusion on the cut-off value of NLR, as different cut-off values of NLR have been reported for diseases in various studies. The study has shown that the normal value of NLR is between 0.78 and 3.53 (Forget et al, 2017). In some studies related to lung infection, NLR $\geq$3.13 was defined as a high-risk group. We refer to the cut-off value in the relevant literature (Liu et al, 2020; Pirsalehi et al, 2020). In comparison to lymphocyte count, NLR can more accurately reflect alterations in cellular immune function among patients with NTM lung disease. This study identifies NLR as an independent factor influencing the extent of lesions and cavities in NTM patients.

Previous studies have demonstrated a significant association between the incidence of NTM lung disease and comorbidities such as diabetes, bronchiectasis, tuberculosis, among others (Bonaiti et al, 2015; Jeon et al, 2023; Li et al, 2022; Wang et al, 2021). However, it is not clear whether these complications are related to the extensive lesions and cavity formation in NTM lung disease. Therefore, we analyzed bronchiectasis, diabetes, and tuberculosis as possible influencing factors in this study. The results of this study showed that there was no statistical difference in the effects of bronchiectasis, diabetes and tuberculosis on the extensive lesions and cavity formation in patients with NTM lung disease. This is different from what we expected, because diabetes is an important factor in the progression of other pulmonary infectious diseases. A past study showed that pulmonary tuberculosis patients with diabetes are more likely to suffer pulmonary cavity (Song et al, 2016). The reason for the unexpected result may be associated with the distinct progression of individual underlying diseases and the varying extent of NTM dissemination within the host. In addition, the incidence of NTM lung disease is lower than that of pulmonary tuberculosis, and there are fewer patients with diabetes. The sample size is insufficient, compromising the robustness of the ultimate findings. A study has shown that the incidence of NTM lung disease in diabetic patients is lower than that in non-diabetic patients, probably attributed to the types of pulmonary flora in diabetic patients (Tan et al, 2021). It is difficult for NTM to become the dominant strain affecting the development of lung disease among diabetic patients.

The study has demonstrated that the incidence of NTM is highly correlated with bronchiectasis (Zhou et al, 2022). Based on a previous meta-analysis, the overall

incidence of NTM lung disease in patients with bronchiectasis was approximately 10% (Zhou et al, 2022). This finding prompted us to investigate whether bronchiectasis affects the extensive lesions and cavity formation in patients with NTM lung disease. In this study, 56.6% of patients with NTM lung disease had bronchiectasis. Univariate analysis revealed a higher likelihood of extensive lung lesions among patients with bronchiectasis; however, multivariate analysis revealed that the impact of bronchiectasis was non-significant. The extent of the lesion is associated with the severity of bronchiectasis, which can be influenced by various factors. Hence, it cannot be considered an independent determinant of lesion extensiveness.

The study has demonstrated that an association between a prior history of pulmonary tuberculosis and an increased likelihood of future development of NTM lung disease, and that patients with NTM lung disease are also at higher risk for developing pulmonary tuberculosis during treatment (Li et al, 2022). The reason may be attributed to the structural alterations of the lung in patients with pulmonary tuberculosis or NTM lung disease, which augment their susceptibility to the disease. In view of this, it was in our expectation that a history of tuberculosis may lead to extensive lesions and cavity formation in patients with NTM lung disease; however, the presence of a history of pulmonary tuberculosis did not emerge as a significant determinant influencing the extent and cavity of lung lesions in patients with NTM in our study. The reason for the unexpected result may be that the severity of lesions in NTM patients is associated with the intensity of prior pulmonary tuberculosis, extent of lung tissue destruction, and duration of medical history. The sample size of patients with a history of pulmonary tuberculosis in this study was insufficient for conducting further stratified analysis, eliminating a chance to unravel the possibility of statistically significant findings.

Smoking is causally associated with a variety of lung diseases. The study has shown that smoking is closely related to bronchiectasis, and the incidence of NTM lung disease is related to bronchiectasis (McShane et al, 2024). Therefore, we anticipate that smoking may lead to extensive lesions and cavity formation in patients with NTM lung disease. In univariate analysis, smoking and bronchiectasis were both factors affecting the extensive lesions in NTM lung disease, while in subsequent multivariate analysis, smoking was not an independent factor affecting the extensive lesions of NTM lung disease. This could be caused by the imbalanced influence of smoking on bronchiectasis and NTM lung disease, with the former being more greatly affected by this habit. In univariate analysis, smoking was a factor affecting the cavity formation of NTM lung disease, while in subsequent multivariate analysis, smoking was not an independent factor affecting the cavity formation of NTM lung disease. The reason may be that gender was also a factor affecting the cavity formation among patients with NTM lung disease in univariate analysis, as smoking habit presents clear, varying engagement distributions across gender categories. Previous study has also shown that smokers face a higher risk for tuberculosis but a lower risk for NTM lung disease than non-smokers (Chung et al, 2024). Such imbalanced levels of risks can be explained with smoking causing chronic airway inflammation and weakened immune barrier (Madan et al, 2016), making patients more susceptible to tuberculosis than to NTM lung disease.

This study has several limitations. Firstly, it is a retrospective study, which may be prone to clinical data incompleteness and inconvenient for prospective monitoring and collection of relevant patient data. Due to incomplete clinical data of outpatients, this study mainly collected relevant clinical data of inpatients. As a result, our results may present some deviations from the actual outcome. Additionally, this study was single-center in nature, along with a small sample size, further restricting generalizability of the results obtained. Therefore, future research should focus on conducting multi-center, large-sample, and prospective studies to validate these findings. It is worth noting that image manifestations could be potentially influenced by factors such as sputum bacterial load at onset, timing of patients' seeking medical care, frequency of physical examinations, drug resistance patterns, and medication for underlying diseases; however, due to limitations in obtaining comprehensive clinical data from this study, further investigations are warranted for confirmation.

Conclusion

This study identified elevated NLR and poor nutritional status (NRS-2002 score $\geq$3) as independent risk factors for extensive lung lesions in patients with NTM lung disease. Additionally, elevated NLR was found to be the key independent factor for cavity formation. These findings highlight the importance of early monitoring and targeted intervention for patients with these risk factors to prevent disease progression and improve clinical outcomes.

Key Points

- This retrospective study investigates the influencing factors that lead to extensive lesions and cavities in the lungs by examining differences in clinical characteristics among patients with non-tuberculous mycobacterial (NTM) lung disease.
- In patients with NTM lung disease, elevated neutrophil-to-lymphocyte ratio (NLR) and poor nutritional status are influencing factors causing extensive lung lesions.
- In patients with NTM lung disease, elevated NLR is considered an influencing factor causing pulmonary cavities.
- The development of extensive pulmonary lesions and cavities in patients with NTM lung disease is influenced by multiple factors. Potential influencing factors include age, gender, lymphocyte levels, CD4+ T cells, CD8+ T cells, NLR, CD4+/CD8+ ratio, smoking history, bronchiectasis, and diabetes mellitus.
- The revelation of these potential risk factors underscores the need for early screening and intervention in NTM lung disease patients to achieve better disease management and control.

Availability of Data and Materials

All data generated or analyzed during this study are available from the corresponding author upon reasonable request.

Author Contributions

XQL and NLM designed the research. XQL and YZ performed the research. XQL and ZSW analyzed the data. XQL drafted the manuscript. NLM provided direction and supervision of the research. All authors contributed to important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study was approved by the Medical Ethics Committee of The Second Hospital of Nanjing (number: 2024-LS-ky070) and in compliance with the Declaration of Helsinki. Informed consent was obtained from all participants throughout the study.

Acknowledgement

Not applicable.

Funding

This work was funded by the Nanjing Health Science and Technology Development Special Fund Project Plan. Grant ID YKK20101.

Conflict of Interest

The authors declare no conflict of interest.

References

Abakay O, Abakay A, Sen HS, Tanrikulu AC. The relationship between inflammatory marker levels and pulmonary tuberculosis severity. Inflammation. 2015; 38: 691–696. https://doi.org/10.1007/s10753-014-9978-y

Alwarawrah Y, Kiernan K, MacIver NJ. Changes in Nutritional Status Impact Immune Cell Metabolism and Function. Frontiers in Immunology. 2018; 9: 1055. https://doi.org/10.3389/fimmu.2018.01055

Amelio P, Portevin D, Hella J, Reither K, Kamwela L, Lweno O, et al. HIV Infection Functionally Impairs Mycobacterium tuberculosis-Specific CD4 and CD8 T-Cell Responses. Journal of Virology. 2019; 93: e01728-18. https://doi.org/10.1128/JVI.01728-18

Bonaiti G, Pesci A, Marruchella A, Lapadula G, Gori A, Aliberti S. Nontuberculous Mycobacteria in Noncystic Fibrosis Bronchiectasis. BioMed Research International. 2015; 2015: 197950. https://doi.org/10.1155/2015/197950

Chung C, Lee KN, Han K, Shin DW, Lee SW. The effect of smoking on nontuberculous mycobacterial pulmonary disease and tuberculosis: a nationwide retrospective cohort study. Scientific Reports. 2024; 14: 22653. https://doi.org/10.1038/s41598-024-72438-4

Cowman S, van Ingen J, Griffith DE, Loebinger MR. Non-tuberculous mycobacterial pulmonary disease. The European Respiratory Journal. 2019; 54: 1900250. https://doi.org/10.1183/13993003.00250-2019

Dahl VN, Mølhave M, Fløe A, van Ingen J, Schön T, Lillebaek T, et al. Global trends of pulmonary infections with nontuberculous mycobacteria: a systematic review. International Journal of Infectious Diseases. 2022; 125: 120–131. https://doi.org/10.1016/j.ijid.2022.10.013

Diem S, Schmid S, Krapf M, Flatz L, Born D, Jochum W, et al. Neutrophil-to-Lymphocyte ratio (NLR) and Platelet-to-Lymphocyte ratio (PLR) as prognostic markers in patients with non-small cell lung cancer (NSCLC) treated with nivolumab. Lung Cancer. 2017; 111: 176–181. https://doi.org/10.1016/j.lungcan.2017.07.024

Forget P, Khalifa C, Defour JP, Latinne D, Van Pel MC, De Kock M. What is the normal value of the neutrophil-to-lymphocyte ratio? BMC Research Notes. 2017; 10: 12. https://doi.org/10.1186/s13104-016-2335-5

Gopalaswamy R, Shanmugam S, Mondal R, Subbian S. Of tuberculosis and non-tuberculous mycobacterial infections - a comparative analysis of epidemiology, diagnosis and treatment. Journal of Biomedical Science. 2020; 27: 74. https://doi.org/10.1186/s12929-020-00667-6

Gramegna A, Lombardi A, Lorè NI, Amati F, Barone I, Azzarà C, et al. Innate and Adaptive Lymphocytes in Non-Tuberculous Mycobacteria Lung Disease: A Review. Frontiers in Immunology. 2022; 13: 927049. https://doi.org/10.3389/fimmu.2022.927049

Hachisu Y, Murata K, Takei K, Tsuchiya T, Tsurumaki H, Koga Y, et al. Prognostic nutritional index as a predictor of mortality in nontuberculous mycobacterial lung disease. Journal of Thoracic Disease. 2020; 12: 3101–3109. https://doi.org/10.21037/jtd-20-803

Hendrix C, McCrary M, Hou R, Abate G. Diagnosis and Management of Pulmonary NTM with a Focus on *Mycobacterium avium* Complex and *Mycobacterium abscessus*: Challenges and Prospects. Microorganisms. 2022; 11: 47. https://doi.org/10.3390/microorganisms11010047

Henkle E, Winthrop KL. Nontuberculous mycobacteria infections in immunosuppressed hosts. Clinics in Chest Medicine. 2015; 36: 91–99. https://doi.org/10.1016/j.ccm.2014.11.002

Hwang H, Lee JK, Heo EY, Kim DK, Lee HW. The factors associated with mortality and progressive disease of nontuberculous mycobacterial lung disease: a systematic review and meta-analysis. Scientific Reports. 2023; 13: 7348. https://doi.org/10.1038/s41598-023-34576-z

Jeon DS, Kim S, Kim MA, Chong YP, Shim TS, Jung CH, et al. Type 2 Diabetes Mellitus- and Complication-Related Risk of Nontuberculous Mycobacterial Disease in a South Korean Cohort. Microbiology Spectrum. 2023; 11: e0451122. https://doi.org/10.1128/spectrum.04511-22

Jhun BW, Moon SM, Jeon K, Kwon OJ, Yoo H, Carriere KC, et al. Prognostic factors associated with long-term mortality in 1445 patients with nontuberculous mycobacterial pulmonary disease: a 15-year follow-up study. The European Respiratory Journal. 2020; 55: 1900798. https://doi.org/10.1183/13993003.00798-2019

Kondrup J, Rasmussen HH, Hamberg O, Stanga Z, Ad Hoc ESPEN Working Group. Nutritional risk screening (NRS 2002): a new method based on an analysis of controlled clinical trials. Clinical Nutrition. 2003; 22: 321–336. https://doi.org/10.1016/s0261-5614(02)00214-5

Ku JH, Henkle E, Aksamit TR, Barker A, Brunton AE, Winthrop KL, et al. Treatment of Nontuberculous Mycobacterial (NTM) Pulmonary Infection in the US Bronchiectasis and NTM Registry: Treatment Patterns, Adverse Events, and Adherence to American Thoracic Society/Infectious Disease Society of America Treatment Guidelines. Clinical Infectious Diseases. 2023; 76: 338–341. https://doi.org/10.1093/cid/ciac788

Kumar K, Loebinger MR. Nontuberculous Mycobacterial Pulmonary Disease: Clinical Epidemiologic Features, Risk Factors, and Diagnosis: The Nontuberculous Mycobacterial Series. Chest. 2022; 161: 637–646. https://doi.org/10.1016/j.chest.2021.10.003

Lange C, Böttger EC, Cambau E, Griffith DE, Guglielmetti L, van Ingen J, et al. Consensus management recommendations for less common non-tuberculous mycobacterial pulmonary diseases. The Lancet. Infectious Diseases. 2022; 22: e178–e190. https://doi.org/10.1016/S1473-3099(21)00586-7

Li Q, Li H, An J, Zhang X, Wang W, Wang Y, et al. Transition between Mycobacterium tuberculosis and nontuberculous mycobacteria in recurrent “tuberculosis” patients. European Journal of Clinical Microbi-

ology & Infectious Diseases. 2022; 41: 1127–1132. https://doi.org/10.1007/s10096-022-04477-6

Liu CF, Song YM, He WC, Liu DX, He P, Bao JJ, et al. Nontuberculous mycobacteria in China: incidence and antimicrobial resistance spectrum from a nationwide survey. Infectious Diseases of Poverty. 2021; 10: 59. https://doi.org/10.1186/s40249-021-00844-1

Liu J, Liu Y, Xiang P, Pu L, Xiong H, Li C, et al. Neutrophil-to-lymphocyte ratio predicts critical illness patients with 2019 coronavirus disease in the early stage. Journal of Translational Medicine. 2020; 18: 206. https://doi.org/10.1186/s12967-020-02374-0

Madan R, Matalon S, Vivero M. Spectrum of Smoking-related Lung Diseases: Imaging Review and Update. Journal of Thoracic Imaging. 2016; 31: 78–91. https://doi.org/10.1097/RTI.0000000000000185

Matsuyama M, Matsumura S, Nonaka M, Nakajima M, Sakai C, Arai N, et al. Pathophysiology of pulmonary nontuberculous mycobacterial (NTM) disease. Respiratory Investigation. 2023; 61: 135–148. https://doi.org/10.1016/j.resinv.2022.12.002

McShane PJ, Brunton AE, Choate R, Marmor M, Richards CJ, Solomon GM, et al. The Impact of Tobacco Smoking in Bronchiectasis: Data from the U.S. Bronchiectasis and Nontuberculous Mycobacteria Research Registry. American Journal of Respiratory and Critical Care Medicine. 2024; 210: 128–130. https://doi.org/10.1164/rccm.202402-0466RL

Miura K, Nakamura M, Taooka Y, Hotta T, Hamaguchi M, Okimoto T, et al. Comparison of the chest computed tomography findings between patients with pulmonary tuberculosis and those with Mycobacterium avium complex lung disease. Respiratory Investigation. 2020; 58: 137–143. https://doi.org/10.1016/j.resinv.2019.12.006

Moon SM, Jhun BW, Baek SY, Kim S, Jeon K, Ko RE, et al. Long-term natural history of non-cavitary nodular bronchiectatic nontuberculous mycobacterial pulmonary disease. Respiratory Medicine. 2019; 151: 1–7. https://doi.org/10.1016/j.rmed.2019.03.014

Morimoto K, Iwai K, Uchimura K, Okumura M, Yoshiyama T, Yoshimori K, et al. A steady increase in nontuberculous mycobacteriosis mortality and estimated prevalence in Japan. Annals of the American Thoracic Society. 2014; 11: 1–8. https://doi.org/10.1513/AnnalsATS.201303-067OC

Neelemaat F, Meijers J, Kruizenga H, van Ballegooijen H, van Bokhorst-de van der Schueren M. Comparison of five malnutrition screening tools in one hospital inpatient sample. Journal of Clinical Nursing. 2011; 20: 2144–2152. https://doi.org/10.1111/j.1365-2702.2010.03667.x

Nguyen MVH, Haas MK, Kasperbauer SH, Calado Nogueira de Moura V, Eddy JJ, Mitchell JD, et al. Nontuberculous Mycobacterial Pulmonary Disease: Patients, Principles, and Prospects. Clinical Infectious Diseases. 2024; 79: e27–e47. https://doi.org/10.1093/cid/ciae421

Pirsalehi A, Salari S, Baghestani A, Vahidi M, Khave LJ, Akbari ME, et al. Neutrophil-to-lymphocyte ratio (NLR) greater than 6.5 may reflect the progression of COVID-19 towards an unfavorable clinical outcome. Iranian Journal of Microbiology. 2020; 12: 466–474. https://doi.org/10.18502/ijm.v12i5.4609

Prevots DR, Marras TK. Epidemiology of human pulmonary infection with nontuberculous mycobacteria: a review. Clinics in Chest Medicine. 2015; 36: 13–34. https://doi.org/10.1016/j.ccm.2014.10.002

Qin B, Ma N, Tang Q, Wei T, Yang M, Fu H, et al. Neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) were useful markers in assessment of inflammatory response and disease activity in SLE patients. Modern Rheumatology. 2016; 26: 372–376. https://doi.org/10.3109/14397595.2015.1091136

Salih MM, Almehmadi M, Shafie A, Alsharif A, Alsiwiehri N, El-Askary A, et al. Evaluation of CD4+:CD8+ Ratio in Patients With Cervical Cancer and the Levels of Inflammatory Markers. In Vivo. 2022; 36: 2414–2421. https://doi.org/10.21873/invivo.12975

Song Q, Zhang G, Jiang H, Ren Y, Lu X. Imaging Features of Pulmonary CT in Type 2 Diabetic Patients with Multidrug-Resistant Tuberculosis. PLoS ONE. 2016; 11: e0152507. https://doi.org/10.1371/journal.pone.0152507

Tan Y, Deng Y, Yan X, Liu F, Tan Y, Wang Q, et al. Nontuberculous mycobacterial pulmonary disease and associated risk factors in China: A prospective surveillance study. The Journal of Infection. 2021; 83: 46–53. https://doi.org/10.1016/j.jinf.2021.05.019

Triplette M, Attia EF, Akgün KM, Soo Hoo GW, Freiberg MS, Butt AA, et al. A Low Peripheral Blood CD4/CD8 Ratio Is Associated with Pulmonary Emphysema in HIV. PloS One. 2017; 12: e0170857.

https://doi.org/10.1371/journal.pone.0170857

Vassallo M, Durant J, Lebrun-Frenay C, Fabre R, Ticchioni M, Andersen S, et al. Virologically suppressed patients with asymptomatic and symptomatic HIV-associated neurocognitive disorders do not display the same pattern of immune activation. HIV Medicine. 2015; 16: 431–440. https://doi.org/10.1111/hiv.12246

Wang JY, Lin HC, Lin HA, Chung CH, Chen LC, Huang KY, et al. Associations between Diabetes Mellitus and Nontuberculous Mycobacterium-Caused Diseases in Taiwan: A Nationwide Cohort Study. The American Journal of Tropical Medicine and Hygiene. 2021; 105: 1672–1679. https://doi.org/10.4269/ajtmh.20-1441

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. American Journal of Respiratory and Critical Care Medicine. 2010; 182: 977–982. https://doi.org/10.1164/rccm.201003-0503OC

Xu L, Xu S. CT Imaging Characteristics of Nontuberculous Mycobacteria Lung Disease, Active Tuberculosis and Multi-Drug Resistant Tuberculosis. Sarcoidosis, Vasculitis, and Diffuse Lung Diseases. 2022; 39: e2022008. https://doi.org/10.36141/svdld.v39i2.11829

Yagi K, Ito A, Fujiwara K, Morino E, Hase I, Nakano Y, et al. Clinical Features and Prognosis of Nontuberculous Mycobacterial Pleuritis: A Multicenter Retrospective Study. Annals of the American Thoracic Society. 2021; 18: 1490–1497. https://doi.org/10.1513/AnnalsATS.202008-938OC

Yang AP, Liu JP, Tao WQ, Li HM. The diagnostic and predictive role of NLR, d-NLR and PLR in COVID-19 patients. International Immunopharmacology. 2020; 84: 106504. https://doi.org/10.1016/j.intimp.2020.106504

Zhou Y, Mu W, Zhang J, Wen SW, Pakhale S. Global prevalence of non-tuberculous mycobacteria in adults with non-cystic fibrosis bronchiectasis 2006-2021: a systematic review and meta-analysis. BMJ Open. 2022; 12: e055672. https://doi.org/10.1136/bmjopen-2021-055672