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ORIGINAL RESEARCH

# Clinical Characteristics of Patients with Nontuberculous Mycobacterium Pulmonary Disease in Fuyang, China: A Retrospective Study

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**Objective:** We retrospectively review consecutive patients with nontuberculous mycobacterium (NTM) pulmonary disease reported from a designated hospital for infectious diseases in the Fuyang district of China to determine the clinical characteristics of these patients.

**Methods:** This research enrolled 234 patients with NTM pulmonary disease between January 2018 and May 2023 in the Fuyang district of China. Data were collected from the electronic medical records. The NTM strain composition and clinical characteristics of NTM pulmonary disease were retrospectively analyzed.

**Results:** 73 (31.20%) patients had previous tuberculosis (TB) or TB exposure history and bronchiectasis. Mixed NTM infection accounted for 12.39%. *Mycobacterium intracellulare* strain was detected in 132 patients (49.62%). Women were found to be more affected by *Mycobacterium avium* infection, and men by *Mycobacterium abscessus* infection. *Mycobacterium avium* (34.21%) and *Mycobacterium abscessus* (33.33%) strains were most common in people with previous TB or TB exposure history. Among respiratory tract-related diseases, patients with bronchiectasis had the highest isolation rate of *Mycobacterium avium* (55.36%). Women were susceptible to bronchiectasis ($P$ <0.01). The median of mononuclear-to-lymphocyte ratio (MLR) was higher in men than in women ($P < 0.01$). The serum albumin (ALB) level was lower in patients with TB or TB exposure history than in those without TB history ($P = 0.034$). The prognostic nutritional index (PNI) was lower in patients with TB or TB exposure history than in those without tuberculosis history ($P = 0.021$). Patients with NTM lung disease were poorly treated.

**Conclusion:** Clinical symptoms of the disease were not species-specific. *Mycobacterium intracellulare* and *Mycobacterium avium* strains were predominant in the Fuyang district of China. Previous TB or TB exposure history immensely enhanced the risk of NTM disease.

**Keywords:** NTM, clinical symptoms, tuberculosis exposure history, bronchiectasis

## Introduction

Nontuberculous mycobacteria (NTMs) are considered as a significant opportunistic pathogen in humans.[1] They most often affect the lungs and can lead to disease progression in susceptible hosts, mainly in individuals with chronic lung diseases, such as chronic obstructive pulmonary disease (COPD), bronchiectasis, cystic fibrosis, and prior tuberculosis (TB).[2–4] Due to the similarity in clinical symptoms between nontuberculous mycobacteria (NTM) infections and pulmonary TB caused by *Mycobacterium tuberculosis* (Mtb), as well as the possibility of positive acid-fast staining in sputum smear microscopy, NTM infections are easily misdiagnosed as pulmonary TB. Moreover, many NTM strains are often resistant to commonly used anti-TB drugs, which can further lead to misdiagnosis as drug-resistant pulmonary TB.[5] The treatment of NTM infection is also challenging, as it requires different antimycobacterial drugs, expert management, and prolonged hospitalization.[6] Therefore, understanding the clinical characteristics of patients with NTM pulmonary disease is essential to help its timely diagnosis and treatment.

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Despite a significant reduction in morbidity due to TB in China since 2000, TB remains a public health concern in this country.[7] In recent decades, the incidence and mortality of NTM infections have substantially increased globally, and the lung is the most critically affected organ in this disease.[8,9] The infection rate of NTM in China is increasing. So far, domestic reports on the characteristics of NTM pulmonary disease are limited.[10,11] In particular, the prevalence of NTM infection in Fuyang has not yet been assessed. In this retrospective study, we summarized the clinical characteristics of NTM infections and analyzed the composition of NTM strains. We also grouped NTM pulmonary cases by gender and different NTM strains to identify potential differences or correlations, intending to provide valuable clues for clinical diagnosis.

# Materials and Methods

## Study Design and Participants

NTM infection is a reportable condition in China. This retrospective study included hospitalized patients with NTM pulmonary disease referred to a designated hospital for specified infectious diseases in the Fuyang district of China between January 2018 and May 2023. The laboratory utilized respiratory samples, such as sputum or bronchoalveolar lavage fluid, to culture mycobacteria and identify strains from positive cultures for the diagnosis of NTM infection. The evaluation of NTM pulmonary disease strictly adhered to the guidelines set forth by the American Thoracic Society and the Infectious Diseases Society of America in 2007. It briefly included the following criteria: (1) assessment of eight pulmonary symptoms 10; (2) identification of nodules or cavities on imaging; and (3) confirmation of at least one positive bronchial lavage fluid sample or repeated two or more positive sputum samples 10. All patient information was obtained from the hospital and laboratory information systems, including sex, age, underlying diseases, strain identification, blood routine, biochemistry, and so forth. A total of 234 patients were included in the analysis, and the flowchart of patient selection is shown in Figure 1.

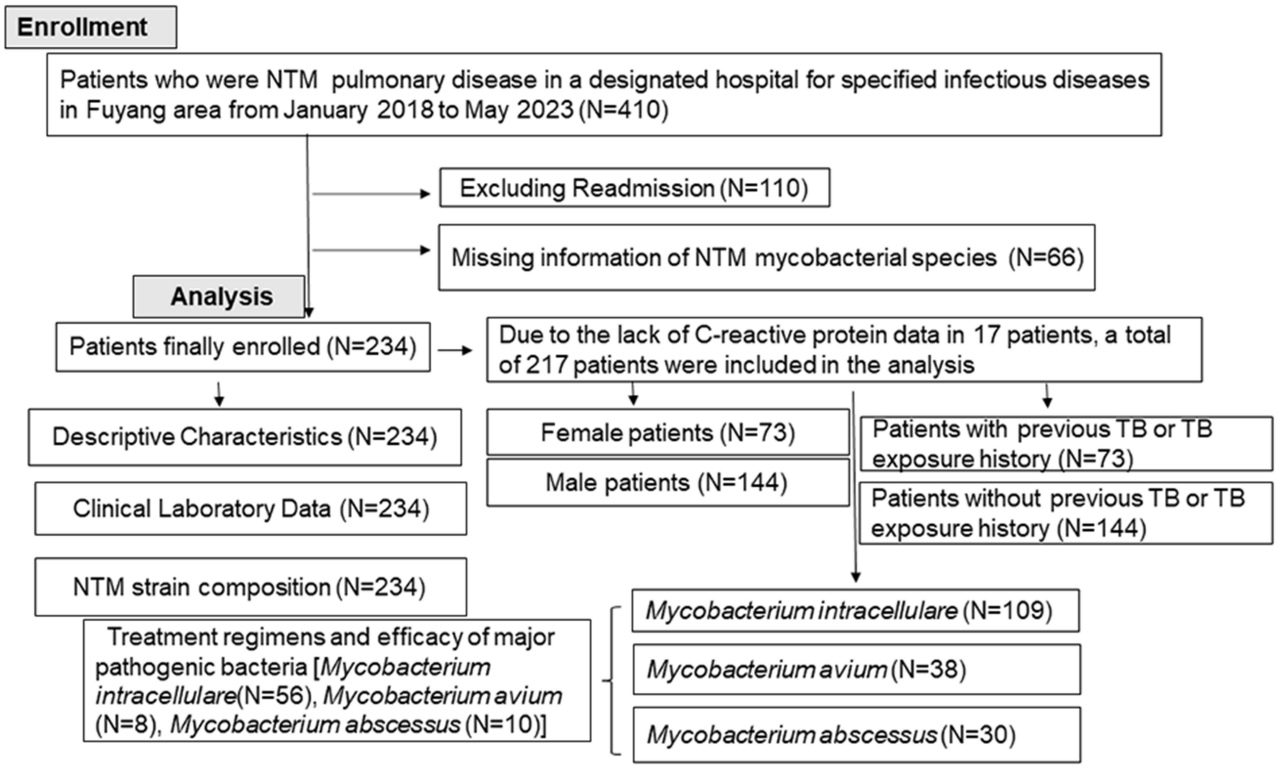


**Figure 1** Flowchart illustrating patient enrollment. NTM, Nontuberculous mycobacteria; TB, tuberculosis.

## Laboratory Analysis

The collected respiratory specimens were cultured using the MGIT 960 Mycobacteria Growth Indicator Tube system (Becton, Dickinson and Company, USA)[12] and the modified Roche method for Mtb isolation. The positive cultures were subjected to preliminary identification of the bacterial strains using P-nitrobenzoic acid/pyridine-2-carboxylic acid hydrazine culture.[13] The DNA microarray chip method (Mycobacterial Species Identification Array Kit, CapitalBio Technology Inc., Beijing, China) and MALDI-TOF mass spectrometry (Bruker Daltonics, Autoflex, USA) were used for the identification of Mtb species.[14] The platelet, lymphocyte, mononuclear, and neutrophil counts were analyzed using an XE-2100 hematology analyzer (Sysmex, Kobe, Japan). The blood biochemistry parameters such as serum albumin (ALB) and C-reactive protein were measured using the HITACHI 7600–020 automated biochemistry analyzer. The neutrophil-to-lymphocyte ratio (NLR), mononuclear-to-lymphocyte ratio (MLR), prognostic nutritional index (PNI), and platelet-to-lymphocyte ratio (PLR) were calculated, where PNI = ALB (g/L) and 5 × total lymphocyte count ($10^9$/L). The data from the first laboratory test at admission were used for all patients. All procedures were performed by specially assigned personnel and in strict accordance with the instructions for using the reagents.

## Treatment Outcome Analyses

All patient information of treatment outcome was obtained from the hospital and laboratory information systems. Treatment Effect Determination: (1) Bacteriological Negative Rate: Bacteriological testing is conducted monthly after treatment using the sputum smear and bacteria medium method. Three tests are performed each month, with visible acid-fast bacilli considered positive and no acid-fast bacilli considered negative. If sputum bacteria are negative for two consecutive months or more, it is deemed negative. The treatment is reviewed over 6 months to determine the rate of conversion to negative. (2) Imaging Efficacy Judgment: Review imaging images of chest CT scans 6 months post-treatment to evaluate lesion absorption and cavity improvement. Specific evaluation criteria include: ① Obvious Absorption: More than 1/2; ② Partial Absorption: Less than 1/2 but more than 1/3; ③ No Change: Less than 1/3 lesion absorption; ④ Deterioration: No lesion absorption, expanded lesion range, and new lesions visible. (3) Cavity Change: Based on the change in cavity size, there are four levels: ① Closed: Cavity completely disappeared; ② Reduction: Cavity diameter reduced by more than 50%; ③ No Change: Cavity diameter reduction degree is less than 50%; ④ Increase: Cavity diameter increased by more than 50%. (4) Comprehensive Efficacy: According to bacteriology, imaging criteria, and a comprehensive evaluation of efficacy, the results are divided into: ① Effective: The patient's clinical symptoms disappeared, sputum bacteria turned negative, X-ray showed significant lesion absorption, the cavity narrowed, and the condition persisted for more than 3 months; ② Invalid: Various clinical symptoms did not change or even showed an increasing trend, with continuous positive sputum bacteria.

## Statistical Analyses

Continuous measurements were expressed as mean and standard deviation (SD) if they were normally distributed, or median and interquartile ranges if they were non-normally distributed. Categorical variables were expressed as count (%). For laboratory results, we also assessed whether the measurements were outside the normal range. The Kolmogorov–Smirnov test was used for the distribution of variables. Bivariate analyses were performed and the chi-square test was used to assess qualitative variables, whereas the Yates continuity correction or Fisher's exact test was used for sample sizes less than 5. For quantitative variables, the Student *t* test or analysis of variance was performed when the distribution was close to normal; otherwise, nonparametric tests including Wilcoxon and Kruskal–Wallis were used. SPSS (version 22.0) was used for statistical analyses.

# Results

## Baseline Characteristics and Clinical Laboratory Data

The clinical records of the 234 patients with NTM pulmonary disease included in this study were reviewed. Table 1 presents baseline characteristics and clinical laboratory data of patients with NTM infection admitted to a designated hospital for specified infectious diseases in the Fuyang district of China between January 2018 and May 2023. Most

**Table 1** Baseline Characteristics and Clinical Laboratory Data of 234 Patients Admitted to a Designated Hospital for Specified Infectious Diseases in the Fuyang Area in China with NTM Pulmonary Disease in This Study

| Baseline Characteristics | Patients (n=234) |
|---|---|
| Age, years, [Mean (SD)] | 63.72 (14.35) |
| Age, Range | |
| ≤19 | 2 (0.85) |
| 20~39 | 15 (6.41) |
| 40~59 | 65 (27.78) |
| 60~79 | 136 (58.12) |
| ≥80 | 16 (6.84) |
| Sex | |
| Female | 79 (33.76) |
| Male | 155 (66.24) |
| Occupation | |
| Agricultural worker | 204 (87.18) |
| Self-employed | 13 (5.56) |
| Employee | 9 (3.85) |
| Retired | 6 (2.56) |
| Student | 1 (0.43) |
| Teacher | 1 (0.43) |
| Underlining diseases | |
| Previous TB or TB exposure history | 73 (31.20) |
| AIDS | 5 (2.14) |
| Hypertension | 32 (13.68) |
| Diabetes | 19 (8.12) |
| Bronchiectasis | 73 (31.20) |
| COPD | 50 (21.37) |
| Pulmonary aspergillosis | 12 (5.13) |
| Respiratory Failure | 21 (8.97) |
| Hospital stay, [Mean (SD)] | 12.81 (8.22) |
| Two types of NTM | |
| Yes | 29 (12.39) |
| No | 205 (87.61) |
| The coincidence between admission diagnosis and discharge diagnosis | |
| Yes | 133 (56.84) |
| No | 101 (43.16) |
| Infections caused by other associated bacterial strains | |
| Yes | 14 (5.98) |
| No | 220 (94.02) |
| Readmission | 110 (47.00) |
| Clinical laboratory data | |
| Leucocytes (× $10^9$ per L; normal range 3.50–9.50), [Mean (SD)] | 7.71 (3.89) |
| Increased | 50 (21.37) |
| Decreased | 13 (5.56) |
| Lymphocytes (× $10^9$ per L; normal range 1.10–3.20), [Mean (SD)] | 1.42 (0.60) |
| Decreased | 76 (32.48) |
| Monocytes (× $10^9$ per L; normal range 0.10–0.60), [Mean (SD)] | 0.70 (0.35) |
| Increased | 135 (57.69) |
| Neutrophils (× $10^9$ per L; normal range 1.80–6.30), [Mean (SD)] | 5.42 (3.71) |
| Increased | 61 (26.07) |

(*Continued*)

**Table 1** (Continued).

| Baseline Characteristics | Patients (n=234) |
|---|---|
| Haemoglobin (g/L; normal range 115.00–150.00), [Mean (SD)] | 110.90 (11.90) |
| Decreased | 102 (43.59) |
| Platelets (× $10^9$ per L; normal range 125.00–350.00), [Mean (SD)] | 257.52 (104.01) |
| Decreased | 209 (89.32) |
| Albumin (g/L; normal range 40.00–55.00), [Mean (SD)] | 34.11 (6.43) |
| Decreased | 194 (82.91) |
| C-reactive protein (mg/L; normal range 0.00–6.00)*, [Mean (SD)] | 7.71 (3.89) |
| Increased | 169 (77.88) |
| CD4 and T helper cells (per L; normal range 404.00–1612.00)#, [Mean (SD)] | 27.30 (246.91) |
| Decreased | 39 (70.91) |

**Notes**: Data are n (%) and mean (SD). Increased means over the upper limit of the normal range, and decreased means below the lower limit of the normal range. *Data available for 217 patients. #Data available for 55 patients.
**Abbreviations**: NTM, nontuberculous mycobacterium; SD, standard deviation;TB, tuberculosis; AIDS, Acquired Immune Deficiency Syndrome; COPD, chronic obstructive pulmonary disease.

patients were men, with a mean age of 63.72 years. Of these, 87.18% were agricultural workers; 73 (31.20%) patients had previous TB or TB exposure history and bronchiectasis. The average length of stay in the hospital was 12.81 days. Mixed NTM infection accounted for 29 (12.39%) patients. The coincidence between admission diagnosis and discharge diagnosis was 133 (56.84%) patients. A few patients had other bacterial infections. The readmission rate was as high as 110 (47.00%) patients. The leucocyte count was below the normal range (3.50–9.50 × $10^9$/L) in 13 (5.57%) patients and above the normal range (3.50–9.50 × $10^9$/L) in 50 (21.37%) patients. The lymphocyte count was below the normal range (1.10–3.20 × $10^9$/L) in 76 (32.48%) patients. The monocyte count was above the normal range (0.10–0.60 × $10^9$/L) in 135 (57.69%) patients. The neutrophil count was above the normal range in 61 (26.07%) patients. The platelet count was below the normal range (125.00–350.00 × $10^9$/L) in 209 (89.32%) patients. The ALB level was below the normal range (40.00–55.00 g/L) in 194 (82.91%) patients. Furthermore, the C-reactive protein level was tested in 217 patients, and 169 (77.88%) patients had levels above the normal range (0–6.00 mg/L). The CD4 and T helper cells were tested in 55 patients, and most had levels below the normal range (404.00–1612.00/L).

## NTM Strain Composition

Figure 2 illustrates NTM strain composition. Among the 234 patients with NTM disease, 10 types of NTM species were detected.The 234 included patients had 266 NTM strains identified at the species level, of which 132 strains (49.62%) belonged to *Mycobacterium intracellulare*, 56 (21.05%) belonged to *Mycobacterium avium*, 37 (13.91%) belonged to *Mycobacterium abscessus*, 13 (4.89%) belonged to *Mycobacterium chelonae*, 12 (4.51%) belonged to *Mycobacterium paracellular*.

## Overview and Pre-Existing Conditions in Patients with NTM Infection

Table 2 presents general information and underlying diseases of 217 patients with NTM infection. The C-reactive protein data were missing for 17 patients; therefore, only 217 patients were included in this study. The mean age of patients in both groups was 68 years. Women were susceptible to bronchiectasis ($P < 0.01$). The average lymphocyte count was higher in women than in men, but the average value was within the normal range (1.10–3.20 × $10^9$/L) ($P = 0.027$). The median of monocyte count was higher in men than in women ($P = 0.019$). The median of MLR was higher in men than in women ($P < 0.01$).

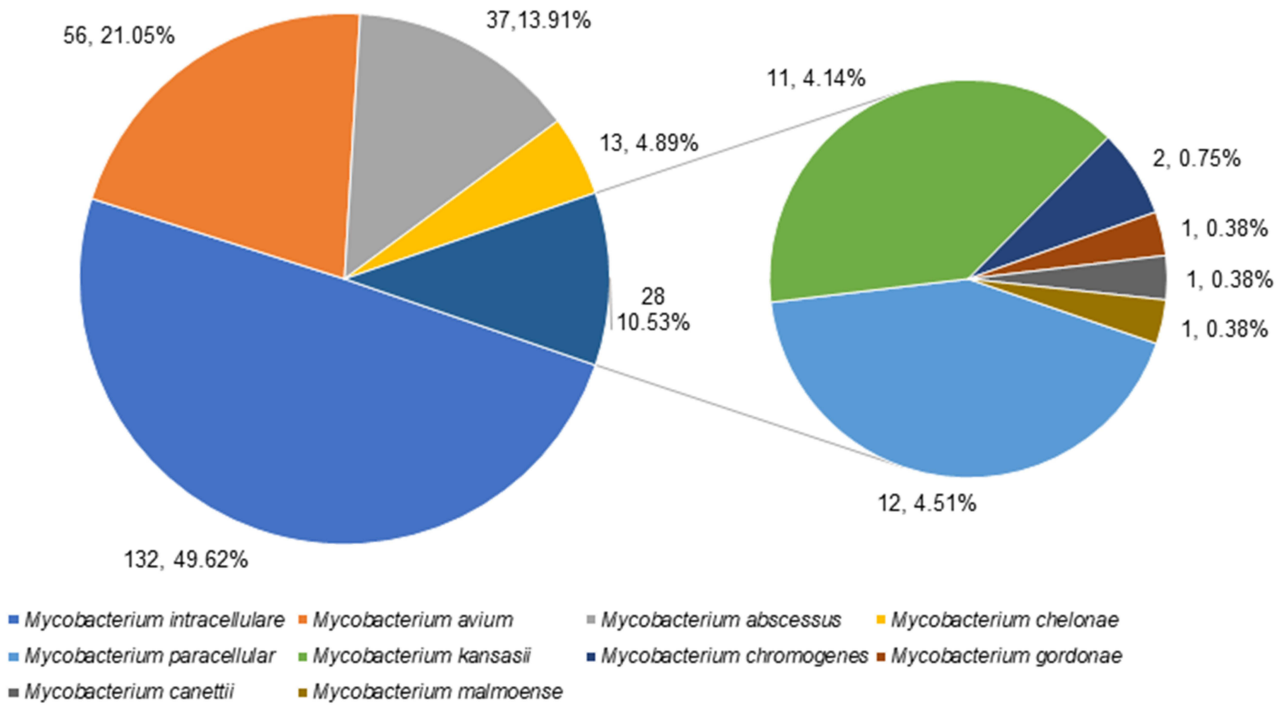


**Figure 2** NTM strain composition.

## Underlying Diseases and Clinical Laboratory Data of Patients with Different NTM Strains

Table 3 presents underlying diseases and clinical laboratory data of patients with different NTM strains. The *Mycobacterium avium* strain was mainly found in women, and the *Mycobacterium abscessus* strain in men. Both 13 *Mycobacterium avium* (34.21%) and 10 *Mycobacterium abscessus* (33.33%) strains were most common in people with previous TB or TB exposure history. Among the respiratory tract–related diseases, patients with bronchiectasis had the highest isolation rate of *Mycobacterium avium* strain (21, 55.36%). The laboratory test data of 217 patients with NTM infection were analyzed, and statistically significant differences were found in C-reactive protein levels ($P = 0.048$).

**Table 2** Overview and Pre-Existing Conditions in 217 Patients with NTM Infection

| Variable | Female (n=73) | Male (n=144) | Statistical value | *P* value |
|---|---|---|---|---|
| Age, years [mean (SD)] | 68.00 (55.50,76.00) | 68.00 (57.00,75.00) | −0.071 | 0.943 |
| Underlining diseases | | | | |
| Previous TB or TB exposure history | 26 (35.62) | 47 (32.64) | 0.192 | 0.661 |
| AIDS | 5 (6.85) | 0 (0.00) | —[a] | 0.004* |
| Hypertension | 12 (16.44) | 12 (8.33) | 3.235 | 0.072 |
| Diabetes | 6 (8.22) | 16 (11.11) | 0.445 | 0.505 |
| Bronchiectasis | 37 (50.68) | 31 (21.53) | 19.140 | < 0.001* |
| COPD | 8 (10.96) | 29 (20.14) | 2.886 | 0.089 |
| Pulmonary aspergillosis | 3 (4.11) | 9 (6.25) | 0.425 | 0.557 |
| Respiratory Failure | 7 (9.59) | 14 (9.72) | 0.001 | 0.975 |
| Hospital stay (median and IQR) | 10.00 (8.00,16.00) | 12.00 (7.00,16.75) | −0.296 | 0.767 |
| Leucocytes (× $10^9$ per L) (median and IQR) | 3.08 (4.64,7.07) | 6.775 (5.53,8.71) | −0.256 | 0.798 |
| Lymphocytes (× $10^9$ per L) [mean (SD)] | 1.53 (0.61) | 1.34 (0.58) | 2.223 | 0.027* |
| Monocytes (× $10^9$ per L) (median and IQR) | 0.57 (0.39,0.81) | 0.71 (0.50,0.90) | −2.366 | 0.019* |
| Neutrophils (× $10^9$ per L) (median and IQR) | 3.08 (4.64,7.07) | 4.54 (6.38,3.47) | −0.249 | 0.804 |
| Platelets (× $10^9$ per L) (median and IQR) | 265.23 (111.63) | 258.93 (101.02) | 0.418 | 0.676 |

(*Continued*)

**Table 2** (Continued).

| Variable | Female (n=73) | Male (n=144) | Statistical value | *P* value |
|---|---|---|---|---|
| Albumin (g/L) [mean (SD)] | 34.54 (7.10) | 33.39 (5.89) | 1.262 | 0.208 |
| Reactive protein (mg/L) (median and IQR) | 18.40 (3.25,73.05) | 40.70 (96.65,11.53) | −1.881 | 0.060 |
| NLR (median and IQR) | 111.49 (185.31,258.76) | 0.26 (0.16,0.43) | −1.554 | 0.120 |
| MLR [mean (SD)] | 0.37 (0.25,0.64) | 0.52 (0.38,0.80) | −3.667 | <0.001* |
| PLR (median and IQR) | 111.49 (185.31,258.76) | 18.80 (125.53,287.34) | −1.260 | 0.208 |
| PNI [mean (SD)] | 41.72 (9.14) | 39.81 (8.01) | 1.578 | 0.133 |

**Notes**: *was statistically significant (P value < 0.05); [a]Fisher's exact test was employed. Data are n (%).
**Abbreviations**: NTM, nontuberculous mycobacterium; SD, standard deviation; TB, tuberculosis; IQR, interquartile range; NLR, neutrophil-to-lymphocyte ratio; MLR, mononuclear-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutritional index.

**Table 3** Underlying Diseases and Clinical Laboratory Data of Patients with Different NTM Mycobacterial Strains

| Variable | *Mycobacterium intracellulare* (n=109) | *Mycobacterium avium* (n=38) | *Mycobacterium abscessus* (n=30) | Statistical value | *P* value |
|---|---|---|---|---|---|
| Sex | | | | 8.494 | 0.004* |
| Female | 35 (32.11) | 16 (42.11) | 3 (10.00)[c] | | |
| Male | 74 (67.89) | 22 (57.89) | 27 (90.00) | | |
| Age, years (median and IQR) | 71.00 (60.00,76.00) | 62.50 (54.25,76.75) | 67.00 (55.75,75.25) | 4.577 | 0.101 |
| Underlining diseases | | | | | |
| Previous TB or TB exposure history | 18 (16.50) | 13 (34.21)[a] | 10 (33.33)[b] | 8.845 | 0.029* |
| AIDS | 2 (1.83) | 0 (0.00) | 0 (0.00) | 0.705 | 0.564 |
| Hypertension | 18 (16.51) | 3 (7.89) | 0 (0.00) | 7.247 | 0.211 |
| Diabetes | 9 (8.26) | 2 (5.26) | 2 (6.67) | 0.294 | 0.821 |
| Bronchiectasis | 33 (30.28) | 21 (55.36)[a] | 6 (20.00)[c] | 12.497 | 0.004* |
| COPD | 28 (25.69) | 5 (13.16) | 4 (13.33) | 3.928 | 0.140 |
| Pulmonary aspergillosis | 5 (4.59) | 2 (5.26) | 2 (6.67) | 0.572 | 0.899 |
| Respiratory Failure | 11 (10.09) | 7 (18.42) | 1 (3.33) | 3.806 | 0.130 |
| Hospital stay (median and IQR) | 12.00 (8.00,18.00) | 11.00 (8.00,14.00) | 12.00 (6.75,17.00) | 5.616 | 0.060 |
| Leucocytes (× $10^9$ per L) [mean (SD)] | 6.94 (5.44,9.52) | 6.97 (5.61,8.72) | 6.45 (5.03,8.16) | 0.212 | 0.900 |
| Lymphocytes (× $10^9$ per L) [mean (SD)] | 1.42 (0.58) | 1.47 (0.68) | 1.29 (0.52) | 0.761 | 0.469 |
| Monocytes (× $10^9$ per L) [mean (SD)] | 0.72 (0.35) | 0.73 (0.34) | 0.70 (0.29) | 0.076 | 0.927 |
| Neutrophils (× $10^9$ per L) (median and IQR) | 4.62 (3.35,6.07) | 4.62 (3.21,6.07) | 4.10 (2.81,6.49) | 0.176 | 0.916 |
| Platelets (× $10^9$ per L) (median and IQR) | 268.83 (114.15) | 262.70 (84.97) | 243.71 (77.68) | 0.657 | 0.519 |
| Albumin (g/L) [mean (SD)] | 33.03 (6.48) | 34.35 (6.52) | 35.10 (6.98) | 1.384 | 0.253 |
| Reactive protein (mg/L) (median and IQR) | 36.80 (9.73,88.18) | 50.05 (6.60,126.28)[a] | 37.60 (13.68,95.43)[c] | 0.305 | 0.048* |
| NLR (median and IQR) | 3.45 (2.23,6.05) | 3.73 (2.32,7.27) | 3.92 (2.32,5.92) | 0.41 | 0.955 |
| MLR (median and IQR) | 0.47 (0.35,0.75) | 0.61 (0.40,0.73) | 0.60 (0.40,0.89) | 0.714 | 0.714 |
| PLR (median and IQR) | 183.15 (128.57,295.39) | 194.73 (118.14,281.54) | 185.42 (134.16,320.77) | 0.065 | 0.968 |
| PNI [mean (SD)] | 40.06 (7.73) | 40.78 (10.02) | 41.33 (7.57) | 0.317 | 0.729 |

**Notes**: [a]*P* value<0.05, Mycobacterium avium vs Mycobacterium intracellulare; [b]*P* value <0.05, Mycobacterium abscessus vs Mycobacterium intracellulare; [c]*P* value <0.05, Mycobacterium avium vs Mycobacterium abscessus.Sex and Underlining diseases; Data are n (%). *was statistically significant (*P* value < 0.05).
**Abbreviations**: NTM, nontuberculous mycobacterium; SD, standard deviation;TB, tuberculosis; AIDS, Acquired Immune Deficiency Syndrome; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; NLR, neutrophil-to-lymphocyte ratio; MLR, mononuclear-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutritional index.

## Clinical Laboratory Data of Patients with NTM Pulmonary Disease Combined with Other Respiratory Diseases

Table 4 presents clinical laboratory data of patients with NTM pulmonary disease combined with previous TB or TB exposure history. The mean age of patients was higher in those with TB or TB exposure history than in those without TB history ($P = 0.001$). NTM pulmonary disease combined with previous TB or TB exposure history were susceptible to bronchiectasis and COPD ($P < 0.05$).

**Table 4** Clinical Laboratory Data of Patients with NTM Pulmonary Disease Combined with Other Respiratory Diseases

| Variable | Patients with Previous TB or TB Exposure History (n=73) | Patients without Previous TB or TB Exposure History (n=144) | Statistical value | *P* value |
|---|---|---|---|---|
| Age, years [mean (SD)] | 66.81 (15.09) | 53.73 (15.92) | −3.600 | 0.001* |
| Bronchiectasis | 33 (45.20) | 25 (17.40) | 19.178 | < 0.001* |
| COPD | 18 (24.70) | 19 (13.20) | 4.501 | 0.034* |
| Pulmonary aspergillosis | 7 (9.60) | 5 (3.50) | 3.469 | 0.063 |
| Respiratory Failure | 11 (5.61) | 10 (18.42) | 3.658 | 0.056 |
| Hospital stay [mean (SD)] | 11.64 (5.61) | 13.43 (6.41) | −1.255 | 0.214 |
| Leucocytes (× $10^9$ per L) [mean (SD)] | 7.01 (2.88) | 7.63 (3.28) | −0.832 | 0.408 |
| Lymphocytes (× $10^9$ per L) [mean (SD)] | 1.47 (0.56) | 1.41 (0.58) | −0.406 | 0.686 |
| Monocytes (× $10^9$ per L) [mean (SD)] | 0.64 (0.29) | 0.73 (0.310) | −1.253 | 0.218 |
| Neutrophils (× $10^9$ per L) [mean (SD)] | 5.26 (3.10) | 4.75 (2.82) | −0.712 | 0.479 |
| Platelets (× $10^9$ per L) [mean (SD)] | 244.73 (81.80) | 272.28 (98.81) | −1.310 | 0.195 |
| Albumin (g/L) [mean (SD)] | 32.69 (7.46) | 36.97 (9.33) | 2.165 | 0.034* |
| C-reactive protein (mg/L) [mean (SD)] | 55.98 (62.04) | 72.81 (68.30) | 0.604 | 0.311 |
| NLR (median and IQR) | 2.68 (1.75,4.81) | 3.34 (2.06,6.13) | −0.730 | 0.235 |
| MLR (median and IQR) | 0.5 (0.35,0.74) | 0.39 (0.27,0.63) | −1.478 | 0.071 |
| PLR (median and IQR) | 156.71 (117.64,224.27) | 179.74 (130.92,347.60) | −1.074 | 0.143 |
| PNI (median and IQR) | 39.30 (32.78,46.78) | 46.15 (37.40,50.70) | −2.023 | 0.021* |

**Note**: *was statistically significant (*P* value < 0.05).
**Abbreviations**: COPD, chronic obstructive pulmonary disease; NTM, nontuberculous mycobacterium; SD, standard deviation;TB, tuberculosis; IQR, interquartile range; NLR, neutrophil-to-lymphocyte ratio; MLR, mononuclear-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutritional index.

The serum ALB levels were lower in patients with TB or TB exposure history than in those without TB history ($P = 0.034$). The PNI was lower in patients with TB or TB exposure history than in those without TB history ($P = 0.021$).

## Treatment Outcome Analyses of Patients with Different NTM Strains

Table 5 presents Treatment outcome analyses of patients with different NTM strains. In the hospital medical records system, for 109 patients with pulmonary Mycobacterium intracellulare disease, only 56 patients had a complete treatment record of 6 months or more. In these records, 14 patients had achieved effective results. For the treatment of 38 patients with pulmonary Mycobacterium avium disease, only 8 patients had a complete treatment record of 6 months or more. In these records, three patients had achieved effective results. For patients with pulmonary Mycobacterium abscessus disease, in 30 cases, 10 patients had a complete treatment record of 6 months or more. Based on these records, we can confirm that five of these patients had achieved effective results. NTM antibiotics mainly include: Rifampicin (RIF), Ethambutol (EMB), Clarithromycin (CLR), Levofloxacin (LEV), Moxifloxacin (MXF), Azithromycin (AZM), Amikacin (AMK), Linezolid (LZD), Cefoxitin (FOX), Imipenem-cilastatin (IMI). The antimicrobial treatment regimen for pulmonary Mycobacterium intracellulare disease primarily consisted of combinations such as RIF and EMB and CLR and LEV, RIF and EMB and CLR and MXF, RIF and EMB and LEV and AZM, RIF and EMB and CLR and AMK, RIF and EMB and MXF and AZM, RIF and EMB and LEV and DA, RIF and EMB and AMK and AZM, RIF and CLR and MXF and AMK. The antimicrobial treatment regimen for pulmonary Mycobacterium avium disease mainly included RIF and EMB and CLR and LEV, RIF and EMB and CLR and AMK. The antimicrobial treatment regimen for pulmonary Mycobacterium abscessus disease consisted mainly include RIF and EMB and CLR and LEV, RIF and AZM and AMK and FOX. In this study, 74 patients were treated with personalized chemotherapy, with 18 overall regimens. The response rates were 25% (Mycobacterium intracellulare), 37.50% (Mycobacterium avium), and 50% (Mycobacterium abscessus). The overall treatment effect was not ideal, at 29.73%.

**Table 5** Treatment Outcome Analyses of Patients with Different NTM Strains

| Treatment Regimens | Mycobacterium intracellulare (n=56) | | Mycobacterium avium (n=8) | | Mycobacterium abscessus (n=10) | |
|---|---|---|---|---|---|---|
| | Treated Patients | Effective Treatment | Treated Patients | Effective Treatment | Treated Patients | Effective Treatment |
| RIF and EMB and CLR and LEVs | 18 (32.14) | 4 (22.22) | 5 (62.50) | 3 (60.00) | 2 (20.00) | — |
| RIF and EMB and CLR and MXF | 9 (16.07) | 3 (33.33) | — | — | — | — |
| RIF and EMB and LEV and AZM | 9 (16.07) | 3 (33.33) | — | — | 1 (10.00) | — |
| RIF and EMB and CLR and AMK | 4 (7.14) | 1 (25.00) | 2 (25.00) | — | — | — |
| RIF and EMB and MXF and AZM | 4 (7.14) | — | — | — | — | — |
| RIF and EMB and LEV and DA | 3 (5.36) | — | — | — | — | — |
| RIF and EMB and AMK and AZM | 3 (5.36) | 1 (33.33) | 1 (12.50) | — | — | — |
| RIF and CLR and MXF and AMK | 2 (3.57) | 1 (50.00) | — | — | — | — |
| RIF and EMB and LEV and LZD | 1 (1.79) | — | — | — | — | — |
| EMB and AZM and MXF and AMK | 1 (1.79) | 1(100.00) | — | — | — | — |
| EMB and AZM and LEV and AMK | 1 (1.79) | — | — | — | — | — |
| RIF and LZD and CLR and AMK | 1 (1.79) | — | — | — | — | — |
| AMK and AZM and FOX and IMI | — | — | — | — | 1 (10.00) | 1 (100.00) |
| RIF and AMK and AZM and MXF | — | — | — | — | 1 (10.00) | 1 (100.00) |
| RIF and AMK and AZM and FOX | — | — | — | — | 1 (10.00) | 1 (100.00) |
| LZD and CLR and MXF and AMK | — | — | — | — | 1 (10.00) | — |
| MXF and AZM and LZD and AMK | — | — | — | — | 1 (10.00) | 1 (100.00) |
| RIF and AZM and AMK and FOX | — | — | — | — | 2 (20.00) | 1 (50.00) |

**Notes**: Data are n (%). —, without treatment outcome.
**Abbreviations**: RIF, Rifampicin; EMB, Ethambutol; CLR, Clarithromycin; LEV, Levofloxacin; MXF, Moxifloxacin; AZM, Azithromycin; AMK, Amikacin; LZD, Linezolid; FOX, Cefoxitin; IMI, imipenem-cilastatin.

## Discussion

The colonization and incidence rate of NTM pulmonary disease vary globally, and the global burden of NTM pulmonary disease is increasing.[15] Fuyang is located in the northwest of Anhui Province and the south of Huaibei Plain. It is the most populous city in Anhui Province, China. Its transportation is developed, and its population density is relatively large, with a relatively large proportion of the rural population. This was an extended descriptive study on the epidemiology and clinical characteristics of patients with NTM pulmonary disease, which included data on 234 patients from the Fuyang district of China between January 2018 and May 2023.

A few studies demonstrated that the incidence of NTM infection varied among different age groups and between sexes.[16,17] In this study, the incidence rate differed among different age groups, and the highest incidence rate was 58.12% between the age group of 60 and 70 years. Most patients were men, with a mean age of 63.72 years. This suggested that NTM pulmonary incidence was more common in men in northwest Anhui, China, which was in contrast to previous 16 older menopausal women. The reason should be related to the geographical[18] and racial[19] differences in the distribution of NTM. Agricultural workers accounted for 87.18% of the patients included. These workers exhibited characteristics such as strong mobility, significant changes in the living environment and lifestyle, heavy workloads, and overwork, making them more susceptible to NTM infections. Moreover, 73 (31.20%) patients had previous TB or TB history and bronchiectasis. NTM pulmonary disease is closely related to bronchiectasis; hence, NTM infection is common in patients with bronchiectasis.[20] However, it is still unclear whether NTM is the cause of bronchiectasis.[21] Distinguishing between NTM and Mtb based on cavity characteristics is difficult because of frequent simultaneous infection of NTM and Mtb. However, multiple cavities indicate severe damage to the lung tissue structure and susceptibility to NTM infection.

The platelet count and hemoglobin level were below the normal range (125.00–350.00 × $10^9$/L and 115.00–150.00 g/L) in many patients. The ALB level was below the normal range (40.00–55.00 g/L) in many patients. Hemoglobin and ALB levels reflect the nutritional status of patients. The findings indicated that patients with NTM infection had poor nutritional

status, emphasizing the importance of nutritional support as a crucial aspect of treatment. Of the 217 patients tested for the C-reactive protein level, most had levels above the normal range (0–6.00 mg/L). The C-reactive protein level was found to be higher in *Mycobacterium avium* infection than in *Mycobacterium intracellulare* versus *Mycobacterium abscessus*. The main species of infection differed between men and women.[16] The underlying disease and clinical laboratory findings for the top three NTM strains in the region differed: Women were found to be more affected by *Mycobacterium avium* infection, and men by *Mycobacterium abscessus* infection.

Among the 234 patients included in this study, 266 NTM strains were identified. Mixed NTM infection accounted for 29 (12.39%) patients. The mixed infection pattern of different NTM strains should be of clinical concern because NTM is highly resistant to first-line anti-TB drugs, and the drug susceptibility results of different strains are quite different. Among the 234 patients with NTM disease, 10 types of NTM species were detected. Multicenter studies in China showed that the main NTM strain was *Mycobacterium intracellulare* in the east, *Mycobacterium abscessus* in the south,[19] and *M. avium* in the north,[19,22] but the data regarding the west are lacking. These data were consistent with those reported in previous studies that *Mycobacterium intracellulare* was the most common NTM strain in China.[11] *Mycobacterium intracellulare* and *Mycobacterium avium* strains were predominant in this area.

The study hospital served as a designated infectious disease hospital. Most of the patients with TB in Fuyang were treated in this hospital. Mandatory registration of NTM is conducted in Fuyang; therefore, a comparison of data of TB/NTM co-infections with NTM figures is possible. TB is a chronic disease that occurs due to poor socioeconomic conditions, and factors such as malnutrition and low immunity increase the incidence of NTM and Mtb co-infection.[10,23,24] In this study, the mean age of patients was higher in those with TB or TB exposure history than in those without TB history ($P = 0.001$). Other studies on the prevalence of NTM isolation found that indeed increasing age in the incidence of NTM pulmonary incidence was associated with an increased risk of NTM infection.[25] NTM pulmonary disease combined with previous TB or TB exposure history were susceptible to bronchiectasis and COPD ($P < 0.05$). This could be associated with the lung damage and inflammatory response triggered by tuberculosis. The prolonged effects on lung tissue result in heightened lung sensitivity, making individuals more prone to developing other chronic pulmonary disorders. The serum ALB level was lower in patients with TB or TB exposure history than in those without TB history ($P = 0.034$). The PNI was lower in patients with TB or TB exposure history than in those without TB history ($P = 0.021$). The results indicated that patients with NTM with TB had a worse nutritional status and might need nutritional support.

The NTM pulmonary disease drug resistance problem is serious, and the personalized chemotherapy regimen is used in clinical practice. A review of positive NTM reports from 2006 to 2017 detected 183 patients, and only 22.4% were treated, with unsatisfactory results and 6 deaths.[26] NTM lung disease drug resistance is complex and difficult to treat.[27] In this study, 74 patients, with 18 options, had a response rate of 29.73%. Suggesting that the anti-NTM drugs have a limited effect. Perhaps because this study is a retrospective study of hospital system, the number of cases with complete treatment plan was small and the observation time with treatment was short. There are numerous reasons for the poor clinical treatment effect of patients with NTM lung disease, The main reasons include: (1) many adverse drug reactions: the combination of multiple drugs in the treatment of NTM lung disease, In particular, the combination of rifampin and fluoroquinolones, Severe drug toxicity and side effects, Easy to cause a variety of adverse reactions, Related adverse effects include liver function damage, gastrointestinal reactions, These adverse effects have prevented some patients from adhering to treatment, Unable to follow the principles of treatment recommended by experts; (2) a relatively slow disease progression in patients with NTM pulmonary disease, While the current lack of specific treatment options, The clinical efficacy of the treatment plan formulated based on the actual situation of the patient is not exact, Many patients have low confidence in their treatment, Inability to adhere to long-term medication, Non-compliant medication problems, May lead to treatment interruption or not following expert opinion issues, Affect the treatment effect. NTM pulmonary disease treatment is difficult, need a long time continuous treatment, at least a year, otherwise, repeated, as the disease delay, serious damage to the lung parenchyma, increase the difficulty of clinical treatment and control, this study only 6 months treatment effect, extend the treatment time may get better treatment effect.

## Conclusion

The main pathogens causing NTM pulmonary disease in the Fuyang area from 2018 to 2023 were *Mycobacterium intracellulare* and *Mycobacterium avium*. Patients were mostly complicated with TB, bronchiectasis, and COPD, and laboratory tests showed low hemoglobin and ALB levels. However, the samples selected in this study were only from hospitalized patients, and the sample size was small. It may be more reasonable to evaluate the treatment effect and immune state by using a prospective study method. Future studies should focus on comprehensively collecting patient data and conducting more specialized research.

## Data Sharing Statement

The datasets created and examined in the present study are available from the corresponding author upon reasonable request.

## Ethical Approval

The research adhered to the principles outlined in the Declaration of Helsinki and received approval from the Ethics Committee at the Second People's Hospital of Fuyang City, identified by the approval code: 2018fyey31. Given the study's retrospective approach, obtaining informed consent was not necessary, a decision that was ratified by the Ethics Committee of the Second People's Hospital of Fuyang City. All patient data were managed with strict adherence to ethical guidelines, guaranteeing both confidentiality and anonymity. No personal identifiers were utilized during the analysis or when presenting the study findings.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Disclosure

The authors declare no conflicts of interest in this work.

## References


1. Cowman S, van Ingen J, Griffith DE, et al. Non-tuberculous mycobacterial pulmonary disease. *Eur Respir J*. 2019;54(1):1900250. doi:10.1183/13993003.00250-2019
2. Daley CL, Iaccarino JM, Lange C, et al. Treatment of nontuberculous mycobacterial pulmonary disease: an official ATS/ERS/ESCMID/IDSA clinical practice guideline. *Eur Respir J*. 2020;56(1):2000535. doi:10.1183/13993003.00535-20203
3. Dean SG, Ricotta EE, Fintzi J, et al. Mycobacterial testing trends, United States, 2009-20151. *Emerg Infect Dis*. 2020;26(9):2243–2246. doi:10.3201/eid2609.200749
4. Marras TK, Campitelli MA, Kwong JC, et al. Risk of nontuberculous mycobacterial pulmonary disease with obstructive lung disease. *Eur Respir J*. 2016;48(3):928–931. doi:10.1183/13993003.00033-2016
5. Shahraki AH, Heidarieh P, Bostanabad SZ, et al. "Multidrug-resistant tuberculosis" may be nontuberculous mycobacteria. *Eur J Intern Med*. 2015;26(4):279–284. doi:10.1016/j.ejim.2015.03.001
6. Philley JV, Griffith DE. Medical management of pulmonary nontuberculous mycobacterial disease. *Thorac Surg Clin*. 2019;29(1):65–76. doi:10.1016/j.thorsurg.2018.09.001
7. Liu H, Zhang T, Wang Y, et al. Clinical features of patients presenting with fever of unknown origin caused by non-tuberculous mycobacterium infection. *J Infect Dev Ctries*. 2023;17(7):1014–1021. doi:10.3855/jidc.17610
8. Lopes M, Batista M, Garcia T, et al. Non-tuberculous mycobacteria: clinical and laboratory characterisation (2009 and 2019). *Epidemiol Infect*. 2022;151(e8). doi:10.1017/S0950268822000899
9. Bi S, Xu KJ, Ji ZK, et al. Sentinel site surveillance of nontuberculous mycobacteria pulmonary diseases in Zhejiang, China, 2011–2013. *Braz J Infect Dis*. 2015;19(6):670–671. doi:10.1016/j.bjid.2015.08.002
10. Hu C, Huang L, Cai M, et al. Characterization of nontuberculous mycobacterial pulmonary disease in Nanjing district of China. *BMC Infect Dis*. 2019;19(1):764. doi:10.1186/s12879-019-4412-6
11. Zhang Z, Pang Y, Wang Y, et al. Differences in risk factors and drug susceptibility between mycobacterium avium and mycobacterium intracellulare lung diseases in China. *Int J Antimicrob Agents*. 2015;45(5):491–495. doi:10.1016/j.ijantimicag.2015.01.012
12. Zhao J, Pu D, Zhang Y, et al. Comparison of performances of genexpert MTB/RIF, Bactec MGIT 960, and Bactec Myco/F systems in detecting mycobacterium tuberculosis in biopsy tissues: a retrospective study. *Microbiol Spectr*. 2023;11(3):e0141422. doi:10.1128/spectrum.01414-22

13. Chen S, Wang F, Xue Y, et al. Doubled nontuberculous mycobacteria isolation as a consequence of changes in the diagnosis algorithm. *Infect Drug Resist*. 2022;15:3347–3355. doi:10.2147/IDR.S368671
14. Huang TS, Lee CC, Tu HZ, et al. Rapid identification of mycobacteria from positive MGIT broths of primary cultures by MALDI-TOF mass spectrometry. *PLoS One*. 2018;13(2):e0192291. doi:10.1371/journal.pone.0192291
15. Kim BG, Kang N, Kim SY, et al. The lung microbiota in nontuberculous mycobacterial pulmonary disease. *PLoS One*. 2023;18(5):e0285143. doi:10.1371/journal.pone.0285143
16. Adjemian J, Frankland TB, Daida YG, et al. Epidemiology of nontuberculous mycobacterial lung disease and tuberculosis, Hawaii, USA. *Emerg Infect Dis*. 2017;23(3):439–447. doi:10.3201/eid2303.161827
17. Wang J, Chen Z, Xu Y, et al. Screening and drug resistance analysis of non-tuberculous mycobacteria in patients with suspected pulmonary tuberculosis on the Hainan Island, China. *Infect Drug Resist*. 2023;16:463–476. doi:10.2147/IDR.S396050
18. Kartalija M, Ovrutsky AR, Bryan CL, et al. Patients with nontuberculous mycobacterial lung disease exhibit unique body and immune phenotypes. *Am J Respir Crit Care Med*. 2013;187(2):197–205. doi:10.1164/rccm.201206-1035OC
19. Li YM, Tong XL, Xu HT, et al. Prevalence and antimicrobial susceptibility of mycobacterium abscessus in a general hospital, China. *Biomed Environ Sci*. 2016;29(2):85–90. doi:10.3967/bes2016.009
20. Schildknecht K, Winthrop KL, Prevots DR, et al. Nontuberculous mycobacterial pulmonary disease incidence among elderly patients with bronchiectasis. *Eur Respir J*. 2022;59(6):2200018. doi:10.1183/13993003.00018-2022
21. Mirsaeidi M, Hadid W, Ericsoussi B, et al. Nontuberculous mycobacterial disease is common in patients with noncystic fibrosis bronchiectasis. *Int J Infect Dis*. 2013;17(11):e1000–e1004. doi:10.1016/j.ijid.2013.03.018
22. Huang JJ, Tong XL, Xu HT, et al. Prevalence of nontuberculous mycobacteria in a tertiary hospital in Beijing, China, January 2013 to December 2018. *BMC Microbiol*. 2020;20(1):158. doi:10.1186/s12866-020-01840-5
23. Karamat A, Ambreen A, Ishtiaq A, et al. Isolation of nontuberculous mycobacteria among tuberculosis patients, a study from a tertiary care hospital in Lahore, Pakistan. *BMC Infect Dis*. 2021;21(1):381. doi:10.1186/s12879-021-06086-8
24. Meghji J, Lesosky M, Joekes E, et al. Patient outcomes associated with posttuberculosis lung damage in Malawi: a prospective cohort study. *Thorax*. 2020;75(3):269–278. doi:10.1136/thoraxjnl-2019-213808
25. Máiz L, Girón R, Olveira C, et al. Prevalence and factors associated with nontuberculous mycobacteria in noncystic fibrosis bronchiectasis: a multicenter observational study. *BMC Infect Dis*. 2016;16(1):437. doi:10.1186/s12879-016-1774-x
26. Almutairi T, Almohaya AM, Alqahtani A, et al. Clinical characteristics and imaging features of patients with nontuberculous mycobacteria in a tertiary care center. *J Clin Tuberc Other Mycobact Dis*. 2021;26:100294. doi:10.1016/j.jctube.2021.100294
27. Pfaeffle HOI, Alameer RM, Marshall MH, et al. Clofazimine for treatment of multidrug-resistant non-tuberculous mycobacteria. *Pulm Pharmacol Ther*. 2021;70:102058. doi:10.1016/j.pupt.2021.102058