# FACTORS ASSOCIATED WITH NONTUBERCULOUS MYCOBACTERIUM PULMONARY INFECTIONS AMONG PATIENTS WITH POSITIVE ACID-FAST BACILLI STAINED SPUTUM IN KHON KAEN, THAILAND

Pongsakorn Kampan[1], Wipa Reechaipichitkul[1] and Prajaub Chaimanee[2]

[1]Division of Pulmonary Unit, Department of Medicine, Faculty of Medicine, Khon Kaen University; [2]Clinical Laboratory Section, Srinagarind Hospital, Khon Kaen University, Khon Kaen, Thailand

**Abstract:** Patients with sputum samples positive for acid-fast bacilli (AFB) are sometimes treated for mycobacterium tuberculosis (TB) infection but some have nontuberculous mycobacterium (NTM) infection which may result in treatment failure and delayed appropriate treatment. In this study we aimed to assess factors significantly associated with NTM pulmonary infection in order to guide initial treatment decisions for patients with AFB in their sputum. Study subjects were patients who presented to Srinagarind Hospital, Khon Kaen, Thailand with a positive sputum sample for AFB during January 2012 - March 2018. This study was retrospective review of study subjected charts. Subjects were divided into those confirmed to have NTM pulmonary infection (cases) and those confirmed to have pulmonary TB (controls); both culture proven. Chest radiography reports were also reviewed for each subject. We used logistic stepwise regression analysis to determine if factors were significantly NTM pulmonary infection or not. A total of 20 cases and 60 controls were included in the study. The median age of cases was 61 years (quartile (Q)1: 58.5, Q3: 72.5) and the median age of controls was 49.5 years (Q1: 31, Q3: 62.5) ($p < 0.01$). Sixty-five percent of cases and 32% of controls were female ($p < 0.01$). The common symptoms in cases were cough ($n$=20, 100%), hemoptysis ($n$=9, 45%) and weight loss ($n$=9, 45%). The common symptoms in controls were cough ($n$=57, 95%), weight loss ($n$=51, 85%), and fever ($n$=41, 68%); 18.3% of controls had hemoptysis. The most common underlying disease among cases was bronchiectasis (35%) and among controls was diabetes mellitus (22%). The common chest radiograph findings among cases were bronchiectasis ($n$= 16, 80%), reticular infiltrations ($n$=9, 45%), reticulonodular lesions ($n$=7, 35%) and atelectasis ($n$=7, 35%). The common chest radiograph findings among controls were a cavitary lesion ($n$=23, 38.3%) and patchy infiltrations ($n$=36, 60%). Factors significantly associated with cases were age >50 years ($p$=0.02), female sex ($p$<0.01), hemoptysis ($p$=0.01), bronchiectasis on chest radiograph ($p$<0.01) and no cavitary lesions on chest radiograph ($p$=0.04). These five independent predictors gave a clinical prediction model for pulmonary NTM infections with area under the receiver operating characteristic curve (AUC ROC) of 0.96 (95%CI: 0.92-0.99). Future studies are needed to determine if these can be applied clinically at the study institution.

**Keywords:** NTM pulmonary infection, sputum AFB positive smear associated factors.

Correspondence: Dr Wipa Reechaipichitkul, Division of Pulmonary Unit, Department of Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen 40002, Thailand.
Tel: +66 (0) 43 363664; Fax: +66 (0) 43 203767
E-mail: wipree@yahoo.com

## INTRODUCTION

Nontuberculous mycobacteria (NTM) are ubiquitous in environment and can cause a variety of diseases in humans, including chronic debilitating pulmonary infection (Kee and Suh, 2017). An increasing prevalence of pulmonary NTM infections have been documented over the past few decades possibly owing to an increased awareness among health care providers, a changing environment and advances in diagnostic methods, in particular, molecular identification technics (Gerogianni *et al*, 2008; van Ingen *et al*, 2009; Thomson, 2010; Adjemian *et al*, 2012; Kee and Suh, 2017). The prevalence of NTM infections varies by country, perhaps due to differences in geographic distribution of the causative organisms, various clinically important definitions of pulmonary disease and diverted epidemiologic methods in studies pertaining to disease prevalence (Gerogianni *et al*, 2008; van Ingenet *et al*, 2009; Thomson, 2010; Adjemian *et al*, 2012; Kee and Suh, 2017). Finding NTM in respiratory specimens, may mean either colonization or a true infections, making estimates of NTM pulmonary infection prevalence difficult to determine (Winthrop *et al*, 2010).

NTM pulmonary infections may be clinically and radiographically indistinguishable from pulmonary tuberculosis (TB). Patients with symptoms and chest X-ray findings typical for these two diseases, who have a positive sputum smear for acid-fast bacilli (AFB) may receive empiric treatment for pulmonary TB. This is considered standard care following World Health Organization (WHO) recommendations in countries unable to culture *Mycobacterium tuberculosis* complex where eradication of TB is the gold (WHO, 2010). This practice will result in a delay in treatment of NTM pulmonary infection.

Differentiating pulmonary NTM from pulmonary TB using clinical and radiographic characteristics could avoid delayed treatment of NTM. Previous studies in other populations attempting to find these differentiating factors have been performed (Al Jarad *et al*, 1996; Koh *et al*, 2006; Kendall *et al*, 2011; Thanachartwet *et al*, 2014; Kone *et al*, 2018). However, none of those studies strictly used American Thoracic Society/Infectious Disease Society of America (ATS/IDSA) 2007 criteria for definite NTM pulmonary infection (Griffith *et al*, 2007) in their studies.

In this study, we aimed to determine clinical and radiological features associated with NTM pulmonary infection in order to inform future studies using these factors in a clinical scenario among patients with acid-fast bacilli (AFB) positive sputum samples.

## MATERIALS AND METHODS

**Study participants and data collection**

We retrospectively conducted this case-control study at Srinagarind Hospital, Khon Kaen, Thailand during January 2012 - March 2018. Study subjects were chosen from those aged ≥ 15 years with a positive AFB smear. Cases were defined as those subjects meeting ATS/IDSA 2007 criteria (Griffith e*t al*, 2007) for NTM pulmonary infection. These criteria were: 1) Definite NTM pulmonary infection - pulmonary symptoms, an abnormal chest radiograph or high resolution computed tomography (HRCT) scan of the chest, at least 2 sputum cultures positive for NTM or at least 1 bronchoalveolar lavage fluid culture positive for NTM, and exclusion of other diagnoses; 2) Probable NTM pulmonary infection - pulmonary symptoms and an abnormal chest radiograph or HRCT with one sputum culture positive for NTM and a clinical response to treatment after specific NTM treatment (Griffith *et al*, 2007). Controls consisted of pulmonary TB cases diagnosed by a culture positive for *Mycobacterium tuberculosis*. Patients with extrapulmonary or disseminated disease were excluded from the study. Study subjects were randomly selected by computer from all subjects meeting inclusion criteria. The minimum number of study subjects required for cases and controls were calculated using the following formula (Charan and Biswas, 2013):

$$n_{case} = \left[ \frac{z_{1-\frac{\alpha}{2}} \sqrt{\bar{p}\bar{q}\left(1+\frac{1}{r}\right)} + z_{1-\beta} \sqrt{p_1 q_1 + \frac{p_2 q_2}{r}}}{\Delta} \right]^2$$

Previous studies (Koh *et al*, 2006; Theerawit *et al*, 2010; Kendall *et al*, 2011) reported female sex was more common in NTM pulmonary infection than pulmonary TB, we used $p_1$ 70%and $p_2$ 30% based on our data at Srinagarind Hospital ($\Delta = p_1 - p_2$). The ratio of cases and controls is 1:3 (r=3). For 80% power ($Z\beta$=0.84), 0.05 significance level ($Z\alpha$=1.96), the minimal numbers of cases and controls were determined to be 19 and 57, respectively.

Data obtained from subject medical records were: demographic data, medical history; including chief complain, history of present illness, duration of symptoms, history of comorbidities, date of diagnosis, results of AFB stains and sputum / respiratory specimen cultures. Microbiological data were verified with the microbiology laboratory unit. Chest radiography was reviewed by a radiologist or the results obtained from the radiology report.

**Statistical analysis**

Means, standard deviations (SD), medians and interquartile ranges (IQR) were calculated for continuous data; numbers and percentages were used to describe categorical data. The Fisher's exact test, Pearson's $\chi^2$ test, unpaired *t*-test, and Mann-Whitney *U* test were used to analyze differences between groups depending on the data. Stepwise logistic regression analysis was used to determine if factors were significantly associated with NTM pulmonary infection or pulmonary TB, and was reported as crude or adjusted odd ratios (ORs) and 95% confidence intervals (CI). A $p$-value <0.05 was considered statistically significant. The Pearson correlation was used to control for collinearity between independent variables; if a correlation had a rho >0.9, the variable was not used in the multiple variable analysis. The Hosmer-Lemeshow goodness-of-fit statistic was used to assess the model fit. The log likelihood ratio was used to determine predictability of the logistic model. The diagnostic yield of the model was assessed by an area under the receiver operating characteristic curve (AUC). Sensitivity, specificity, positive predictive value and negative predictive value were determined from the selected probability cut-off. All statistical analysis was performed using STATA, version 14.0 (StataCorp, College Station, TX).

**Ethical considerations**

This study was approved by the Human Research Ethics Committee, Khon Kaen University (approval no. HE611114).

## RESULTS

A total of 20 cases (14 definite and 6 probable) and 60 controls were included in the study (Table 1). The overall median age of all the study subjects was 56 years [quartile (Q)1: 34.5 years, Q3 67.5 years]; 40% (*n*=32) females. The median age of cases was 61 years (Q1: 58.5, Q3: 72.5) and of controls was 49.5 years (Q1: 31.0, Q3: 62.5) ($p$<0.01). Sixty-five percent of cases (*n*=13) and 31.7% of controls (*n*=19) were females ($p$<0.01). The most common symptoms among cases were cough (100%), hemoptysis (45%) and weight loss (45%). The most common symptoms among controls were cough (95%), weight loss (85%) and fever (68.3%). The symptoms that differed significantly were: fever was significantly ($p$<0.01) more common among controls, night sweats were more common among controls ($p$=0.03), hemoptysis was more common among cases ($p$=0.02) and weight loss was significantly more common among controls ($p$<0.01). Cases were significantly more likely to be female, non-smokers, afebrile, no night sweats, no dyspnea, no anorexia and no weight loss (Table 1). Pathogens seen among cases were: *M. abscessus* (*n*=12, 60%), *M. intracellulare* (*n*=5, 25%), *M. avium complex* (MAC) (*n*=2, 10%) and *M. fortuitum* (*n*=1, 5%).

Eighty-five percent of cases had comorbidities while 58.3% of controls had

Table1
Demographic and clinical characteristics of study subjects.

| Characteristics | Cases (Pulmonary NTM) (*n* = 20) | Controls (Pulmonary TB) (*n* = 60) | *p*-value |
|---|---|---|---|
| Median age in years (Q1, Q3) | 61 (58.5, 72.5) | 49.5 (31, 62.5) | **< 0.01** |
| Female sex (*n*, %) | 13 (65) | 19 (31.7) | **< 0.01** |
| Median weight in kg (IQR) | 47.6 (9.6) | 52.95 (13.7) | **0.02** |
| Median symptom duration in months (range) | 2.5 (0.07-96) | 1.75 (0.07-24) | 0.32 |
| Symptoms, *n* (%) | | | |
| Fever | 4 (20) | 41 (68.3) | **< 0.01** |
| Night sweats | 0 (0) | 12 (20) | **0.03** |
| Dry cough | 20 (100) | 57 (95) | 0.57 |
| Productive cough | 15 (75) | 40 (66.7) | 0.49 |
| Hemoptysis | 9 (45) | 11 (18.3) | **0.02** |
| Dyspnea | 1 (5) | 9 (15) | 0.44 |
| Anorexia | 4 (20) | 24 (40) | 0.10 |
| Weight loss | 9 (45) | 51 (85) | **< 0.01** |
| Pleuritic chest pain | 3 (15) | 2 (3.3) | 0.10 |
| Smoking history, *n* (%) | | | |
| Never smoked | 16 (80) | 31 (51.7) | **0.03** |
| Current smoker | 2 (10) | 17 (28.3) | 0.13 |
| Ex-smoker | 2 (10) | 12 (20) | 0.50 |

BW, body weight; Q1, first quartile; Q3, third quartile; IQR, interquartile range; min, minimum; max, maximum.

co-morbidities (Table 2). Five controls had HIV infection while none of cases did. No cases received immunosuppressive agents but 1 control did; they received systemic chemotherapy for bladder cancer. The most common underlying disease among cases was bronchiectasis (35%). The most common underlying diseases among controls were diabetes mellitus (21.7%), asthma (10%) and chronic liver disease (10%) (Table2).

Eighty-five percent of lesions on chest X-ray among cases were in more than one lobe of the lungs; 70% were in the right upper lobe. The most common findings on chest X-ray among cases were: bronchiectasis (80%), reticular lesions (45%), reticulonodular lesions (35%) and atelectasis (35%). Sixty-six point seven percent of controls had a pulmonary lesion on chest X-ray in the left upper lobe of the lungs *versus* 25% of cases. Controls were more likely to have the following on chest X-ray than cases: patchy alveolar infiltrations (60%) and cavitary lesions (38.3%) (Table 3).

Factors significantly associated with cases were subject age >50 years, female sex, presence of bronchiectasis, symptom of hemoptysis, no cavitary lesion seen on chest X-ray and non-upper lobe lesions with bronchiectatic lesions on chest X-ray (Table 4).

On multivariate analysis, 5 factors were independently associated with cases: subject age >50 years (Adjusted OR=14.3; 95% CI: 1.6-124.3; $p$=0.02), female sex (Adjusted OR=19.4; 95% CI: 2.3-161.7; $p$<0.01), hemoptysis (Adjusted OR=21.6; 95% CI: 2.1-224.0; $p$=0.01), bronchiectasis on chest radiograph (Adjusted OR=22.3; 95% CI: 3.4-145.5; $p$<0.01) and having no cavitary lesion on chest radiograph (Adjusted OR=40.4; 95%CI: 1.3-1,249.6; $p$=0.04) (Table 4). No collinearity was found among independent variables (rho <0.9). The Hosmer-Lemeshow goodness-of-fit test for the logistic regression model had a $p$ = 0.07, indicating a good fit.

The diagnostic performance of the regression model for these five independent

Table 2
Co-morbidities among study subjects.

| Co-morbidities | Cases (Pulmonary NTM) ($n$ = 20) | Controls (Pulmonary TB) ($n$ = 60) | $p$-value |
|---|---|---|---|
| With any co-morbidities ($n$, %) | 17 (85) | 35 (58.3) | **0.03** |
| HIV infection | 0 (0) | 5 (8.3) | 0.32 |
| Diabetes mellitus | 3 (15) | 13 (21.7) | 0.75 |
| COPD | 0 (0) | 3 (5) | 0.33 |
| Asthma | 0 (0) | 6 (10) | 0.57 |
| Bronchiectasis | 7 (35) | 4 (6.7) | **< 0.01** |
| Cardiovascular disease | 2 (10) | 0 (0) | 0.06 |
| Chronic renal disease | 0 (0) | 3 (5) | 0.57 |
| Chronic liver disease | 0 (0) | 6 (10) | 0.33 |
| Connective tissue disease | 2 (10) | 1 (1.7) | 0.15 |
| Hematological disease | 0 (0) | 1 (1.7) | 1.00 |

HIV, human immunodeficiency virus; COPD, chronic obstructive pulmonary disease.

Table 3
Chest radiography results of study subjects.

| Chest radiograph result | Case (Pulmonary NTM) ($n$ = 20) | Control (Pulmonary TB) ($n$ = 60) | $p$-value |
|---|---|---|---|
| Location in lungs ($n$, %) | | | |
| Right upper lobe | 14 (70) | 48 (80) | 0.37 |
| Right middle lobe | 11 (55) | 28 (46.7) | 0.52 |
| Right lower lobe | 8 (40) | 24 (40) | 1.00 |
| Left upper lobe | 5 (25) | 40 (66.7) | **< 0.01** |
| Left lingular lobe | 9 (45) | 20 (33) | 0.35 |
| Left lower lobe | 9 (45) | 17 (28) | 0.17 |
| Not in upper lobes | 5 (25) | 4 (6.7) | **0.04** |
| Multiple lobes | 17 (85) | 50 (83.3) | 1.00 |
| Unilateral lung | 9 (45) | 19 (31.7) | 0.28 |
| Characteristics ($n$, %) | | | |
| Cavitary lesions | 2 (10) | 23 (38.3) | **0.02** |
| Nodular lesions | 0 (0) | 4 (6.7) | 0.57 |
| Bronchiectasis | 16 (80) | 10 (16.7) | **<0.01** |
| Reticular lesions | 9 (45) | 11 (18.3) | **0.02** |
| Patchy infiltrations | 5 (25) | 36 (60) | **<0.01** |
| Reticulonodular infiltrations | 7 (35) | 34 (56.7) | 0.09 |
| Pleural effusions | 0 (0) | 3 (5) | 0.6 |
| Lymphadenopathy | 0 (0) | 3 (5) | 0.6 |
| Hyperinflation | 4 (20) | 3 (5) | 0.06 |
| Atelectasis | 7 (35) | 9 (15) | 0.1 |

factors: age >50 years, female sex, hemoptysis, bronchiectasis and no cavitary lesions on chest radiograph associated with NTM pulmonary infection as quantified by the area under the receiver-operating-characteristic curve (AUC) was excellent (AUC 0.96; 95%CI: 0.92-0.99).

The logistic regression model written as a linear logistic equation expressing a relationship between the natural logarithm of odds of having a NTM pulmonary infection (being a case) and the independent factors associated with cases is shown below.

$$\text{In}\left(\frac{p}{1-p}\right) = 2.67(\text{Age}>50) + 2.97(\text{female sex}) + 3.07(\text{hemoptysis}) + 3.70(\text{no cavity CXR}) + 3.11(\text{bronchiectasis CXR}) - 10.13$$

Where p is the probability of being a case, each predictive factor that is denoted with its corresponding coefficient in the equation was assigned a value of 1 or 0 according to the presence or absence of individual factors in a patient, the probability of having NTM pulmonary infection could then be derived from the logistic regression model (Table 5). The performance of the model at various cut offs of probability of having NTM pulmonary infection is shown in Table 6. It was found that the cut-off probability between 0.21- 0.41 resulted in mostly correctly classified patients with NTM pulmonary infection according to the model.

By choosing a cut-off point for the probability of being case of 0.31, the sensi-

Table 4
Univariate and multivariate analysis of factors associated with cases (NTM pulmonary infection).

| Studied factor | Crude OR (95%CI) | Adjusted OR (95%CI) | *p*-value* |
|---|---|---|---|
| Age > 50 years | 9.6 (2.0-45.2) | 14.3 (1.6-124.3) | 0.02 |
| Female sex | 4.0 (1.4-11.7) | 19.4 (2.3-161.7) | <0.01 |
| Current smoking | 0.3 (0.1-1.3) | - | - |
| Diabetes mellitus | 0.6 (0.2-2.5) | - | - |
| History of bronchiectasis | 7.5 (1.9-29.6) | - | - |
| Symptom duration | 1.1 (1.0-1.2) | - | - |
| Hemoptysis | 3.6 (1.2-10.9) | 21.6 (2.1-224.0) | 0.01 |
| No cavitary lesions on CXR | 5.6 (1.2-26.4) | 40.4 (1.3-1,249.6) | 0.04 |
| Non upper lobe lesions on CXR | 4.7 (1.1-19.6) | - | - |
| Bronchiectasis on CXR | 20.0 (5.5-72.6) | 22.3 (3.4- 145.5) | <0.01 |

CXR, chest radiography; **p*-value of 95%CI of adjusted OR.
Blank data (-) represent unavailable adjusted OR from factors excluded by multiple logistic regression analysis.

Table 5
Predictors of being a case (NTM pulmonary infection).

| Predictor | Coefficient | 95% Confidence interval | *p*-value |
|---|---|---|---|
| Age > 50 years | 2.67 | 0.50-4.82 | 0.02 |
| Female sex | 2.97 | 0.85-5.09 | <0.01 |
| Hemoptysis | 3.07 | 0.73-5.41 | 0.01 |
| No cavitary lesions on CXR | 3.70 | 0.27-7.13 | 0.04 |
| Bronchiectasis on CXR | 3.11 | 1.23-4.98 | <0.01 |

CXR, chest radiography.

tivity, specificity, positive predictive value and negative predictive values were: 95% (95%CI: 90.2-99.8), 80% (95%CI: 71.2-88.8), 61.3% (95%CI: 50.6-72.0), 98% (95%CI 94.9-101.1), respectively.

## DISCUSSION

Increasing age has been reported to be a risk factor for NTM pulmonary infection (Prevots and Marras, 2015). In our study, we found cases were significantly more likely to be age >50 years than controls, similar to studies from South Korea and Thailand (Koh *et al*, 2006; Theerawit *et al*, 2010). Cases in our study were significantly more likely to be female than controls, similar to some previous studies (Koh *et al*, 2006; Theerawit *et al*, 2010; Kendall *et al*, 2011) but differ from another study (Prevots and Marras, 2015). In our study, cases were more likely to have bronchiectasis and non-specific pulmonary findings than controls, similar to previous studies (Taiwo and Glassroth, 2010; Stout *et al*, 2016). Cases in our study were significantly more likely to have hemoptysis than controls; this would be due to the high prevalence

Table 6
Diagnostic performance of NTM pulmonary infection based on various probability cut-offs from the regression model.

| Cut-offs | Sensitivity (%) | Specificity (%) | Positive predictive value (%) | Negative predictive value (%) |
|---|---|---|---|---|
| 0.21 | 95.0 (90.2-99.8) | 78.3 (69.3-87.6) | 59.4 (48.6-70.1) | 97.9 (94.8-101.0) |
| 0.31 | 95.0 (90.2-99.8) | 80.0 (71.2-88.8) | 61.3 (50.6-72.0) | 98.0 (94.9-101.1) |
| 0.41 | 75.0 (65.5-84.5) | 93.3 (87.9-98.8) | 79.0 (70.0-87.9) | 91.8 (85.8-97.8) |
| 0.84 | 70.0 (60.0-80.0) | 98.3 (95.5-101.1) | 93.3 (87.9-98.8) | 90.8 (84.4-97.1) |
| 0.91 | 60.0 (49.3-70.8) | 98.3 (95.5-101.1) | 92.3 (86.5-98.2) | 88.1 (81.0-95.2) |

of bronchiectasis among cases, higher than previous studies (Kendall *et al*, 2011; Theerawit *et al*, 2010; Shaarawy and Elhawary, 2014). Patients with NTM pulmonary infection may have either fibrocavitary or nodular bronchiectasis (Griffith *et al*, 2007); the majority of our cases had nodular bronchiectasis. This might be explained by the finding the most common species of NTM in our study was *M. abscessus* which has been reported to be associated with nodular bronchiectasis (Reich and Johnson, 1992; Griffith *et al*, 1993). In our study, in addition to finding a greater prevalence of bronchiectasis, we also found a lower prevalence of cavity lesions among cases than controls, similar to previous studies (Theerawit *et al*, 2010; Kendall *et al*, 2011; Shaarawy and Elhawary, 2014). The majority of cases in our study consisted of slender, non-smoking, older women with bronchiectasis involving the middle lobe and lingular segments of the lungs, described previously as Lady Windermere syndrome (Reich and Johnson, 1992). The most common pathogen in our cases was *M. abscessus,* similar to a previous study from Thailand (Theerawit *et al*, 2010) but different from the study of Prevots and Marras (2015).

In our study, the specified factors gave a good sensitivity and specificity for differentiating between cases and controls. These factors obtained by history taking and simple chest radiography that can be implemented at all levels of a healthcare institution. To the best of our knowledge, this is the first study evaluating independent factors for differentiating between NTM pulmonary infection and pulmonary TB among subjects with a positive AFB sputum smear.

Our study had some limitations: first, some confounding factors and selection bias could not be totally avoided due to the retrospective design, though we used systematic approach to data collection and analysis. Second, the number of cases might not be large enough to determine significance of all potential associated factors. Third, the prediction model we developed has not been externally validated and may only be specific and sensitive for the study population. We need to perform a larger prospective study among a broader study population to determine its validity and applicability to other populations.

In summary, factors significantly associated with cases in our study were age >50 years old, female sex, the presence of hemoptysis and bronchiectasis and finding no cavitary lesions on chest radiographs. Future studies are needed to determine applicability of this model to differentiating NTM pulmonary infection from pulmonary TB.

## ACKNOWLEDGEMENTS

The authors thank the Faculty of Medicine, Khon Kaen University for support, and Prof James A Will, University of Wisconsin-Madsion through the Khon Kaen University Publication Clinic KKU for editing the manuscript.

## REFERENCES

Adjemian J, Olivier KN, Seitz AE, Holland SM, Prevots DR. Prevalence of nontuberculous mycobacterial lung disease in U.S. Medicare beneficiaries. *Am J Respir Crit Care Med* 2012; 15: 881-6.

Al Jarad N, Demertzis P, Jones DJ, *et al*. Comparison of characteristics of patients and treatment outcome for pulmonary nontuberculous mycobacterial infection and pulmonary tuberculosis. *Thorax* 1996; 51: 137-9.

Charan J, Biswas T. How to calculate sample size for different study designs in medical research? *Indian J Psychol Med* 2013; 35: 121-6.

Gerogianni I, Papala M, Kostikas K, Petinaki E, Gourgoulianis KI. Epidemiology and clinical significance of mycobacterial respiratory infections in Central Greece. *Int J Tuberc Lung Dis* 2008; 12: 807-12.

Griffith DE, Aksamit T, Brown-Elliott BA, *et al*. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. *Am J Respir Crit Care Med* 2007; 175: 367-416.

Griffith DE, Girard WM, Wallace RJ. Clinical features of pulmonary disease caused by rapidly growing mycobacteria: an analysis of 154 patients. *Am J Respir Crit Care Med* 1993; 147: 1271-8.

Kee SJ, Suh SP. Increasing burden of nontuberculous mycobacteria in Korea. *J Korean Med Sci* 2017; 32:1215-6.

Kendall BA, Varley CD, Choi D, *et al*. Distinguishing tuberculosis from nontuberculous mycobacteria lung disease, Oregon, USA. *Emerg Infect Dis* 2011; 17: 506-9.

Koh WJ, Yu CM, Suh GY, *et al*. Pulmonary TB and NTM lung disease: comparison of characteristics in patients with AFB smear-positive sputum. *Int J Tuberc Lung Dis* 2006; 10: 1001-7.

Kone B, Sarro YS, Maiga M, *et al*. Clinical characteristics of nontuberculous mycobacterial pulmonary infections in Bamako, Mali. *Epidemiol Infect* 2018; 146: 354-8.

Prevots DR, Marras TK. Epidemiology of human pulmonary infection with nontuberculous mycobacteria: a review. *Clin Chest Med* 2015; 36: 13-34.

Reich JM, Johnson RE. *Mycobacterium avium* complex pulmonary disease presenting as an isolated lingular or middle lobe pattern: the Lady Windermere syndrome. *Chest* 1992; 101:1605-9.

Shaarawy H, Elhawary AT. Risk factors for atypical mycobacterial disease in patients with smear positive pulmonary TB. *Egypt J Chest Dis Tuberc* 2014; 63: 657-61.

Stout JE, Koh WJ, Yew WW. Update on pulmonary disease due to non-tuberculous mycobacteria. *Int J Infect Dis* 2016; 45: 123-34.

Taiwo B, Glassroth J. Nontuberculous mycobacterial lung diseases. *Infect Dis Clin North Am* 2010; 24: 769-89.

Thanachartwet V, Desakorn V, Duangrithi D, *et al*. Comparison of clinical and laboratory findings between those with pulmonary tuberculosis and those with nontuberculous mycobacterial lung disease. *Southeast Asian J Trop Med Public Health* 2014; 45: 85-94.

Theerawit P, Vongsoasup A, Kiatboonsri S. Identifying non-tuberculous mycobacterium lung diseases in acid-fast bacilli positive patients. *Southeast Asian J Trop Med Publiic Health* 2010; 41: 1432-7.

Thomson RM. Changing epidemiology of pulmonary nontuberculous mycobacteria infections. *Emerg Infect Dis* 2010;16:1576-83.

van Ingen J, Bendien SA, Lange WCM de, *et al*. Clinical relevance of non-tuberculous mycobacteria isolated in the Nijmegen-Arnhem region, the Netherlands. *Thorax* 2009; 64: 502-6.

Winthrop KL, McNelley E, Kendall B, *et al*. Pulmonary nontuberculous mycobacterial disease prevalence and clinical features: an emerging public health disease. *Am J Respir Crit Care Med* 2010; 182: 977-82.

World Health Organization (WHO). Guidelines for treatment of tuberculosis. 4th ed. Geneva: WHO, 2010. *WHO/HTM/TB/2009.420*.