FACTORS ASSOCIATED WITH IMPAIRED HEALTH-RELATED QUALITY OF LIFE IN PULMONARY NONTUBERCULOSIS MYCOBACTERIUM INFECTIONS

By

Katherine E. Berger

A THESIS

Presented to the Oregon Health & Science University School of Public Health and School of Medicine in partial fulfillment of the requirements for the degree of Master in Public Health.

May 3, 2017

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF APPENDICES

LIST OF ABBREVIATIONS

AFB	Acid fast bacilli
ALA	American Lung Association
ATS	American Thoracic Society
BMI	Body mass index
CF	Cystic fibrosis
CFTR	Cystic fibrosis transmembrane conductance regulator
CT	Computerized tomography scan
FEV1	Forced expiratory volume in one second
FVC	Forced vital capacity
HRQL	Health-related quality of life
IDSA	Infectious Diseases Society of America
MAB	*Mycobacterium abscessus*
MAC	*Mycobacterium avium complex*
NTM	Nontuberculosis mycobacterium

PFT	Pulmonary function test
QOL	Quality of life
SGRQ	St. George's Respiratory Questionnaire

ACKNOWLEDGMENTS

Throughout the course of my medical and public health education, I have been guided and inspired by countless individuals whose support and patience have helped me to grow into a public health practitioner and clinician. The success of this project is specifically thanks to the following tremendous people:

To Dr. Winthrop, thank you for your mentorship throughout the thesis process and in the clinical realm. Not only did you welcome me into your research group and challenge me to think innovatively, you also allowed me to work alongside you in clinic to see what excellent patient care and bench-to-bedside research really means. I am forever indebted for your guidance.

To Dr. Choi, I owe a great deal of my thesis success to your thoughtful and considerate perspective, thorough oversight and neverending patience. Thank you for spending time teaching me the art and nuances of model building, clarifying and teaching me the abstract concepts of biostatistics, and offering guidance and reassurance over emails at all hours of the day.

To Dr. Schafer, you never cease to bring a fresh perspective to the research process and always remind me to enjoy the thesis process. I am grateful for your openness to welcome me into the public health realm and encourage me in clinical aspirations as a Family Medicine physician. Thank you for your positivity, creativity and humor.

To Dr. Henkle, I am forever indebted to you for orienting me into the research group and allowing me to be involved in all steps of the research realm. Your patience in answering my

many clarifying questions and serving as the benevolent caretaker of these data were crucial to my success in completing this thesis.

To Dr. Stull, from the start of my public health and medical school education almost five years ago, you have served as the greatest cheerleader a learner could ask for. You refined our cohort into progressive thought leaders who are prepared to step up and tackle the challenges of our professions. I owe all of my successes and growth as a student to you. Thank you for cultivating us as a family and always serving as our compassionate leader.

To my fellow MD/MPH classmates, you are my people. Thank you for the laughter, for asking the questions no one wants to, and never being afraid to push the envelope. You inspire me to be better and I consider you my dearest companions in this crazy world.

ABSTRACT

Introduction

Nontuberculosis mycobacterium (NTM) infections often result in a chronic, debilitating pulmonary disease. Diagnosis and recognition of NTM infections is increasing, yet research and evidence are lacking and more is needed to provide optimized counseling and informed decisions surrounding interventions. More information is needed about detailed clinical and demographic predictors for impaired health-related quality of life among patients with NTM pulmonary infections.

Methods

A prospective cohort study was performed utilizing extensive chart review and questionnaires from patients with NTM pulmonary disease (n=194) in Oregon. A variety of clinical and demographic predictors were examined as potential factors associated with impaired health-related quality of life using cross-sectional data. The primary outcome of interest was health-related quality of life measured by the total, numeric score from the validated St. George's Respiratory Questionnaire (SGRQ). A multivariate linear regression was conducted to determine notable factors associated with impaired health-related quality of life among the NTM patient population.

Results

Among NTM cases, male gender ($p=0.027$), ages 50-59 ($p<0.001$), ages 70-79 ($p=0.044$), and cavitary lesion on imaging ($p=0.002$) were significantly associated with lower SGRQ total scores

(better quality of life). Obesity (0.007), former smoking history (p=0.044), past immunosuppressive use (p<0.001), and individuals with COPD and cavitary lesions (p<0.001) were associated with higher SQRQ total scores (worse quality of life) among NTM cases. Out of 27 individuals in the culture follow-up cohort, six converted from positive cultures at enrollment to negative cultures only during the follow-up period.

Discussion

The results of this study help to contribute to a burgeoning body of literature regarding pulmonary NTM infections. Given that obesity, former smoking history, and immunosuppressive history were notable factors associated impaired quality of life in NTM cases, clinicians should identify patients at risk for poor quality of life and counsel patients appropriately. Further studies need to clarify the natural history and predictors of culture conversion.

INTRODUCTION

Nontuberculosis mycobacteria

Nontuberculosis mycobacterium (NTM) is an agent of pulmonary disease that is increasing in prevalence despite relative anonymity in the literature. The pulmonary manifestations of NTM infections can lead to a chronic and oftentimes incapacitating disease course. More information is needed to predict clinical course and patient outcomes with this burgeoning disease.

While both tuberculosis and leprosy are well-known diseases in the *Mycobacterium* family, research is increasingly focused on NTM which includes consideration of a diverse array of organisms. NTM is composed of over 150 species; *Myocbacterium avium complex* (MAC), also known as *Mycobacterium avium-intracellulare* (MAI), and *M. abscessus/chelonae* are the most common isolates[1–3]. Species are differentiated into slow-growers such as MAC and rapid-growers which include *M. abscessus/chelonae*. These mycobacteria are abundantly present in biofilms within soil and water[1,3,4]. Infection is opportunistic and thought to occur from environmental exposure, with specific concerns for municipal water aerosolization or even household plumbing or showerheads[3–6]. And while many may be exposed to NTM in the environment, those who are colonized and become infected with the bacteria stand to develop debilitating disease.

Most NTM infections are pulmonary in origin; an estimated 77% of cases in Oregon are composed of lung disease which is most often caused by MAC[2,5]. Like tuberculosis, NTM is difficult for the immune system to eradicate. NTM infections, then, often become chronic and cause an inflammatory response, which leads to irreversible lung damage.

Epidemiology and risk factors

According to recent estimates, NTM infections are growing. Both clinical diagnoses according to the American Thoracic Society and laboratory isolates have increased[1,7]. A statewide laboratory-based surveillance project conducted in Oregon showed a prevalence of 8.6 per 100,000 individuals[6,7]. NTM disproportionately affects the elderly, and in Oregon the prevalence among those over fifty years old was more than double that of the general population at 20 per 100,000 individuals[6]. Additionally, those in urban environments might be more often infected with NTM than rural-residing individuals[6]. Incidence of NTM is also reported to be higher than that of tuberculosis[6]. Because curative treatment for NTM is difficult, the prevalence of chronic NTM lung disease continues to increase[3,4,8].

NTM initially was implicated in causing disease in immune-compromised individuals, such as those infected with HIV prior to the advent of highly active antiretroviral therapy. Now, most individuals infected with NTM are over 50 years old[5,7]. Women are affected more than men, despite historical literature demonstrating the opposite[1,2,5,7]. The stereotypical presentation in women includes low BMI, tall stature, increased risk of scoliosis, and nodules and bronchiectasis on radiography (see appendix B); this phenotypic findings may represent a structural susceptibility or association with an underlying genetic predisposition[1,3,9].

Underlying lung disease is associated with NTM pulmonary infections. Bronchiectasis remains a notable predisposing factor to later development of NTM[2–4]. Furthermore, any number of predisposing pulmonary conditions such as chronic obstructive pulmonary disease, asthma, and past history of tuberculosis are also associated with NTM infections[1,2,5]. Individuals with

impaired airway-surface defense also may be at increased risk[4,9]. One study identified NTM in specimens from twenty percent of cystic fibrosis patients and ten percent of patients with primary ciliary dyskinesia[4]. Additionally, those with NTM pulmonary infections had an increased incidence of cystic fibrosis transmembrane conductance regulator (CFTR) gene mutations[4,9]. Thus, there are a number of conditions that convey a structural or immunity weakness leading to an increased susceptibility to NTM pulmonary infections.

Therapeutic agents such as TNF-α blockers, commonly utilized in autoimmune diseases, increase the risk of not only tuberculosis infections but in NTM disease as well[2,4,6].

Clinical manifestations and diagnosis

Individuals infected with NTM can cause be asymptomatic or manifest as symptomatic disease. Those with a symptomatic presentation often have non-specific symptoms such as cough, fatigue and weight loss. Pulmonary symptoms can include chronic cough, recurring cough, hemoptysis, chest pain, and dyspnea[1–4]. NTM can also manifest with gastrointestinal symptoms including diarrhea and poor appetite. The severity of other symptoms such as fever, night sweats, and weight loss tend to correlate with increased progression of NTM disease[1].

Radiographic features can vary but are typically either fibrocavitary or bronchiectatic and nodular in presentation (see Appendix B)[1]. Fibrocavitary findings are difficult to differentiate from tuberculosis infections[1–3,10]. Bronchiectatic and nodular findings are more often localized to the mid and lower lungs[1,10,11]. While a chest radiograph can initially identify abnormal lung pathology, high-resolution CT is the preferred imaging modality[1].

The vast majority, over 75%, of NTM isolates are derived from pulmonary isolates[1,2]. Because NTM can be an environmental contaminant, a single sputum culture is not sufficient. In fact, the collection of three sputum cultures are recommended for proper analysis; at least two sputum isolates must be positive[1,2,12]. Bronchial wash, bronchial lavage or lung biopsies have a slightly lower risk of contamination; only one positive culture is needed to lend towards a diagnosis[1].

The American Thoracic Society (ATS) and Infectious Disease Society of America (IDSA) guidelines from the diagnosis of NTM lung disease contain multiple criteria. Clinical and radiographic criteria include bronchopulmonary symptoms, nodular or cavitary opacities on chest radiograph, or multifocal bronchiectasis with multiple small nodules on high-resolution CT scan as well as exclusion of other diagnoses. Microbiologic criteria in two positive culture results from expectorated sputum or one positive culture from bronchial wash or lavage or transbronchial or lung biopsy with positive histopathologic findings in addition to at least one positive culture from sputum or bronchial wash[1]. Both clinical/radiographic and microbial criteria must be met for a diagnosis[1].

Treatment regimens and adverse effects

The management and subsequent treatment of pulmonary NTM disease can be challenging. Chronic NTM infections may require long-term antimycobacterial treatment or even lung resections.[1,13,14] The antimicrobial agents utilized in treatment require a long duration of therapy and adverse effects are not uncommon. Those who are treated with the years-long course of antibiotics may have difficulty tolerating the medications and require a different regimen or discontinuation in entirety. Thresholds for initiating treatment are vague and often rely on joint

decision making between the patient and clinician. No accepted metrics exist to predict or even categorize which patients will remain untreated, be prescribed antibiotic therapy or recommended for surgical removal of the infected lung.

In terms of pharmacotherapy, macrolides including azithromycin and clarithromycin are the cornerstone of therapy. However, monotherapy is avoided to prevent development of resistance and subsequent clinical relapse[4,15]. A complete regimen includes a macrolide, a rifamycin such as rifampin, and ethambutol which is administered over the course of 18-24 months or until cultures are negative for 12 months[1,10,15]. Amikacin is another potential pharmacologic tool, and it is used more readily in *M. abscessus* infections[16]. To avoid adverse effects and toxicity, treatment is typically administered three times weekly instead of daily[4]. However, the initial treatment regimen is oftentimes more aggressive with the intent to cure and prevent relapse or reinfections which can hasten the onset of adverse effects[15]. Patients with rapid-grower isolates have an especially poor response to pharmacologic therapy[16]. Of note, in-vitro susceptibility testing of isolates does not often correlate with successful in-vivo response and thus potential for individual optimization of therapy is limited[3].

Adverse effects are unfortunately common in the pharmacologic treatment of NTM. The macrolides azithromycin and clarithromycin can cause gastrointestinal issues including nausea, vomiting and diarrhea, hepatitis and ototoxicity. Rifamycins such as rifampin and rifabutin can cause orange discoloration of urine and secretions, nausea, vomiting, hypersensitivity rash, hepatitis, thrombocytopenia and renal failure with rifabutin also rarely causing uveitis. Ethambutol is concerning for development of optic neuritis[1,10]. Amikacin can lead to nephrotoxicity and otoxicity[16].

Health-related quality of life

As the natural history suggests, pulmonary NTM is often difficult to treat. Many patients live with pulmonary NTM as chronic infections that are debilitating and difficult to cure. Health-related quality of life (HRQL) is an amalgamation of physical, emotional, social and functional components. HRQL projects the patient's own perception of disease and treatment burden in their well-being. Rather than utilizing solely laboratory or clinical outcomes, HRQL can serve as a meaningful outcome in assessing outcomes that are relevant to patient well-being.

The St. George's Respiratory Questionnaire (SGRQ) is a validated metric that was developed as a means to measure health in chronic airflow limitation[17]. Unlike other HRQL metrics, this instrument is specific to pulmonary disease and has been validated in chronic obstructive pulmonary disease as well as bronchiectasis[17–19]. Limited studies have evaluated HRQL in NTM and they have utilized the SGRQ in their analyses; one abstract demonstrated that the SGRC is a valid instrument in immunocompetent patients with pulmonary MAC disease whereas a cross-sectional study from a single clinic showed its utility in those with pulmonary NTM not limited solely to MAC[20,21]. Patients with NTM pulmonary disease have worse quality of life than healthy individuals[21]. Abnormal lung function and presence of underlying emphysema are associated with higher total SGRQ scores, indicating worse impairment[21]. However, there have been no recently published studies that confirm these findings among those NTM pulmonary disease or explore more clinical and demographic variables, thus the use of the SQRC in this study will be of great utility in clarifying these risk factors.

Given that the focused study of pulmonary NTM is still in its infantile stages, learning about clinical and demographic predictors of HRQL is crucial in determining thresholds for interventions, facilitating evidence-based treatment discussions, and improving the counseling available to patients.

RESEARCH QUESTION

Among nontuberculosis mycobacterium pulmonary infection patients, what are the clinical and demographic factors associated with impaired health-related quality of life?

Specific Aims

The goal of this study is to determine factors associated with impaired health-related quality of life and further characterize the population characteristics among NTM pulmonary infection patients in Oregon. The specific aims are:

> **Specific Aim 1:** Determine demographic and clinical factors associated with impaired health-related quality of life as measured by the St. George's Respiratory Questionnaire total score among NTM cases.
>
> **Specific Aim 2:** Determine demographic and clinical factors associated with impaired health-related quality of life as measured by the St. George's Respiratory Questionnaire total score among non-cases.

Specific Aim 3: Quantify the natural history of culture results in one year follow-up and identify if differences exist in initial quality of life in culture converters compared to others.

METHODS

Study Design

The overarching study is a prospective cohort study. Cross-sectional data from the enrollment visit were used to assess the relationship between clinical factors and quality of life. Limited, prospective cohort data regarding patient microbiology and culture results was used to identify predictors for negative culture conversion. Figure 1 demonstrates the study timeline.

Study Subjects and Data Source

All patients in this study are a part of the OHSU American Lung Association (ALA) database which contains approximately 250 patient records. These patients are derived from a handful of sources. Patients identified in 2005-2006 through the population-based cohort pilot study, the Oregon NTM Cohort (ONTMC), who are still living are included in the database; see figure 2 for further information. NTM is a reportable disease and representatives at the Oregon Health Authority (OHA) identify new cases through the NTM surveillance program; cases from 2012 and later were given information by the OHA regarding research opportunities at OHSU. Other patients who have received a NTM diagnosis from 2012 or later and are referred to OHSU by outside clinicians are also included. Finally, certain OHSU patients from 2012 and later who intended to enroll in NTM clinical trials were also recruited to participate in this study.

All those who attend a visit with the NTM team at OHSU are given information about this study. If they choose to participate and meet inclusion criteria, they are consented by the OHSU NTM research team. During the initial enrollment visit, they complete three to four symptom surveys. Specifically, the St. George's Respiratory was used to assess HRQL. Clinical data including treatment regimen, treatment duration, radiography, microbiology culture results, spirometry, and reported symptoms are then obtained from comprehensive chart reviews. Other pertinent demographic variables such as age, BMI, comorbidities, history of immunosuppression, and history of tobacco use were also collected. Data are entered into the anonymized ALA database. Subjects with NTM pulmonary disease are selected and analyzed from this database.

Health-related Quality of Life Metrics

The St. George's Respiratory Questionnaire is a metric by which to determine health-related quality of life impairment among those with pulmonary disease[17,22]. While this metric is validated for COPD, asthma and bronchiectasis, it is not validated in NTM disease specifically[22]. The questionnaire contains 50 items that are a combination of frequency scales, true or false, and Likert scales. The first part of the tool assesses symptoms and the patients' perceptions of their respiratory condition. The second portion of the tool asks questions regarding activity and impact on daily functioning. Three component scores are reported and include symptoms, activity and impacts. A total score is also calculated. Scores range from 0 to 100 with higher scores indicating greater impairment and limitations[22]. See Appendix C for the questionnaire.

Selection Criteria

See figure 3 for representation of subject selection. Inclusion and exclusion criteria for this substudy are as follows:

Inclusion criteria

i. Age at least 18 years old
ii. At least one positive NTM culture
iii. Completion of St. George's Respiratory Questionnaire

Exclusion criteria

i. Age less than 18 years old
ii. No culture results
iii. Diagnosis of cystic fibrosis
iv. Positive human immunodeficiency virus (HIV) status
v. Positive immunosuppressive disease
vi. Extrapulmonary or disseminated NTM disease

Measurements and Variables

Outcome variables

There are two outcome variables of interest. Primarily, the outcome of interest for the cross-sectional data is the health-related quality of life as measured by the total weighted score from St. George's Respiratory Questionnaire (SGRQ) obtained at the initial enrollment visit. The

second outcome used for the culture cohort follow-up data is culture conversion. Culture conversion is defined as an individual with positive culture results within six months of enrollment and only negative culture results during the follow-up period.

Covariates

A variety of variables are utilized as covariates and considered as exposures and potential factors associated with impaired quality of life. These covariates included both clinical and demographic factors. Demographics included are gender (male or female), age (years, 50 years old or younger; 50-59 years old; 60-69 years old; 70-79 years old; 80 years old or older), race (Caucasian; other; unknown), BMI class (underweight <18.5; normal weight 18.5-24.9; overweight 25-29.9; obese ≥30), and smoking history (present; past; never). Clinical variables examined included disease duration (time between first culture isolation and enrollment, years, <1 year, 1-3 years, 3-5 years, 5-7 years, 7-9 years, ≥9 years), comorbid COPD (yes or no), comorbid bronchiectasis (yes or no), comorbid asthma (yes or no), treatment history as of enrollment (present; past; never), treatment initiation at enrollment visit (yes or no), last culture result within 6 months of enrollment (negative; positive; no culture), last AFB smear result (negative; positive, no smear), NTM species (MAC; MAB; none), bronchiectasis on CT (yes or no), cavitary lesion on imaging (yes or no), last FEV1 on spirometry (percentage predicted, normal ≥80%, impaired <80%; unknown) and last FEV1/FVC (ratio, normal ≥70%, impaired <70%; unknown).

Statistical Analysis

Descriptive studies determined the demographic and clinical makeup of the entire NTM population. Chi-square, Fisher's exact, and ANOVA were used as appropriate to produce

frequency distributions of the categorical covariates. Differences in means were assessed using the Student t-test.

The SGRQ quality of life metric outcomes are continuous and thus, the Student t-test or ANOVA were utilized to compare independent variables by culture status. Tests were noted to be statistically significant with a two-sided p-value of less than 0.05. Simple linear regressions were conducted to examine the crude relationship between covariates and the quality of life outcome metric. Simple logistic regression was used to explore if any covariates served as predictors for negative culture conversion. Tests for confounding and interaction were conducted for all covariates.

Multiple linear regression was used to estimate the association between covariates and SGRQ quality of life total score in the cross-sectional data from the enrollment visit.

Model diagnostics were run to determine if there were any violations of the assumptions of linear regression (see Appendix E). Normality was tested using a Shapiro-Wilk goodness of fit test and residual analysis. Influential points and outliers were identified use DFITS, DFBETA, Cook's Distance and leverage testing methods. Collinearity was assessed using postestimation tools.

All analyses were conducted with STATA 13.0 (StataCorp, College Station, TX).

Quality Control, Data Management and Patient Protections

This study has received IRB approval from Oregon Health & Sciences University. All patients provided consent to participate in this study and completed a release of information for inclusion in the chart review. Only IRB-approved personnel conducted chart review. A singular research

coordinator trained each individual aiding in chart review. A chart review manual was created by the research coordinator which included explicit instructions on how to record information from charts into the REDCap database. Data derived from charts was anonymized and entered into REDCap, a secure, electronic web-based application utilized by OHSU for data storage. Patients were given a random subject number and de-identified upon entry into REDCap. Chart review and subsequent entry into REDCap were confirmed as correct and accurate by the research coordinator who verified completion of each chart and selected random charts to review in detail.

Patient information is anonymized upon entry into the database. There is limited access to identifiable patient information which is only granted to IRB-approved personnel. All patient information and the database exist on a password-protected drive on the OHSU server which includes a secure firewall; this is in compliance with the OHSU Information and Security Guide.

RESULTS

Overall study population characteristics

Table 1 presents the population characteristics of the entire study population, including demographic and clinical factors. A total of 194 participants were eligible for inclusion into the analyses. Table 2 stratifies the cross-sectional population characteristics by whether they were denoted as an NTM case by IDSA/ATS NTM case guidelines or a non-case. A total of 169 participants were noted as NTM cases whereas 25 patients were non-cases. Table 3 displays the population characteristics for the cohort of 27 patients with one year follow-up microbiology and culture data available. Comparisons were made between those with the outcome of interest,

negative culture conversion, versus those who had any other microbiological results for follow-up. No statistically significant differences among the negative conversion and non-conversion group were detected.

Individual quality of life score components

Table 4 demonstrates the average SGRQ scores of all participants and provides the component scores for chosen, limited covariates. No statistical tests were performed.

Among female participants, the highest individual component score was the symptoms score (38.9±23.5). Males had a higher activity score (45.6±29.2) than the other components. In patients without bronchiectasis, the activity score demonstrated the most impairment (48.2±27.2). Those with bronchiectasis had a higher symptoms score (39.3±24.0). Individuals without COPD had the highest score in the symptoms component (36.1±48.0) whereas those with COPD had the most impairment in activity score (51.8±27.0). Never smokers had the highest component score in the symptoms domain (36.4±22.6) while current and former smokers had the most impairment in activities scores (65.1±27.2; 45.9±26.9).

Factors associated with impaired health-related quality of life among NTM cases

Population characteristics: cross-sectional assessment of NTM cases

The majority of NTM cases were female (78.7%), Caucasian (90.5%), and had a normal BMI (62.3%). Most patients were between 60-79 years old (61.0%). Approximately half of the patients were never-smokers (55.6%), but a substantial minority were former smokers (39.1%).

Bronchiectasis was the most common pulmonary comorbidity (83.4%) with a notable faction of patients reporting COPD (29.6%) and asthma (27.2%). Most patients had never used immunosuppressive medications (68.6%) and few were actively taking immunosuppressives at enrollment (4.7%). In terms of antimycobacterial treatment history, approximately one third of participants had never had any targeted treatment (31.4%) and one quarter had received treatment in the past prior to enrollment (25.4%). Most patients did not have any sputum cultures obtained within 6 months of enrollment (50.3%), one third had negative culture results closest to enrollment (32.0%) and fewer had positive cultures (17.8%). Most recent acid fast bacilli smear showed that the majority were negative (62.7%). On those with recent cultures, the majority resulted MAC (57.4%) although most were negative and did not result any species (40.2%); only four individuals resulted MAB (2.4%). Most patients had bronchiectasis noted on CT imaging (76.3%) whereas only one third had a cavitary lesion present on imaging (32.5%). In assessing spirometry, approximately one third had normal FEV1 and FEV1/FVC ratio (31.4% for both) with more individuals having an impaired FEV1 and FEV1/FVC ratio (38.5%, 36.7%). The mean SGRQ total score was 31.0 ± 20.8.

Univariate analysis: NTM cases

Results are presented in Table 5.

Obesity was associated with 13.8 point increase in quality of life score ($p=0.036$). Smoking history of significantly associated with an increased total score ($p<0.001$), with 23.2 more points for current smokers and 10.6 points for former smokers ($p=0.001$, $p=0.001$). COPD as a comorbidity was associated with a 13.1 point increase in total score ($p<0.001$). Past use of

immunosuppressive medication was associated with a 15.4 increase in total score (p=0.009). The presence of a cavitary lesion on imaging was associated with a 7.4 point increase (p=0.03). Impaired FEV1 and FEV1/FVC ratio on spirometry were associated with a 5.8 and 11.7 point increase in score, respectively (p=0.022, p=0.002). Gender, age, race, disease duration, comorbid bronchiectasis, comorbid asthma, antimycobacterial treatment history, last culture result, last AFB smear result, NTM species, and bronchiectasis on CT imaging were not significantly associated with any change in total score.

Multiple variable analysis: NTM cases

Results are displayed in Table 6.

Variables included in multiple analysis from univariate analysis were gender, age, BMI, smoking history, comorbid COPD, immunosuppressive treatment history, last AFB smear, cavitary lesion on imaging, FEV1 on spirometry, and FEV1/FVC on spirometry.

Age, BMI, smoking history, comorbid COPD, immunosuppressive treatment history and FEV1/FVC ratio were initially selected during model building. Gender, last AFB smear, cavitary lesion on imaging, and FEV1 on spirometry were identified as confounders. The interaction between COPD and immunosuppressive treatment history as well as the interaction between COPD and cavitary lesion on imaging were statistically significant and thus included in the final model.

In the final multiple linear regression model, male gender was associated with a 8.6 point lower total score than females (p=0.027). Patients between 50 and 59 years old had an almost 20 point

lower total score while patients between 70 and 79 years old had a 9.6 point lower score than patients who were less than 50 years old ($p<0.001$, $p=0.044$). Past immunosuppressive treatment was associated with a 26.6 point increase score ($p<0.001$). Presence of a cavitary lesion on imaging was associated with an 11.5 point decrease in total score ($p=0.002$).

Among patients with COPD, having an unknown immunosuppressive treatment history was associated with an increased total score of 29.7 points ($p<0.001$). Furthermore, patients with COPD and a cavitary lesion had a 33.2 point increased score ($p<0.001$). Given this interaction, patients without COPD who have a cavitary lesion on imaging have an 11.5 decrease in total score whereas patients with COPD who have a cavitary lesion on imaging have a net 22.0 increased total score.

The final model contained a sample size of 161, after the removal of eight outliers, and 12 covariates. The p-value was less than 0.001, R^2 was 0.449, and the adjusted R^2 was 0.348.

Factors associated with impaired health-related quality of life among non-cases

Population characteristics: cross-sectional assessment of non-cases

Results are displayed in Table 2.

Non-case patients were also predominantly female (72.0%), Caucasian (92.0%), and had a normal BMI (70.8%). The majority were between 60 and 79 years old (76.0%) with all others below 50 years old (24.0%). Most were former smokers (60.0%) and there were no current smokers. Two thirds had comorbid bronchiectasis (64.0%), one third had comorbid COPD (36.0%), and a minority had comorbid asthma (20.0%). The vast majority had never used

immunosuppressive medications (80.0%) or received antimycobacterial treatment (88.0%). Most non-case patients had a negative culture result within six months (56.0%) or no recent culture (36.0%); only two non-case patients had a positive recent culture result (8.0%). Similarly, most had negative AFB smears (72.0%) or no smear (24.0%). All follow-up patients had a history of speciation with MAC (72.0%) and none had speciated MAB. The majority had bronchiectasis identified on CT (68.0%) and nearly one quarter had a cavitary lesion on imaging (24.0%). Over one third of patients had normal FEV1 and FEV1/FVC ratios on spirometry (36.0%, 40.0%). The mean SGRQ total score was 29.3 ±16.7.

Univariate analysis: non-cases

Results are presented in Table 7.

Non-case patients who were between 70 and 79 years old had a 18.6 point increase in total score compared to those less than 50 years old (p=0.022). Present antimycobacterial treatment was associated with a 36.4 point increased score (p=0.033). Impaired FEV1/FVC ratio was associated with a 17.7 point increase in total score (p=0.041). Gender, race, BMI, smoking history, comorbid bronchiectasis, comorbid COPD, comorbid asthma, immunosuppressive treatment history, last culture result, last AFB smear result, bronchiectasis on CT, cavitary lesion on imaging, and FEV1 on spirometry were not significantly associated with changes in total score.

Given limited sample size, there was not sufficient power to perform a multiple linear regression.

Culture conversion in one year follow-up

Population characteristics: culture follow-up cohort

Results are reported in Table 3.

In examining the individuals with follow-up culture data available, patient characteristics were stratified by the outcome of interest, negative culture conversion.

Negative converters (N=6) were all female, all Caucasian, and predominantly had normal BMI (83.3%). Two thirds were never-smokers (66.7%) and one third had a past history of smoking (33.3%). All of negative converters had comorbid bronchiectasis. None had comorbid COPD and only one had asthma. Most had never received immunosuppressive treatment (66.7%) with one reporting past treatment (16.7%). Half of the negative converters had past antimycobacterial treatment and half were presently receiving antimycobacterial treatment. The majority had bronchiectasis on CT (83.3%) and cavitary lesion on imaging (66.7%). Two thirds had impaired FEV1 on spirometry (66.7%), whereas only one third had an impaired FEV1/FVC ratio (33.3%). The average SGRQ total score at enrollment was 22.8 points (SD 20.1). There were no statistically significant differences in patient characteristics among the negative converters compared to all others in the follow-up cohort.

Follow-up outcomes: microbiology findings and culture results

Results are displayed in Figure 4 and Table 8.

Of the 27 patients with both recent culture results at enrollment and one year culture follow-up data available, six converted from positive cultures at enrollment to negative cultures during follow-up. Seven patients were persistently negative from enrollment into follow-up. Two patients had positive cultures at enrollment remained positive during follow-up. Five individuals

had negative cultures at enrollment and had positive culture results during follow-up. The remaining seven individuals had both positive and negative cultures throughout the follow-up period.

The persistently negative group had an average SGRQ total score of 21.5 points (SD 18.1) at enrollment. Those who converted from positive to negative cultures had an average initial total score of 22.8 points (SD 20.1). Those with persistently positive cultures had an average total score of 30.2 points (SD 41.7) at enrollment. Patients that initially had negative cultures but converted to positive culture results during the follow-up period had a mean total score of 41.8 points (SD 29.9) at enrollment. Individuals who had either positive or negative cultures at enrollment but continued to have both positive and negative results during the follow-up period had an average total score of 25.4 points (SD 15.2) at enrollment. One-way ANOVA did not find a statistically significant different among the total score means of each follow-up culture group.

Univariate analysis: culture follow-up

Results are noted in Table 9.

Age, BMI, smoking history, asthma, antimycobacterial treatment history, bronchiectasis on CT, cavitary lesion on imaging, FEV1 on spirometry and FEV1/FVC ratio on spirometry were considered in univariate analysis. The covariates age, race, comorbid COPD, and immunosuppressive treatment were not included given statistical instability on modeling.

Given the limited sample size, there was not sufficient power to perform a multivariate logistic regression.

DISCUSSION

Notable Findings

Study population characteristics

The study population echoes the predominant characteristics of the typical NTM patient: a middle-aged to elderly, immunocompetent, Caucasian woman. Lady Windermere's Syndrome, characterized by the aforementioned characteristics, is the archetype of NTM infections[1,8,11]. This may suggest, as many in the past have, that patients infected with MAC may have a certain structural makeup that predisposes them to infection[1,8,9,11]. However, it may also be possible that clinicians have a heightened suspicion to look for NTM infections in this subset of the population given the predominant stereotype and thus are more likely to work-up and identify NTM cases.

Furthermore, this study population overwhelmingly lacked racial and ethnic diversity with greater than 90% of participants identifying as Caucasian. The aggregate of African-American, Asian, Pacific Islander, Native American and Alaskan Native, and Hispanic populations was only eight (4.1%) of the study population. The issue of race has often been discussed regarding NTM pulmonary infections. Given that the population this study draws from, those residing in Oregon state, is already largely Caucasian, it is not surprising that the study population contains many Caucasian patients. Some consider that a genetic predisposition to NTM may be at play in a mutated CFTR gene, which can lead to cystic fibrosis (CF); while this study did not include those with CF, there were no routine genetic tests performed in these patients and others have suggested that more mild mutations or a single mutation might lead to predisposition to NTM

pulmonary infections[1,2,8,23]. Because of the racial homogeneity, generalization of this study to Oregon may be appropriate but limitations might arise in applying these findings to a more racially diverse population until the role of race in NTM infections is further clarified.

The majority of the study population had a normal BMI. It is not a surprise that a notable proportion of patients were also categorized as underweight given that a tenet of the physical manifestations of NTM pulmonary infections, similar to its cousin tuberculosis, is weight loss[1,9]. However, one study suggested that individuals with NTM had a lower weight than matched controls even prior to isolation of NTM, again harkening back to the NTM morphotype that may predispose one to infection[3,4,9]. Thus, the presence of a notable proportion of underweight patients in this study population, whether due to inherent leanness or acquired with symptomatic weight loss, is consistent with previous studies[3,4,9].

In this study population, over half of patients had never smoked (53.6%). Very few patients were current smokers (4.6%), and approximately 40% of patients were former smokers. When NTM was initially characterized, there was a large population of males who were smokers that were found to have the disease; however, for many decades there has been a growing population of female nonsmokers who have NTM disease, akin to the previously mentioned Lady Windermere's syndrome[11,24]. The prototype, again, emphasizes that the majority of NTM patients have no smoking history[11,25]. More recent studies have reported the prevalence of nonsmokers at anywhere from 40% to 68% among individuals with NTM pulmonary disease; thus this proportion of nonsmokers is consistent with past studies[9,24].

Bronchiectasis has long been known to be linked to NTM disease, so much so that there has been discussion regarding whether all individuals with bronchiectasis should be routinely screening for NTM infections[3]. Similar to other clinical characteristics, it is unclear if the presence of bronchiectasis predisposes one to NTM infections or if bronchiectasis develops as a result of the infection[1,2]. This study's predominance of comorbid bronchiectasis in greater than 80% of patients is consistent with or even at higher proportion that other studies published[1,4]. Furthermore, the association between bronchiectasis and female gender is present and statistically significant in this study as well (see Appendix D)[1,4].

Chronic obstructive pulmonary disease (COPD) was present in 30% of the patients, with a statistically significant proportion of those being male (see Appendix D). Similar to bronchiectasis, the presence of a structural disease COPD is thought to potentially predispose patients to NTM infection, specifically in males[2,6].

Immunosuppressive treatment, a known risk factor for NTM infection, was less prevalent than previous studies from Oregon[1,6]. Previously, one quarter of patients were on immunosuppressive medication at time of NTM isolation[6]. Only 8% of patients had received immunosuppressive treatment in the past and even fewer (4.6%) were on any immunosuppressive treatment at enrollment. Immunosuppressive treatment as a variable did not differentiate from systemic steroids, newer biologic agents, chemotherapy or others in this study.

Most participants had received antimycobacterial treatment in some capacity; almost one quarter (23.2%) had past treatment and over one third (38.1%) were on a treatment regimen at time of enrollment. Antimycobacterial treatment history is a convoluted and complex variable. There are

recommended regimens, alternative regimens, and a high rate of discontinuation given the likelihood of adverse effects[1,10,13,16]. This study only examined whether a patient had ever received targeted antimycobacterial treatment and did not consider the specific regimen or duration, which is a noteworthy limitation.

Culture result and status is not only used to formally diagnose NTM, but it is also often utilized by clinicians to assess what the threshold for initiating treatment should be. Despite its clinical importance, cultures can be difficult to obtain. If a patient does not produce sputum, they will be unable to provide a sputum culture and either need to induce a sputum with hypertonic saline, an uncomfortable experience, or undergo a costly procedure such as a bronchoalveolar lavage for the sample. Thus, many patients do not have regular and updated culture statues. In the interest of capturing most recent culture status, only the most recent culture within six months of enrollment was used for the culture result variable. Unfortunately, almost half of participants (48.4%) did not have a recent culture upon enrollment. Patients were also more likely to have a negative culture (35.1%) than a positive culture (16.5%) at enrollment. Similarly, AFB smears which are grown directly from the sample, are thought to represent a higher microbial burden. The last AFB smear, not limited to six months prior to enrollment, was predominantly negative in this population (63.9%) with a small faction having positive smears (19.1%) and a similar number having no smear (17.0%). A more ideal protocol would enroll patients at a time when they have produced a sputum sample or recently undergone a procedure where a sufficient sample was obtained.

Similar to the comorbid pulmonary condition of bronchiectasis, confirmed bronchiectasis on CT imaging is a known risk factor for NTM given that it may provide a structural predisposition to

disease. It also may represent the slower development of a long-term disease process[1,4]. Bronchiectasis on CT imaging was present in three quarters of study participants (75.3%) which is higher than previous estimates in Oregon[6]. For this study, limited radiologists reviewed CT scans with a specific protocol, so this might have resulted in a heightened suspicion for bronchiectasis that in previous studies. There is a possibility that more individuals have bronchiectasis given that only CT imaging was used to assess for radiographic evidence of bronchiectasis; that is, if a study participant only had radiographs performed, bronchiectasis was not assessed in this study from a radiographic perspective.

Cavitary lesions were less common than bronchiectasis on imaging with only 31.4% of participants having an identified cavitary lesion on imaging. However, this prevalence is similar to others studies were cavitary disease is found in anywhere from 15% to 42% of patients[1,9]. Fibrocavitary disease was initially described in older males with underlying lung disease and a smoking history[2]. Cavitary disease was significantly associated with male gender in this study as well (see Appendix D).

Spirometry, or pulmonary function tests (PFTs), are an objective proxy for obstructive airway disease. Similar to sputum cultures, PFTs can be inconvenient; they are time consuming and thus not routinely performed by all clinicians. Approximately one third of patients did not have any recent spirometry performed as evidenced by unknown FEV1 and FEV1/FVC values (30.9%, 32.5%). Greater than one third (37.1%, 35.1%) of individuals had an impaired FEV1 or FEV1/FVC ratio, respectively indicating active obstructive disease in many participants. The utility of PFTs would best be explored if all individuals had a PFT performed prior to enrollment.

The exploratory analysis looking at component makeup of total score, while not a statistical test, did reveal interesting findings. Within each of the select covariates, the component with highest impairment differed among the subgroups. Symptoms score was the highest among women, individuals with bronchiectasis, those without COPD, and never smokers. Activity score was highest among men, individuals without bronchiectasis, those with COPD, former smokers, and current smokers. Those more affected by symptoms seem to represent the Lady Windermere morphotype whereas those affected predominantly by activity limitations seem to be the male smoker with COPD. This demonstrates that total score may not provide the complete picture of impairment and that differences likely exist among subgroups or morphotypes. Further analyses examining individual components would be of use.

Factors associated with impaired QOL among NTM cases

Male gender was associated with a lower QOL score (adjusted β -8.6±7.6, p=0.027) and thus a less impaired quality of life. It seems that studies have shown equivocal differences between genders and others noted women had worse QOL. For instance, one study looked at SGRQ in NTM patients and found that while there was a trend that men scored worse, although this was not significant[20]. Another study compared COPD patients to matched controls showed that females had a two point higher, or more impaired, QOL score on average compared to their male counterparts[26]. Whether female patients experience more severe disease than males is unknown. This study in particular suggests that men may have a better QOL than women with NTM disease and that may be an encouraging factor in estimating how an individual patient might fare in the disease course.

Patients who were neither young (below 50 years old) nor elderly (above 80 years old) had lower QOL scores, indicating less impairment. Specifically, those who were 50 to 59 years old had an almost 20 point lower total score than those who were less than 50 (adjusted β -19.5±5.39, $p<0.001$). Similarly, those who were ages 70 to 79 years old had a nine point lower, and less impaired, total QOL score than those under 50 years old (adjusted β -9.39±4.63, $p=0.044$). While the trend was consistent for 60 to 69 year olds with a 3 point lower score, this group's association was not statistically significant. These findings suggest that the very young and the very old may have a poorer quality of life. However, the choice to utilize the under 50 year old group as the reference group could have led to these results given that NTM infection is typical in late middle-aged and early-elderly cohorts, and other underlying but undetected conditions could have predisposed the younger, reference group to this disease. Additionally, suffering from NTM disease at a younger age may result in a greater relative burden of impaired QOL compared to older peers, although this is uncertain. Clinicians, then, should be wary of the well-being of their younger and older patients with NTM disease.

Obesity remained significantly associated with a 16 point higher QOL score, implying worse impairment (adjusted β 15.9±5.81, $p=0.007$). Interestingly, both underweight and overweight individuals had a trend toward lower quality of life scores, although neither were statistically significant. Other studies examining quality of life among obese patients have demonstrated that BMI and body fat percentage are positively correlated with higher HRQL scores in both the SGRQ and other metrics; thus obese patients have a poorer perception of quality of life than non-obese counterparts[27–29]. While NTM patients often suffer from weight loss as a symptom leading to a lower BMI, it still appears that those patients who remain obese continue to have the greatest

quality of life impairment. Patients are additionally likely to be categorized correctly given that BMI was calculated by weights and heights recorded in clinic rather than by self-report.

Current smoking has been shown to be associated with a three point higher SGRQ score in one past study of a general population[26]. In this population, while there was a trend that current smokers would have a worse quality of life score, this was not statistically significant (unadjusted β 23.2±6.91, adjusted β 15.9±5.81, p=0.11). The magnitude of the effect present in the univariate analysis was much decreased in the multivariate linear regression. Overall, there were only nine current smokers in this study population so perhaps if more robust numbers of current smokers had participated then a statistically significant effect might have been seen. Perhaps, also, other sequelae of smoking such as COPD or an obstructive respiratory process as evidenced by impaired FEV1 or FEV1/FVC ratio on spirometry are what results in worse quality of life in current smokers; the final model controlled for both of these variables, therefore the inclusion of these covariates may have resulted in the non-significance of current smoking on QOL. There was a much larger sample size of former smokers among the NTM case group (N=66).

A history of past immunosuppressive use was significantly associated with a higher total score and worse quality of life (adjusted β 26.6±7.0, $p<0.001$). It is difficult to parse out if this marked impairment is due to an increased severity of disease manifestations after having used immunosuppressive medications or whether it is related to the autoimmune or other disease, oftentimes debilitating, that requires chronic treatment.

Interestingly, neither past nor present antimycobacterial treatment had any association with QOL scores. Given that this study did not thoroughly include the nuances of treatment, including if it was an IDSA/ATS recommended regimen or not, how many regimens the patient had received in total, if doses were optimized, whether or not adjuvant treatments were used, and whether a course was completed or discontinued, it is difficult to confidently conclude that antimycobacterial treatment has no effect on quality of life. Certainly, further studies are needed to explore these potential exposures.

Cavitary disease can lead to a more difficult to treat disease process with a higher burden of microbes as evidenced by persistently positive AFB smears[15]. While it would be expected that a cavitary lesion might worsen quality of life, surprisingly, the opposite was found in this study. Even more curious is that cavitary lesions were, indeed, found to be associated with a higher total score and worse QOL in the univariate analysis (unadjusted β 7.4±3.4). The final model showed that, with all relevant covariates included, cavitary lesions were associated with a decreased score and thus better QOL (adjusted β -11.5±3.7, $p=0.002$). This conundrum is further convoluted by the presence of an interaction between those with COPD and cavitary lesions which exceeds the magnitude of the aforementioned association (adjusted β 33.2±6.6, $p<0.001$). Therefore, it appears that in patients with COPD and cavitary disease on imaging, the net effect is that of a higher score and worse quality of life. In patients without COPD, cavitary disease on its own is associated with a lower score and better quality of life. See figure 5 for elucidation of this relationship.

Quality of life in non-cases

While initially discussed as a potential control, non-cases were instead assessed independently of NTM cases given their uncertain natural history. Case status is defined by a set of characteristics (see Appendix A) wherein a patient may never have an official diagnosis for a variety of reasons. Specifically, patients must report symptoms, have more than one positive sputum sample, or have a clinician who has ruled out all other likely diagnoses. While some patients may indeed have an incidental positive sputum in the absence of symptoms, then never have evidence of disease again, others will progress to case status. In the absence of confirmation that these non-cases remained as such, a more appropriate direction was to explore whether or not the factors associated with quality of life in NTM were similar in non-cases.

Age was significantly associated with changes in quality of life (p=0.031). However, each of the individual age categories did not have a significant association. Only the individuals older than 70 demonstrated a trend towards increased score but that was not significant.

History of present antimycobacterial treatment was significantly associated with a higher score (p=0.033). However, only one individual in the non-case subgroup had present treatment and thus the score represented that singular person. Furthermore, an individual who is a non-case yet still had treatment initiated may have more comorbidities or be a sicker individual at baseline, thus triggering a provider to initiate treatment before case status is met. Thus, that association is limited and likely cannot be generalized.

Finally, impaired FEV1/FVC ratio was associated with a higher score (p=0.041). This is consistent with the univariate findings for the NTM cases. It seems sensible that an individual

with an inability to breathe would have worse quality of life, perhaps in the activities and symptoms components, leading to a higher score overall.

All other covariates were not significantly associated with quality of life.

Exploring culture outcomes in the follow-up period

A total of 27 participants had recent culture data available at enrollment and had one year follow-up microbiology and culture data collected at the time of this study. The outcome of interest was whether an individual who, at enrollment, had positive cultures converted to only have negative cultures during the follow-up period. Of the 27 studied, six were so-called negative converters. In the negative converter population, all were female and Caucasian. The majority were normal weight, nonsmokers and had comorbid bronchiectasis. None of the patients had COPD and only one reported a history of asthma, however most (66.7%) did have an impaired FEV1. Only one had used immunosuppressive medication in the past. All of the participants had received antimycobacterial treatment in the past, half had past treatment and half were receiving treatment already at the time of enrollment. None of the patients initiated treatment at enrollment. On average, those who were negative converters had a lower SGRQ total score (22.8±20.1) compared to the other follow-up culture patients who had an average score of 28.5 (±22.3) although that difference was not statistically significant (p=0.58).

None of the covariates were statistically significant predictors of culture conversion in univariate analysis. The homogeneity of those who were negative converters as well as the limited sample size of the cohort may have prevented any trends from being seen. As more robust follow-up

data arrives and the cohort size increases, these relationships should be repeated to see if predictors become more apparent.

Limitations and Considerations

Study design

This study contains notable limitations. While the overarching prospective cohort database seeks to provide prospective data from the one year follow-up period, the model here regarding quality of life only utilize the cross-sectional data from the initial enrollment visit. This study succeeds in providing information on the baseline characteristics of a sizeable NTM population, but its results cannot be used to project how patients will perform over time. Additionally, the limited follow-up data available, that of culture results, was the only variable that had data available. Isolating the culture data as the follow-up outcome did not capture other variables that might have changed in the interim such as treatment regimen or new imaging findings.

Subject selection

Study recruitment did not limit enrollment to those with new disease only. Instead, patients have different natural histories of their individual disease processes. Certain individuals, involved in the original Oregon cohort from 2005-2006, were included; thus, these individuals would have a much more convoluted and complex disease process consisting of treatment failures and multiple comorbidities than newly diagnosed patients. Because these findings were not stratified by initial group classification, mostly due to concerns with sample sizes, it is difficult to say whether the factors associated with poor quality of life were disproportionately influenced by the handful of

participants with multifaceted disease processes. As enrollment in this study continues, it would be helpful to stratify and study whether factors differ among those with a heavy disease burden versus new or treatment naïve populations.

Missing values

The chart review phase of this study was difficult in insuring complete chart information was available for chart review. This was hindered by the mention of results, treatment regimens or procedures in the text portion of notes in the absence of objective laboratory or testing reports.

In considering whether individuals with missing values should be removed, if variables had a substantial proportion with missing data such as PFTs or recent culture results, they were coded as unknown and left in the analysis. This preserved sample size but could have inadvertently diminished or exaggerated an effect that would have been seen. When variables were missing data and the unknown category was found to be significantly different than the known categories, those individuals were excluded from the final model.

Non-validated quality of life metrics

While the SGRQ is validated for many respiratory diseases including bronchiectasis, there is no literature suggesting it is presently validated for NTM disease. There are other questionnaires gaining traction that may serve as better metrics including the QOL-B survey as well as the QOL-B-NTM survey which specifically looks at quality of life in NTM patients. These are newer metrics and will be studied in this cohort in the future.

Potential confounding

There likely exists confounding that was not accounted for. Specifically, information regarding treatment was distilled down to treated in the past, presently on treatment during enrollment, and never treated. This did not include for confounding variables such as total duration of treatment, number of treatments failed, number of regimens, treatments that were IDSA/ATS recommended or other, whether additional adjuvant medications were used, and whether drug level troughs were appropriate. Further exploration of these individual components could constitute an independent research project of its own.

Culture data was also simplified in this study as the data were preliminary. The number of cultures taken during the follow-up period were not identified. Individuals with a higher burden of disease could potentially have more cultures taken at regular intervals. Others may have been due for a routine culture. It is possible that simple by testing samples more frequently that one increases the sensitivity and likelihood that a positive result is detected, whether or not those results are sustained. There are also occasions were multiple samples were given on one day and a portion have positive results and others have negative results; in these circumstances the positive result was noted for that date. However, it is unclear if these results should be treated as if the positive result is a contaminant or incidental finding if there are negative results from the same day.

Selection bias

Selection bias is probable in this study as all patients were recruited through two primary methods: clinician referral or self-referral after being identified by state surveillance. Clinician referral likely occurs more regularly in specialized practitioners such as infectious diseases or

pulmonology as they are aware of the services and studies at OHSU. Additionally, OHSU is geographically located in the northwest part of Oregon which could be difficult for patients to travel to if they are not in the immediate vicinity. While Oregon's population is also concentrated in this area, there are likely other patients who live farther away and there is a greater obstacle for these patients to attend a visit and be enrolled in a study at OHSU. Involving remote sites and physicians in this study could improve access to these studies from all Oregonians.

Information bias

The concern for information lies primarily in whether patients were accurately classified as "non-cases". In patients whose reason for not meeting case criteria from only having one positive sputum culture, it is possible that in individuals who have only had one culture, that they would continue to have positive cultures if that were tested. There was not an examination on whether these individuals simply had negative cultures in the subsequent period after initial isolation, in which case their designation as non-cases holds, or whether there was only a total of one sputum culture obtained and more information and testing may be needed to determine whether that patient meets case criteria. Overall, individuals who were misclassified as non-cases might be earlier in their disease course, have a lower burden of disease, or fewer complications so if they were categorized correctly as NTM cases this may diminish some effects seen in this analysis. It is unlikely that a patient was misclassified as NTM case as the criteria are well-outlined and these diagnoses were confirmed by individual performing chart review; thus, if there is misclassification it would be differential in nature.

CONCLUSION

In spite of limitations, there exist several notable findings from this study. Among NTM cases, not only is male gender less common in patients but it also is associated with a better quality of life. Quality of life remains poor among obese patients, former smokers, and the youngest and oldest patients. Patients with a past history of immunosuppressive use had a markedly more impaired quality of life. And while COPD and cavitary lesions independently were associated with less impaired, the coexistence of both in a patient is associated with poor quality of life. Findings differ in non-cases, where only patients over 70 years old were associated with a worse quality of life while those with bronchiectasis had less impairment.

Substantial work needs to be completed to better characterize the natural history of NTM in terms of microbial findings. While this study did not note any factors associated with culture conversion, its results are limited by a small sample size and a homogenous population among those with the outcome of interest.

The overarching prospective dataset is still growing, and upon its completion, many more studies characterizing the NTM disease course and predictors for impaired quality of life will be identified. For now, information is still lacking to provide patients with accurate and individualized counseling regarding their anticipated disease course. While this study identified factors associated with impaired quality of life, more work characterizing the disease in different subsets of individuals will lead to more informed patient care and better optimized interventions in the treatment of NTM pulmonary disease.

REFERENCES

1. 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(4):367-416. doi:10.1164/rccm.200604-571ST.

2. Johnson MM, Odell JA. Nontuberculous mycobacterial pulmonary infections. *J Thorac Dis*. 2014;6(3):210-220. doi:10.3978/j.issn.2072-1439.2013.12.24.

3. Griffith DE. Nontuberculous mycobacterial lung disease. *Curr Opin Infect Dis*. 2010;23(2):185-190. doi:10.1097/QCO.0b013e328336ead6.

4. Aksamit TR, Philley J V, Griffith DE. Nontuberculous mycobacterial (NTM) lung disease: The top ten essentials. *Respir Med*. 2014;108(3):417-425. doi:10.1016/j.rmed.2013.09.014.

5. Cassidy PM, Hedberg K, Saulson A, McNelly E, Winthrop KL. Nontuberculous Mycobacterial Disease Prevalence and Risk Factors: A Changing Epidemiology. *Clin Infect Dis*. 2009;49(12):e124-e129. doi:10.1086/648443.

6. Winthrop KL, Varley CD, Ory J, Cassidy PM, Hedberg K. Pulmonary Disease Associated with Nontuberculosis Mycobacteria, Oregon, USA. *Emerg Infect Dis*. 2011;17(9):1759-1761. doi:10.1128/JVI.02118-09.

7. Winthrop KL. Pulmonary disease due to nontuberculous nycobacteria: an epidemiologist's

view. *Future Microbiol*. 2010;5:1517-1527. doi:10.1378/chest.15-0458.

8. Iseman MD, Marras TK. The importance of nontuberculous mycobacterial lung disease. *Am J Respir Crit Care Med*. 2008;178(10):999-1000. doi:10.1164/rccm.200808-1258ED.

9. Kim RD, Greenberg DE, Ehrmantraut ME, et al. Pulmonary nontuberculous mycobacterial disease: Prospective study of a distinct preexisting syndrome. *Am J Respir Crit Care Med*. 2008;178(10):1066-1074. doi:10.1164/rccm.200805-686OC.

10. Ryu YJ, Koh WJ, Daley CL. Diagnosis and treatment of nontuberculous mycobacterial lung disease: Clinicians' perspectives. *Tuberc Respir Dis (Seoul)*. 2016;79(2):74-84. doi:10.4046/trd.2016.79.2.74.

11. 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(6):1605-1609. doi:10.1378/chest.101.6.1605.

12. Winthrop KL, Mcnelley E, Kendall B, et al. Pulmonary Nontuberculous Mycobacterial Disease Prevalence and Clinical Features An Emerging Public Health Disease. 2006;2006(4):2005-2006. doi:10.1164/rccm.201003-0503OC.

13. Griffith DE, Aksamit TR. Therapy of refractory nontuberculous mycobacterial lung disease. *Curr Opin Infect Dis*. 2012;25(2):218-227. doi:10.1097/QCO.0b013e3283511a64.

14. Nelson KG, Griffith DE, Brown BA, Wallace RJ. Results of operation in Mycobacterium

avium-intracellulare lung disease. *Ann Thorac Surg*. 1998;66(2):325-330. doi:10.1016/S0003-4975(98)00401-9.

15. Griffith DE. Therapy of nontuberculous mycobacterial disease. *Curr Opin Infect Dis*. 2007;20(0951-7375):198-203. doi:10.1097/QCO.0b013e328055d9a2.

16. Benwill J, Wallace Jr. R. Mycobacterium abscessus: challenges in diagnosis and treatment. *Curr Opin Infect Dis*. 2014;6(6):506-510. doi:10.1128/JCM.00753-12.

17. Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation. *Am Rev Respir Dis*. 1992;145(6):1321-1327. doi:10.1164/ajrccm/145.6.1321.

18. England LJ, Kim SY, Shapiro-Mendoza CK, et al. Effects of maternal smokeless tobacco use on selected pregnancy outcomes in Alaska Native women: a case-control study. *Acta Obstet Gynecol Scand*. 2013;92(6):648-655. doi:10.1111/aogs.12124.

19. Jones PW. Interpreting thresholds for a clinically significant change in health status in asthma and COPD. *Eur Respir J*. 2002;19(3):398-404. doi:10.1183/09031936.02.00063702.

20. Mehta M, Marras TK. Impaired health-related quality of life in pulmonary nontuberculous mycobacterial disease. *Respir Med*. 2011;105(11):1718-1725. doi:10.1016/j.rmed.2011.08.004.

21. Maekawa K, Ito Y, Imai S, et al. Validation of the St. George Respiratory Questionnaire

in pulmonary mycobacterium avium complex disease. *Am J Respir Crit Care Med*. 2010;181:A2597.

22. Jones PW. *St. George's Respiratory Questionnaire Guide*.; 2009. doi:10.1136/thx.2010.139121.Development.

23. Yeager H. The Lady Windermere syndrome: Is there a racial as well as a gender bias? *Chest*. 2008;134(4):889-890. doi:10.1378/chest.08-1428.

24. Panagiotou M, Papaioannou AI, Kostikas K, et al. Epidemiology of pulmonary nontuberculous mycobacteria: data from a general hospital in Athens, Greece, 2007 - 2013. *Pulm Med*. 2014;2014:9. doi:10.1155/2014/894976.

25. Wallace Jr. RJ, O'Brien R, Glassroth J, Raleigh J, Dutt A. Diagnosis and treatment of disease caused by nontuberculous mycobacteria. 1990;142(20):940-953.

26. Ferrer M, Villasante C, Alonso J, et al. Interpretation of quality of life scores from the St. George's Respiratory Questionnaire. *Eur Respir J*. 2002;19(3):405-413. doi:10.1183/09031936.02.00213202.

27. Padilla A, Olveira G, Olveira C, et al. Validity and reliability of the St. George's Respiratory Questionnaire in adults with cystic fibrosis. *Arch Bronconeumol*. 2007;43(4):205-211. doi:10.1016/S1579-2129(07)60052-4.

28. Kolotkin RL, Meter K, Williams GR. Quality of life and obesity. *Obes Rev*. 2001;2(4):219-229. doi:10.1111/j.1467-789X.2001.00040.x.

29. Jia H, Lubetkin EI. The impact of obesity on health-related quality-of-life in the general adult US population. *J Public Health (Bangkok)*. 2005;27(2):156-164. doi:10.1093/pubmed/fdi025.

FIGURES

FIGURE 1. Study timeline and data sources

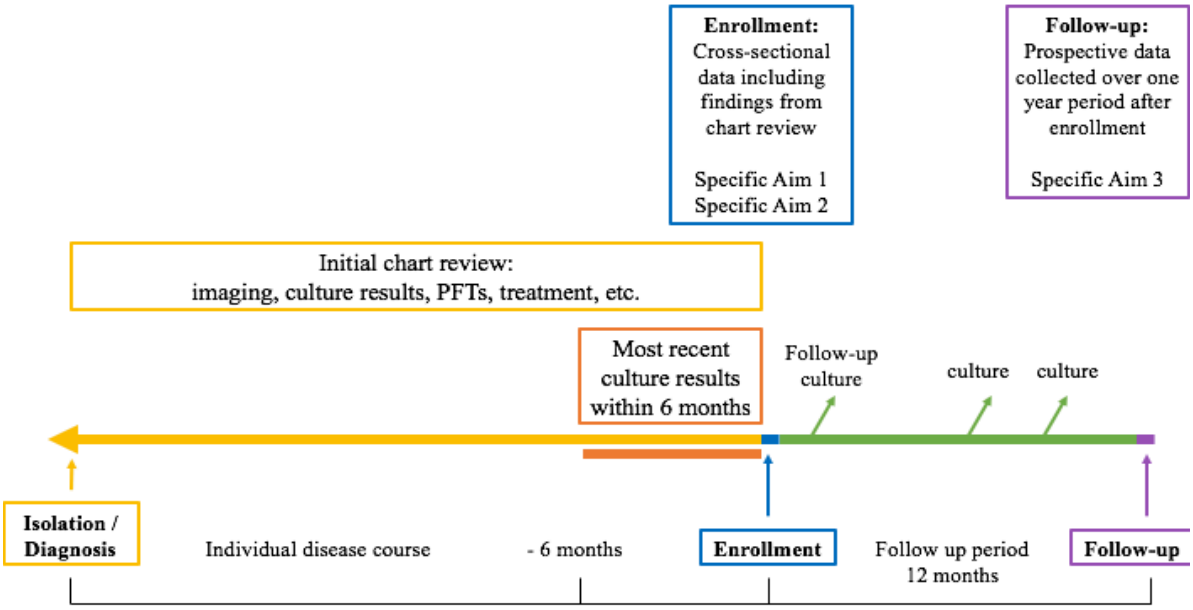


FIGURE 2. Study subject origin

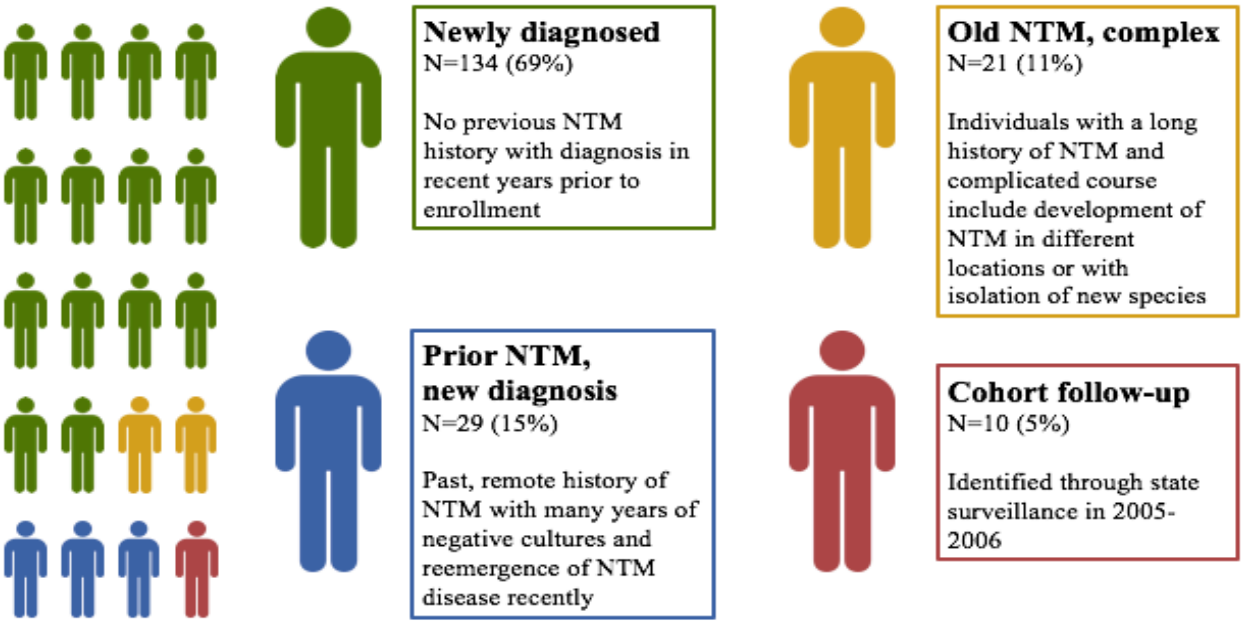


FIGURE 3. Study subject selection

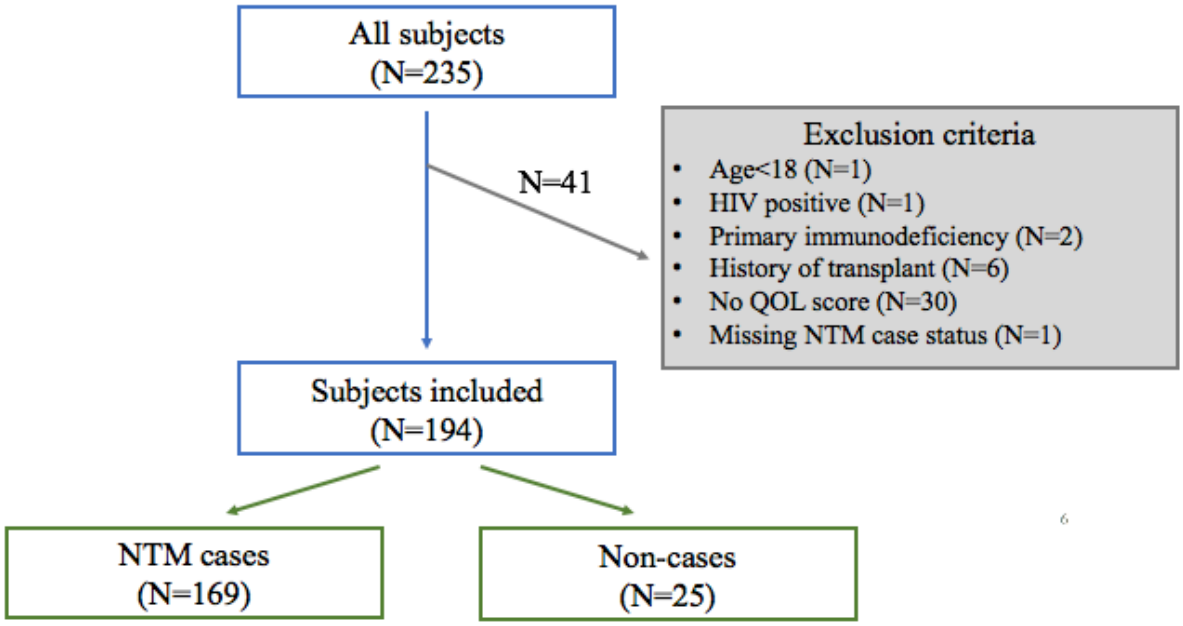


FIGURE 4. Culture follow-up outcomes

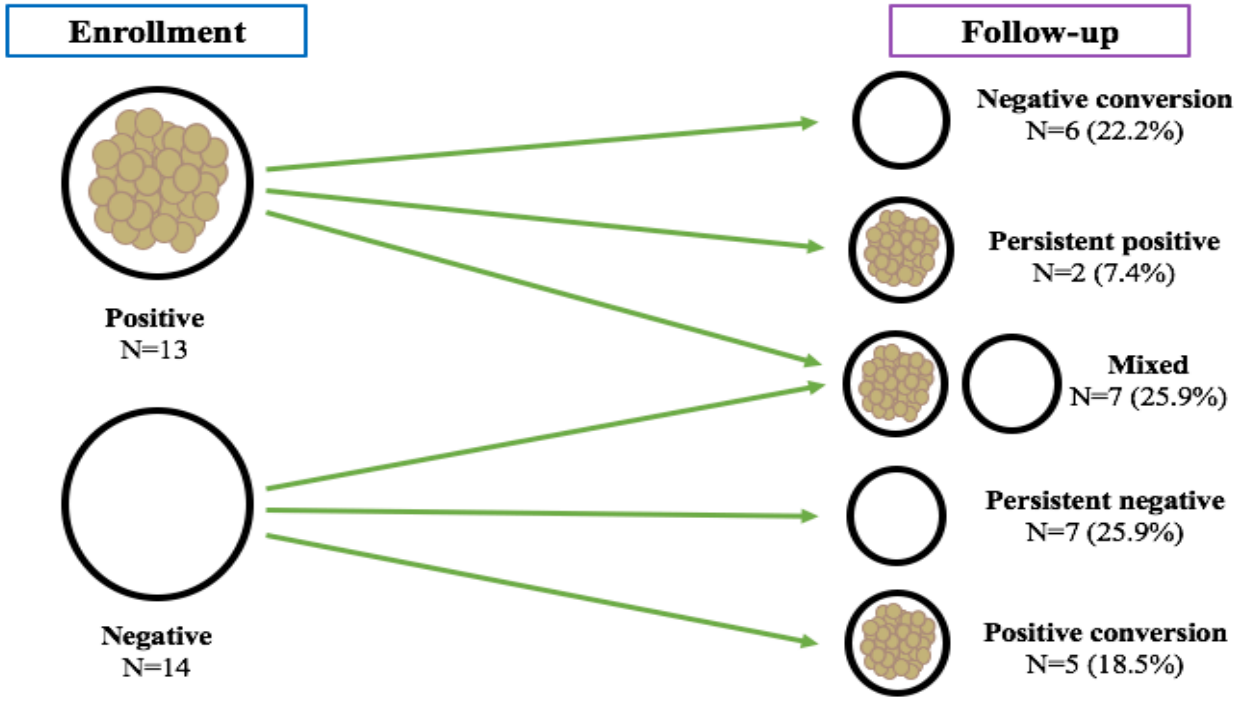
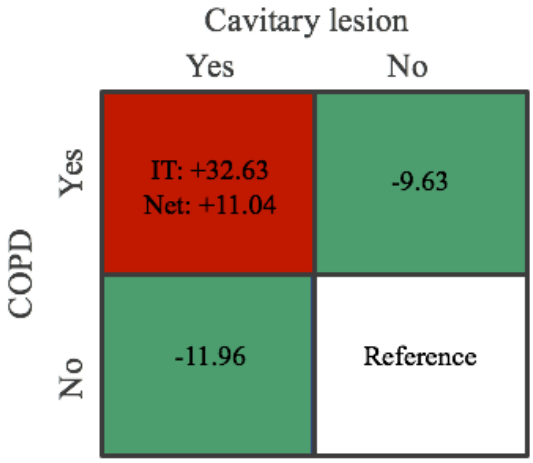


FIGURE 5. Representation of interaction between COPD and cavitary lesions



- Net effect of interaction with independent variables
  - COPD=1: -9.63
  - Cav=1: -11.96
  - COPD*Cav= +32.63
  - *Net*: +11.04
- More impaired QOL
  - Those with a cavitary lesion on imaging who did have COPD had a +11 point net higher score (worse QOL) than those without a cavitary lesion that did not have COPD, due to an interaction between COPD and cavitary lesions ($p<0.001$).
- Less impaired QOL
  - COPD patients without a cavitary lesion had a 9.6 point lower score (better QOL) than those without COPD ($p=0.036$)
  - Those with a cavitary lesion on imaging who did not have COPD had a 12.0 point lower score (better score) than non-COPD patients without a cavitary lesion ($p=0.002$)

TABLES

TABLE 1. Demographic and clinical population characteristics among study participants. A total of 194 participants were utilized in the analysis.

	N=194
Gender, No. (%)	
Female	152 (77.5)
Male	43 (22.2)
Age in years, No. (%)	
<50	24 (12.4)
50-59	23 (11.9)
60-69	58 (29.9)
70-79	64 (33.0)
≥80	25 (12.9)
Race, No. (%)	
White	176 (90.7)
Nonwhite	8 (4.1)
Unknown	10 (5.2)
Body mass index in kg/m^2, No. (%)	
Underweight	28 (14.7)
Normal	121 (63.4)
Overweight	29 (15.2)
Obese	13 (6.8)
Smoking history, No. (%)	
Nonsmoker	104 (53.6)
Current	9 (4.6)
Former	81 (41.8)
NTM case criteria met, No. (%)	
No	25 (12.9)
Yes	159 (87.1)
Disease duration in years, No. (%)	
<1	31 (19.0)
1-3	71 (42.5)
3-5	22 (13.2)
5-7	18 (10.8)
7-9	7 (4.2)
≥9	18 (10.8)
Pulmonary comorbidities, No. (%)	
Bronchiectasis	157 (80.9)
Chronic obstructive pulmonary disease	59 (30.4)
Asthma	51 (26.3)
Immunosuppressive treatment history, No. (%)	
Never	136 (70.1)
Past	16 (8.3)
Present	9 (4.6)
Unknown	33 (17.0)
Antimycobacterial treatment history, No. (%)	
Never	75 (38.7)
Past	45 (23.2)
Present	74 (38.1)
Last culture result within 6 months, No. (%)	
Negative	68 (35.1)

Positive	32 (16.5)
No culture	94 (48.4)
NTM species, No. (%)	
Mycobacterium avium complex	115 (59.3)
Mycobacterium abscessus	4 (2.1)
None	75 (38.7)
Radiographic findings, No. (%)	
Bronchiectasis	146 (75.3)
Cavitary lesion	61 (31.4)
FEV1 % predicted on last spirometry, No. (%)	
Normal ≥80%	62 (32.0)
Impaired <80%	72 (37.1)
Unknown	60 (30.9)
FEV1/FVC ratio on last spirometry, No. (%)	
Normal ≥70%	63 (32.5)
Impaired <70%	68 (35.1)
Unknown	63 (32.5)
Quality of Life Metrics	
St. George's Respiratory Questionnaire (±SD)	
Total score	30.8 (±20.3)

TABLE 2. Demographic and clinical population characteristics among study participants, stratified by NTM case status. NTM case status is determined by a set of guidelines published by the IDSA/ATS (see Appendix A). A total of 194 participants were utilized in the analysis

	NTM cases N=169	Non-cases N=25	p-value
Gender, No. (%)			0.45
Female	133 (78.7)	18 (72.0)	
Male	36 (21.3)	7 (28.0)	
Age in years, No. (%)			0.023*
<50	18 (10.7)	6 (24.0)	
50-59	23 (13.6)	0 (0.0)	
60-69	50 (29.6)	8 (32.0)	
70-79	53 (31.4)	11 (44.0)	
≥80	25 (14.8)	0 (0.0)	
Race, No. (%)			0.96
White	153 (90.5)	23 (92.0)	
Nonwhite	7 (4.1)	1 (4.0)	
Unknown	9 (5.3)	1 (4.0)	
Body mass index in kg/m^2, No. (%)			0.74
Underweight	25 (15.0)	3 (12.5)	
Normal	104 (62.3)	17 (70.8)	
Overweight	27 (16.2)	2 (8.3)	
Obese	11 (6.6)	2 (8.3)	
Smoking history, No. (%)			0.10
Nonsmoker	94 (55.6)	10 (40.0)	
Current	9 (5.3)	0 (0.0)	
Former	66 (39.1)	15 (60.0)	
Bronchiectasis, No. (%)			0.021*
No	28 (16.6)	9 (36.0)	
Yes	141 (83.4)	16 (64.0)	
Chronic obstructive pulmonary disease, No. (%)			0.52
No	119 (70.4)	16 (64.0)	
Yes	50 (29.6)	9 (36.0)	
Asthma, No. (%)			0.44
No	123 (72.8)	20 (80.0)	
Yes	46 (27.2)	5 (20.0)	
Immunosuppressive treatment history, No. (%)			0.62
Never	116 (68.6)	20 (80.0)	
Past	14 (8.3)	2 (8.0)	
Present	8 (4.7)	1 (4.0)	
Unknown	31 (18.3)	2 (8.0)	
Antimycobacterial treatment history, No. (%)			<0.001*
Never	53 (31.4)	22 (88.0)	
Past	43 (25.4)	2 (8.0)	
Present	73 (43.2)	1 (4.0)	
Last culture result within 6 months, No. (%)			0.056
Negative	54 (32.0)	14 (56.0)	
Positive	30 (17.8)	2 (8.0)	
No culture	85 (50.3)	9 (36.0)	
NTM species, No. (%)			0.33
Mycobacterium avium complex	97 (57.4)	18 (72.0)	
Mycobacterium abscessus	4 (2.4)	0 (0.0)	

None	68 (40.2)	7 (28.0)	
Bronchiectasis on CT imaging, No. (%)			0.37
Absent	40 (23.7)	8 (32.0)	
Present	129 (76.3)	17 (68.0)	
Cavitary lesion on imaging, No. (%)			0.39
Absent	114 (67.5)	19 (76.0)	
Present	55 (32.5)	6 (24.0)	
FEV1 % predicted on last spirometry, No. (%)			0.60
Normal ≥ 80%	53 (31.4)	9 (36.0)	
Impaired <80%	65 (38.5)	7 (28.0)	
Unknown	51 (30.2)	9 (36.0)	
FEV1/FVC ratio on last spirometry, No. (%)			0.45
Normal ≥ 70%	53 (31.4)	10 (40.0)	
Impaired <70%	62 (36.7)	6 (24.0)	
Unknown	54 (32.0)	9 (36.0)	
Quality of Life Metrics			
St. George's Respiratory Questionnaire (±SD)			0.68
Total score	31.0 (±20.8)	29.3 (±16.7)	

TABLE 3. Population characteristics of patients with culture results over the one year follow-up period. Comparisons are made between those participants who at enrollment had positive cultures then converted solely to negative cultures, referred to as "negative conversion" (N=6), in follow-up period compared to all others who did not negatively convert (N=21).

	Conversion N=6	Others N=21	P-value
Gender, No. (%)			0.19
Female	6 (100.0)	16 (76.2)	
Male	0 (0.0)	5 (23.8)	
Age in years, No. (%)			0.66
<50	1 (16.7)	1 (4.8)	
50-59	-	5 (23.8)	
60-69	2 (33.3)	6 (28.6)	
70-79	2 (33.3)	6 (28.6)	
>80	1 (16.7)	3 (14.3)	
Race, No. (%)			0.59
White	6 (100.0)	20 (95.2)	
Nonwhite	0 (0.0)	1 (4.8)	
Body mass index in kg/m^2, No. (%)			0.56
Underweight	1 (16.7)	1 (75.0)	
Normal	5 (83.3)	15 (5.0)	
Overweight	0 (0.0)	3 (15.0)	
Obese	0 (0.0)	1 (5.0)	
Smoking history, No. (%)			0.85
Nonsmoker	4 (66.7)	14 (66.7)	
Current	0 (0.0)	1 (4.8)	
Former	2 (33.3)	6 (28.6)	
Pulmonary comorbidities, No. (%)			
Bronchiectasis	6 (100.0)	19 (90.5)	0.43
Chronic obstructive pulmonary disease	0 (0.0)	8 (38.1)	0.07
Asthma	1 (16.7)	5 (23.8)	0.71
Immunosuppressive treatment history, No. (%)			0.22
Never	4 (66.7)	14 (66.7)	
Past	1 (16.7)	0 (0.0)	
Present	0 (0.0)	3 (14.3)	
Unknown	1 (16.7)	4 (19.1)	
Antimycobacterial treatment history, No. (%)			0.40
Never	0 (0.0)	2 (9.5)	
Past	3 (50.0)	5 (23.8)	
Present	3 (50.0)	14 (66.7)	
Radiographic findings, No. (%)			
Bronchiectasis	5 (83.3)	18 (85.7)	0.89
Cavitary lesion	4 (66.7)	10 (47.6)	0.41
FEV1 % predicted on last spirometry, No. (%)			0.73
Normal ≥80%	1 (16.7)	3 (14.3)	
Impaired <80%	4 (66.7)	11 (52.4)	
Unknown	1 (16.7)	7 (33.3)	
FEV1/FVC ratio on last spirometry, No. (%)			0.44
Normal ≥70%	3 (50.0)	5 (23.8)	
Impaired <70%	2 (33.3)	9 (42.9)	
Unknown	1 (16.7)	7 (33.3)	
Quality of Life Metrics			
St. George's Respiratory Questionnaire (±SD)			0.58

Total score	22.8 (±20.1)	28.5 (±22.3)	

ANOVA and Chi-squared tests were used to compare for baseline differences between the two groups. No significant differences exist between the negative converter group and others at the 5% level.

TABLE 4. Total, symptoms, activity, and impacts SGRQ scores by gender, comorbid bronchiectasis, comorbid COPD and smoking history.

	Symptoms Score		Activity Score		Impacts Score		Total Score	
	Mean (SD)	**Range**	**Mean (SD)**	**Range**	**Mean (SD)**	**Range**	**Mean (SD)**	**Range**
Gender								
Female	38.9 (23.5)	0.0 – 94.9	38.5 (27.1)	0.0 – 100.0	21.5 (17.4)	0.0 – 75.4	29.5 (19.4)	0.0 – 78.8
Male	42.7 (24.1)	0.0 – 94.8	45.6 (29.2)	0.0 – 100.0	27.2 (21.7)	0.0 – 87.4	35.3 (22.6)	0.0 – 92.5
Bronchiectasis								
No	41.4 (22.0)	0.0 – 90.3	48.2 (27.2)	0.0 – 92.5	25.1 (17.3)	0.0 – 61.1	34.8 (18.6)	0.7 – 74.0
Yes	39.3 (24.0)	0.0 – 94.9	38.1 (27.5)	0.0 – 100.0	22.2 (18.8)	0.0 – 87.4	29.9 (20.6)	0.0 – 92.5
COPD								
No	36.1 (23.1)	0.0 – 94.9	34.9 (26.4)	0.0 – 100.0	19.4 (16.0)	0.0 – 63.0	26.9 (18.3)	0.0 – 78.8
Yes	48.0 (23.0)	0.0 – 94.8	51.8 (27.0)	0.0 – 100.0	30.3 (21.6)	0.0 – 87.4	39.8 (21.7)	0.0 – 92.5
Smoking history								
Never	36.4 (22.6)	0.0 – 94.9	33.3 (26.2)	0.0 – 87.2	18.2 (15.7)	0.0 – 57.4	25.8 (17.9)	0.0 – 69.3
Current	51.2 (18.0)	25.2 – 90.5	65.1 (27.2)	12.1 – 93.3	38.9 (25.7)	3.5 – 77.3	48.9 (23.3)	9.7 – 84.3
Past	42.7 (24.8)	0.0 – 94.8	45.9 (26.9)	0.0 – 92.5	26.8 (19.3)	0.0 – 87.4	35.2 (20.8)	0.0 – 92.5

TABLE 5. Univariate analysis using simple linear regression for SGRQ total score and all covariates among NTM cases. Covariates with p-value <0.25 were selected for multivariable model building.

	Variable Type	SGRQ mean	SGRQ Std. Dev.	Coefficient	Std. Err.	p-value
Gender	dichotomous					
Female		29.43	19.94	Reference	-	-
Male		37.01	22.89	7.59	3.87	0.052*
Age in years	categorical					0.11*
<50		31.17	18.82	Reference	-	-
50-59		27.03	26.25	-4.14	6.47	0.52
60-69		35.66	21.09	4.49	5.65	0.43
70-79		26.18	19.10	-4.99	5.60	0.38
>80		35.71	17.49	4.55	6.35	0.48
Race	categorical					
White		31.16	21.1	Reference	-	-
Nonwhite		33.15	16.02	1.99	8.07	0.81
Unknown		27.30	20.30	-3.87	7.16	0.59
Body mass index in kg/m^2	categorical					0.20*
Underweight		32.11	24.74	3.16	4.58	0.49
Normal		27.95	18.81	Reference	-	-
Overweight		31.46	20.89	2.51	4.44	0.57
Obese		56.28	4.76	13.77	6.51	0.036*
Smoking history						<0.001*
Nonsmoker		25.68	18.52	Reference	-	-
Current		48.92	23.33	23.24	6.91	0.001*
Former		36.23	21.07	10.55	3.18	0.001*
Disease duration in years	categorical					0.91
<1		34.01	16.83	Reference	-	-
1-3		30.13	21.33	-3.88	4.48	0.39
3-5		32.17	21.02	-1.83	5.80	0.75
5-7		29.50	21.17	-4.50	6.17	0.47
7-9		26.42	17.93	-7.59	8.71	0.39
≥9		28.28	24.75	-5.72	6.16	0.36
Bronchiectasis	dichotomous					
No		34.37	19.92	Reference	-	-
Yes		30.38	20.94	-3.99	4.30	0.35
COPD	dichotomous					
No		27.17	18.87	Reference	-	-
Yes		40.25	22.32	13.08	3.36	<0.001*
Asthma	dichotomous					
No		30.46	20.78	Reference	-	-
Yes		32.60	20.88	2.15	3.59	0.55
Immunosuppressive treatment	categorical					0.045*
Never		28.83	18.58	Reference	-	-
Past		44.19	29.13	15.36	5.79	0.009*
Present		27.32	16.52	-1.51	7.48	0.84
Unknown		34.34	23.38	5.52	4.14	0.18*
Antimycobacterial treatment	categorical					0.60
Never		32.59	20.92	Reference	-	-
Past		28.37	19.44	-4.22	4.27	0.33
Present		31.48	21.53	-1.11	3.76	0.77
Last culture result within 6 months	categorical					0.42
Negative		29.73	21.34	Reference	-	-

Positive		27.78	18.08	-1.95	4.73	0.68
No culture		33.02	21.30	3.29	3.62	0.37
NTM species	categorical					0.52
None		28.80	19.10	Reference	-	-
Mycobacterium avium complex		32.54	21.89	3.74	3.29	0.26
Mycobacterium abscessus		32.71	22.04	3.91	10.71	0.72
Bronchiectasis on CT imaging	dichotomous					
No		34.24	22.19	Reference	-	-
Present		30.05	20.30	-4.20	3.76	0.27
Cavitary lesion on imaging	dichotomous					
No		28.63	18.47	Reference	-	-
Present		36.03	24.30	7.40	3.37	0.03*
FEV1 % predicted on last spirometry	categorical					0.07*
Normal ≥ 80%		25.90	16.24	Reference	-	-
Impaired <80%		34.68	23.15	8.78	3.81	0.022*
Unknown		31.74	21.06	5.84	4.03	0.15*
FEV1/FVC ratio on last spirometry	categorical					0.009*
Normal ≥ 70%		24.43	16.58	Reference	-	-
Impaired <70%		36.16	22.43	11.73	3.80	0.002*
Unknown		31.65	21.07	7.21	3.93	0.068*

Variables selected for inclusion into multivariable modeling given a p-value <0.25 were gender, age, BMI, smoking history, COPD, immunosuppressive treatment history, AFB smear, cavitary lesion, FEV1, and FEV1/FVC ratio.

TABLE 6. Final multivariate linear regression model for factors associated with SGRQ total score in NTM cases (n=161, p<0.001*).

	Coefficient	Std. Err.	95% CI Lower Limit	95% CI Upper Limit	p-value
Gender					
Female	Reference	-	-	-	-
Male	-8.13	3.86	-15.77	-0.50	0.037*
Age in years					
<50	Reference	-	-	-	-
50-59	-19.95	5.28	-30.38	-9.52	<0.001*
60-69	-3.86	4.70	-13.16	5.44	0.41
70-79	-9.78	4.62	-18.91	-0.65	0.036*
>80	0.21	5.17	-10.01	10.43	0.97
Body mass index in kg/m^2					
Underweight	-3.22	3.82	-10.76	4.33	0.40
Normal	Reference	-	-	-	-
Overweight	-4.89	3.77	-12.33	2.56	0.20
Obese	15.17	5.82	3.66	26.68	0.01*
Smoking history					
Nonsmoker	Reference	-	-	-	-
Current	16.64	7.51	1.80	31.48	0.028*
Former	5.79	2.90	0.06	11.52	0.048*
COPD					
No	Reference	-	-	-	-
Yes	-9.63	4.56	-18.64	-0.63	0.036*
Immunosuppressive treatment history					
Never	Reference	-	-	-	-
Past	24.61	6.98	10.92	38.29	0.001*
Present	-6.83	6.89	-20.43	6.77	0.32
Unknown	-5.32	4.16	-13.59	2.94	0.21
Cavitary lesion on imaging					
No	Reference	-	-	-	-
Present	-11.96	3.70	-19.27	-4.65	0.002*
FEV1 % predicted on last spirometry					
Normal ≥ 80%	Reference	-	-	-	-
Impaired <80%	1.32	3.42	-5.44	8.08	0.82
Unknown	5.91	8.46	-10.83	22.64	0.49
FEV1/FVC ratio on last spirometry					
Normal ≥ 70%	Reference	-	-	-	-
Impaired <70%	5.73	3.53	-1.26	12.73	0.11
Unknown	1.20	8.42	-15.44	17.84	0.89
COPD*Immuno treatment					
COPD*past	-16.61	11.13	-38.62	5.41	0.14
COPD*present	-	-	-	-	-
COPD*unknown	32.41	7.37	17.83	46.98	<0.001*
COPD*Cavitary lesion					
COPD*Cavitary lesion present	32.63	6.58	19.60	45.65	<0.001*

Final multivariate linear regression model characteristics. N=161, p<0.001. R2=0.458 with adjusted R2=0.372. 8 outliers were removed from the final analysis which improved the fit. Factors significantly associated with more impaired quality of life were obesity, past smoking history, current smoking history and past immunosuppressive medication use. Factors significantly associated with less quality of life impairment were male gender, ages 50-59 or 70-79, and cavitary lesion on imaging. Interactions were significant between COPD and those with unknown immunosuppressive status (worse quality of life) as well as COPD and cavitary lesions (worse quality of life).

TABLE 7. Univariate analysis using simple linear regression for SGRQ total score and all covariates among non-cases.

	Variable Type	SGRQ Mean	SGRQ Std. Dev.	Coefficient	Std. Err.	p-value
Gender	dichotomous					
Female		30.25	15.78	Reference	-	-
Male		26.67	20.08	-3.58	7.58	0.64
Age in years	categorical					0.031*
<50		20.22	9.96	Reference	-	-
60-69		22.86	14.62	2.64	5.65	0.43
70-79		38.82	17.03	-4.99	5.60	0.38
Race	categorical					0.33
White		30.73	16.62	Reference	-	-
Nonwhite		11.64	-	-19.10	16.98	0.27
Unknown		12.64	-	-18.10	16.98	0.30
Body mass index in kg/m^2	categorical					0.68
Underweight		37.29	25.83	9.75	10.56	0.37
Normal		27.54	13.54	Reference	-	-
Overweight		37.23	34.77	9.69	12.61	0.45
Obese		35.72	14.55	8.19	12.61	0.52
Smoking history	dichotomous					
Never		26.90	11.66	Reference	-	-
Former		30.81	19.64	3.91	6.93	0.58
Bronchiectasis	dichotomous					
No		36.16	14.44	Reference	-	-
Yes		25.36	17.10	-10.80	6.75	0.123
COPD	dichotomous					
No		24.89	14.09	Reference	-	-
Yes		36.99	19.03	12.10	6.65	0.082
Asthma	dichotomous					
No		27.48	17.56	Reference	-	-
Yes		36.34	11.65	8.86	8.34	0.30
Immunosuppressive treatment	categorical					0.45
Never		28.81	16.97	Reference	-	-
Past		20.18	21.02	-8.63	12.47	0.50
Present		53.83	-	25.03	17.24	0.16*
Unknown		30.46	5.04	1.65	12.47	0.90
Antimycobacterial treatment	categorical					0.60
Never		28.12	15.66	Reference	-	-
Past		24.08	15.50	-4.04	11.56	0.73
Present		64.50	-	36.39	16.01	0.033*
Last culture result within 6 months	categorical					0.67
Negative		31.18	18.19	Reference	-	-
Positive		19.70	8.61	-11.48	12.97	0.39
No culture		28.37	16.20	-2.81	7.33	0.71
Bronchiectasis on CT	dichotomous					
No		37.46	14.86	Reference	-	-
Yes		25.39	16.54	-12.08	6.88	0.09
Cavitary lesion on imaging	dichotomous					
No		28.15	15.83	Reference	-	-
Yes		32.73	20.53	4.58	7.95	0.57
FEV1 % predicted on last spirometry	categorical					0.20

Normal ≥ 80%		22.30	12.04	Reference	-	-
Impaired <80%		37.45	20.59	15.16	8.19	0.078
Unknown		29.82	16.22	7.52	7.66	0.34
FEV1/FVC ratio on last spirometry	categorical					
Normal ≥ 70%		22.27	12.32	Reference	-	-
Impaired <70%		40.02	20.30	17.74	8.19	0.041*
Unknown		29.82	16.22	7.54	7.29	0.31

TABLE 8. Total SGRQ score by culture conversion among patients with follow-up culture results (N=27).

	N	Culture result at enrollment	Culture result during follow-up	Mean (points)	SD (points)
Persistent negative	7	Negative	Negative only	21.5	18.1
Persistent positive	2	Positive	Positive only	30.2	41.7
Conversion	5	Positive	Negative only	22.8	20.1
Reversion	6	Negative	Positive only	41.8	29.9
Mixed cultures	7	Negative or Positive	Negative and Positive	25.4	15.2
One-way ANOVA did not demonstrate statistically significant different means among the culture conversion groups (p=0.57).					

TABLE 9. Univariate analysis using simple logistic regression for culture conversion and all covariates. The variables age, race, COPD, and immunosuppressive treatment were not included.

	Variable Type	Coefficient	Std. Err.	p-value	OR (95% CI)
Age in years	categorical				
<50		Reference	-	-	
60-69		-1.10	1.63	0.50	0.33 (0.01-8.18)
70-79		-1.10	1.63	0.50	0.33 (0.01-8.18)
>80		-1.10	1.83	0.55	0.33 (0.01-11.94)
Body mass index in kg/m^2	categorical				
Underweight		1.10	1.51	0.47	3.0 (0.15-57.36)
Normal		Reference	-	-	
Smoking history					
Nonsmoker		Reference	-	-	
Former		0.15	0.99	0.88	1.17 (0.17-8.19)
Asthma	dichotomous				
No		Reference	-	-	
Yes		-0.45	1.21	0.71	0.64 (0.06-6.85)
Antimycobacterial treatment history, No	categorical				
Never		Reference	-	-	
Past		1.03	0.97	0.29	2.8 (0.42-18.69)
Bronchiectasis on CT imaging	dichotomous				
No		Reference	-	-	
Present		-0.18	1.26	0.89	0.83 (0.07-9.86)
Cavitary lesion on imaging	dichotomous				
No		Reference	-	-	
Present		0.79	0.97	0.42	2.20 (0.33-14.73)
FEV1 % predicted on last spirometry	categorical				
Normal ≥ 80%		Reference	-	-	
Impaired <80%		0.09	1.29	0.95	1.09 (0.09-13.78)
Unknown		-0.85	1.57	0.59	0.43 (0.02-9.36)
FEV1/FVC ratio on last spirometry	categorical				
Normal ≥ 70%		Reference	-	-	
Impaired <70%		-0.99	1.07	0.35	0.37 (0.05-3.01)
Unknown		-1.44	1.30	0.27	0.24 (0.02-3.01)

APPENDICES

APPENDIX A. IDSA/ATS NTM Case Criteria

TABLE 3. CLINICAL AND MICROBIOLOGIC CRITERIA FOR DIAGNOSING NONTUBERCULOUS MYCOBACTERIAL LUNG DISEASE*

Clinical (both required)

1. Pulmonary symptoms, nodular or cavitary opacities on chest radiograph, or a high-resolution computed tomography scan that shows multifocal bronchiectasis with multiple small nodules (A, I)*

and

2. Appropriate exclusion of other diagnoses (A, I)

Microbiologic

1. Positive culture results from at least two separate expectorated sputum samples (A, II). If the results from (1) are nondiagnostic, consider repeat sputum AFB smears and cultures (C, III).

or

2. Positive culture result from at least one bronchial wash or lavage (C, III)

or

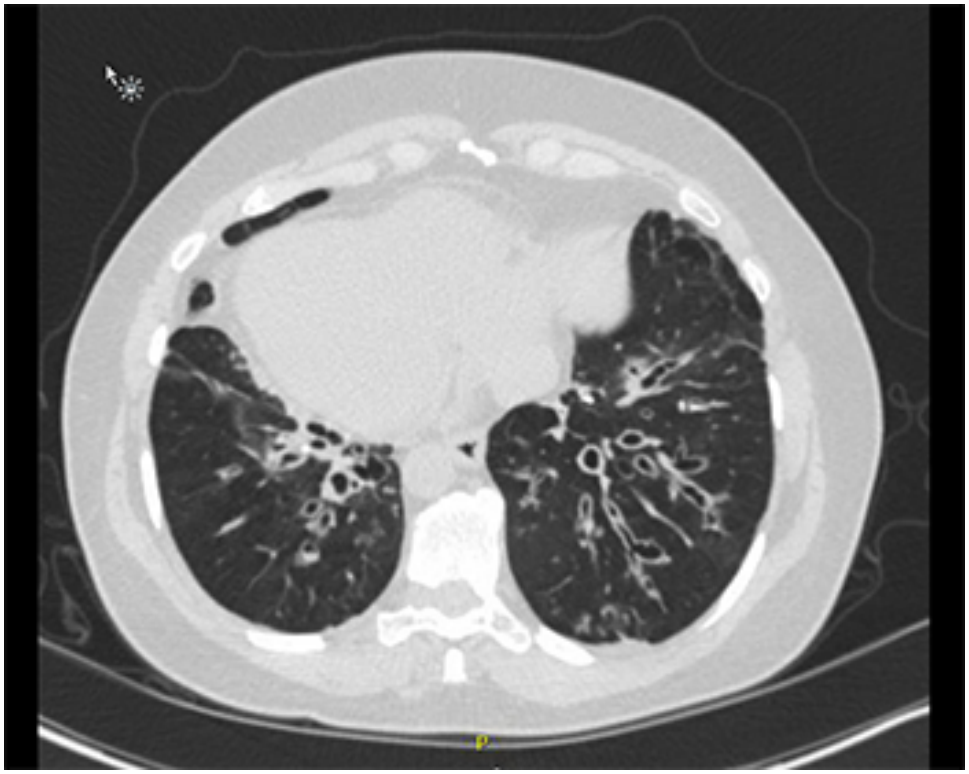
3. Transbronchial or other lung biopsy with mycobacterial histopathologic features (granulomatous inflammation or AFB) and positive culture for NTM or biopsy showing mycobacterial histopathologic features (granulomatous inflammation or AFB) and one or more sputum or bronchial washings that are culture positive for NTM (A, II)
4. Expert consultation should be obtained when NTM are recovered that are either infrequently encountered or that usually represent environmental contamination (C, III)
5. Patients who are suspected of having NTM lung disease but do not meet the diagnostic criteria should be followed until the diagnosis is firmly established or excluded (C, III)
6. Making the diagnosis of NTM lung disease does not, *per se*, necessitate the institution of therapy, which is a decision based on potential risks and benefits of therapy for individual patients (C, III)

* For evidence quality, *see* Table 1.

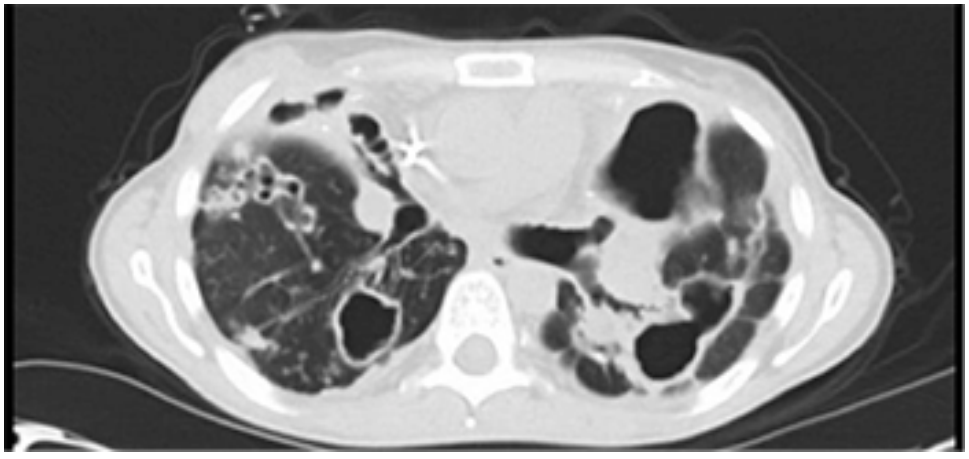
Griffith, David E., et al. "An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases." *American journal of respiratory and critical care medicine* 175.4 (2007): 367-416.

APPENDIX B. Imaging findings in NTM

Bronchiectasis



Fibrocavitary disease



Source: https://www.med.unc.edu/pulmonary/bronchiectasis/patient-care

APPENDIX C. St. George's Respiratory Questionnaire Guide 2009

1. A GUIDE TO THE SGRQ

What is the St George's Respiratory Questionnaire?

The SGRQ is designed to measure health impairment in patients with asthma and COPD. It is also valid for use in bronchiectasis and has been used successfully in patients with kyphoscoliosis and sarcoidosis. There is a report of its validation in a small study of adults with cystic fibrosis (Archivos de Bronconeumologia Volume 43, Issue 4, April 2007, pages 205-211). It is in two parts. Part I produces the Symptoms score, and Part 2 the Activity and Impacts scores. A Total score is also produced.

Part 1(Questions 1 to 8) covers the patients' recollection of their symptoms over a preceding period that may range 1 month to 1 year. It is not designed to be an accurate epidemiological tool, its purpose is to assess the patient's perception of their recent respiratory problems. The original version was validated using a 12-month recall period. More recently a 1 month recall version (appropriately worded) has been validated. This has slightly weaker psychometric properties than the 12-month version and produces a marginally lower Symptoms score and Total score. A 3-month recall period has been used very satisfactorily. In summary, the 3-month and 1-year versions provide the best properties, with no specific advantages to either. The 1-month version should only be used when the time frame of the study dictates.

Part 2 (Questions 9 to 16) addresses the patients' current state (i.e. how they are these days). The Activity score just measures disturbances to patients daily physical activity. The Impacts score covers a wide range of disturbances of psycho-social function. Validation studies showed that this component relates in part to respiratory symptoms, but it also correlates quite strongly with exercise performance (6-minute walking test), breathlessness in daily life (MRC breathlessness score) and disturbances of mood (anxiety and depression). The Impacts score is, therefore, the broadest component of the questionnaires, covering the whole range of disturbances that respiratory patients experience in their lives.

2. STRUCTURE OF SGRQ

Part 1 (Questions 1-8) addresses the frequency of respiratory symptoms. It is not designed to be a precise epidemiological tool, but to assess the patient's perception of their recent respiratory problems.

Part 2 (Sections 9-16) addresses the patient's current state (i.e. how they are these days). The Activity score measures disturbances to daily physical activity. The Impacts score covers a range of disturbances of psycho-social function. Validation studies for the original SGRQ showed that this component relates in part to respiratory symptoms, but it also correlates quite strongly with exercise performance (6-minute walking test), breathlessness in daily life (MRC breathlessness score) and disturbances of mood (anxiety and depression). The Impacts score is, therefore, the broadest component of the questionnaires, covering the whole range of disturbances that respiratory patients experience in their lives.

Note: the general scale on the front page is not part of the SGRQ or SGRQ-C, but some investigators find it useful as an additional global measure.

3. ADMINISTRATION

The questionnaire should be completed in a quiet area, free from distraction and the patient should ideally be sitting at a desk or table. Explain to the patient why they are completing it, and how important it is for clinicians and researchers to understand how their illness affects them and their daily life. Ask him or her to complete the questionnaire as honestly as they can and stress that there are no right or wrong answers, simply the answer that they feel

best applies to them. Explain that they must answer every question and that someone will be close at hand to answer any queries about how to complete the questionnaire.

It is designed for supervised self-administration. This means that the patients should complete the questionnaire themselves, but someone should be available to give advice if required. It is designed to elicit the patient's opinion of his/her health, ***not*** someone else's opinion of it, so family, friends or members of staff should not influence the patient's responses. If the spouse or partner has accompanied the patient they should be asked to wait in a separate area. Similarly, do not allow patients to take the SGRQ-C home to be completed since you cannot be sure that it will be completed without the help of family or friends. A recent study of the use of surrogates to complete the questionnaire has shown small but significant differences in scores obtained from the patients themselves (Santiveri et al Respiratory Medicine (2007) 101, 439–445)

Once the patient has finished, it is very important that you check the questionnaire to make sure a response has been given to every question. If they have missed an item return it to the patient for completion, *before they leave*.

Telephone administration of the SGRQ has been validated (Anie et al J Clin Epidemiol 1996;49:653-6.), as has computer based presentation (Meguro and Jones, unpublished), but postal administration has not.

What should I do about queries regarding completion of the questionnaire?

If a patient asks for help with a question, do not provide an answer for them. The point of the questionnaire is to get an understanding of how the patient views his or her illness. It is appropriate to clarify a question but not to provide an answer. Questions may be read aloud if patients have difficulty with reading, but the responses must be theirs alone. If a patient gives an answer you disagree with it is not appropriate to challenge their response or to query it. It is their view of their condition we are interested in – no matter how strange the response!

The following are notes which may help you explain to patients what is required

1. In Part 1 of the questionnaire, emphasise to patients that you are interested in how much chest trouble they have had over the last year. The exact period is not important. We are looking for an impression or perception of health.

2. Asthma and COPD can vary day-to day. In Part 2, we want to know about the patient's current state (these days).

3. A severe or very unpleasant attack of chest trouble (Part 1, Question 5) is any attack that could be described that way *in the patient's own judgement*. Not 'severe' as defined by medical staff.

4. For Question 7 emphasise that you are interested in the number of good days that they have had.

5. Question 10 regarding employment can cause patients some problems. We are interested in how a patient's chest trouble affects their current working life or how it affected life when they were working. For example, if a patient took early retirement because of their chest condition, the response would be 10a – 'My chest trouble made me stop work', if a patient's retirement was unrelated to their chest trouble, their response would be 10c 'My chest trouble does not affect my work'.

6. Questions 11 to 16 require a response to every question. It may be worth emphasising this to the patient.

7. Many patients do not engage in physical activity. It is important to determine whether this is because they do not wish to (in which case the answer would be 'False') or cannot engage in these activities because of their chest trouble (in which case the answer would be 'True').

8. Medication questions refer to medications and treatments given for a patients chest disease and may interfere with their life if, for example, they are on oxygen support and have to carry it around with them.

9. It should be emphasised that responses to Question 15 are in terms of breathing difficulties and not any other problems. If patients do not engage in activities described in certain items, they should tick 'False'. Patients who do not engage in these activities because they are limited by their breathlessness, should tick 'True'.

4. EXCEL-BASED SCORING CALCULATOR

Three component scores are calculated for the SGRQ:

Symptoms - this component is concerned with the effect of respiratory symptoms, their frequency and severity.
Activity - concerned with activities that cause or are limited by breathlessness
Impacts - covers a range of aspects concerned with social functioning and psychological disturbances resulting from airways disease

A **Total** score is also calculated which summarises the impact of the disease on overall health status. Scores are expressed as a percentage of overall impairment where 100 represents worst possible health status and 0 indicates best possible health status.

You will find an Excel spreadsheet accompanying this manual called 'SGRQ Calculator' which can be used to calculate the three SGRQ component scores and the Total score.

Data Entry

Open the calculator and select the sheet called 'SGRQ Template'. This is where data from the questionnaire is entered. Individual patient identification numbers are entered in the column named 'ID'. Columns B to CH are for data-entry from the questionnaire and column names correspond to the question numbers on the questionnaire. One patient on the spreadsheet = one row. All positive responses are entered as 1 and all negative responses are entered as 0. **Where data are missing the cells must be left blank**. Data entry guidelines are as follows for each question:

Questions 1 – 7 Where a patient has ticked a box, a value of 1 is entered for the appropriate question. The empty boxes are entered as 0. Where a patient has missed a question the cells on the spreadsheet are left blank.

Example: Response = 1c, 'Over the last year I have coughed a few days a month'. A value of 1 is entered for 1c and a value of 0 is entered for 1a, 1b, 1d and 1e. If no tick was present for question 1 then 1a to 1e would be left blank.

Question 8 Where a patient has ticked 'Yes' to having a worse wheeze in the morning, a value of 1 is entered for the appropriate question. All other responses are entered as 0.

Example: Do you have a wheeze? = 'Yes' and Worse in the morning = 'Yes'. Then response to question 8 = 1.

Do you have a wheeze? = 'Yes' and Worse in the morning = 'No'. Or, Do you have a wheeze? = 'No'. Then response to question 8=0.

Questions 9, 10 & 17 Where a patient has ticked a box, a value of 1 is entered for the appropriate question. The empty boxes are entered as 0. Where a patient has missed the question the cells on the spreadsheet are left blank.

Example: Response = 10a, 'My chest trouble made me stop work'. A value of 1 is entered for 10a and a value of 0 is entered for 10b and 10c. If no tick was present for question 10, then 10a to 10c would be left blank.

Questions 11 – 16 Where a patient has ticked 'True' a value of 1 is entered for the appropriate question and where a patient has ticked 'False' a value of 0 is entered. Where a patient has missed a question the cell on the spreadsheet is left blank.

Example: 15a = 'True' then 15a = 1.
14c = 'False' then 14c = 0.
13h = missing then 13h is left blank

In response to question 14, if a patient is not receiving medication, enter the responses as zero, otherwise the calculator will read the values as missing.

Columns CJ to CV on the SGRQ Template sheet are part of the calculation formulae and you will not be able to alter these cells. This is to ensure that your SGRQ scores are valid.

Missing Questions
The calculator is designed to handle multiple entries in part 1 (Symptoms) by producing an average of the multiple responses. The scoring program adjusts for up to 24% of missing items in the questionnaire. If more than 24% of items are missing the scoring programme will return a value of 'Missing'.

Maximum number of patients
The spreadsheet is designed to calculate a maximum of 1300 patients. If you have more patients than this you will have to enter the first batch of data and calculate the scores and then clear the cells and enter the next batch of data.

The calculated scores
Once all data has been entered onto the SGRQ Template sheet select the sheet called 'SGRQ Scores'. The patient ID numbers and their scores are in the first five columns. To copy these values to another dataset or document select only the SGRQ scores corresponding to the number of patients you have entered on the database and **COPY**. These scores are pasted as follows; from the **EDIT** menu select **PASTE SPECIAL** then the select the option marked **VALUES.**

5. SGRQ SCORES IN HEALTHY SUBJECTS

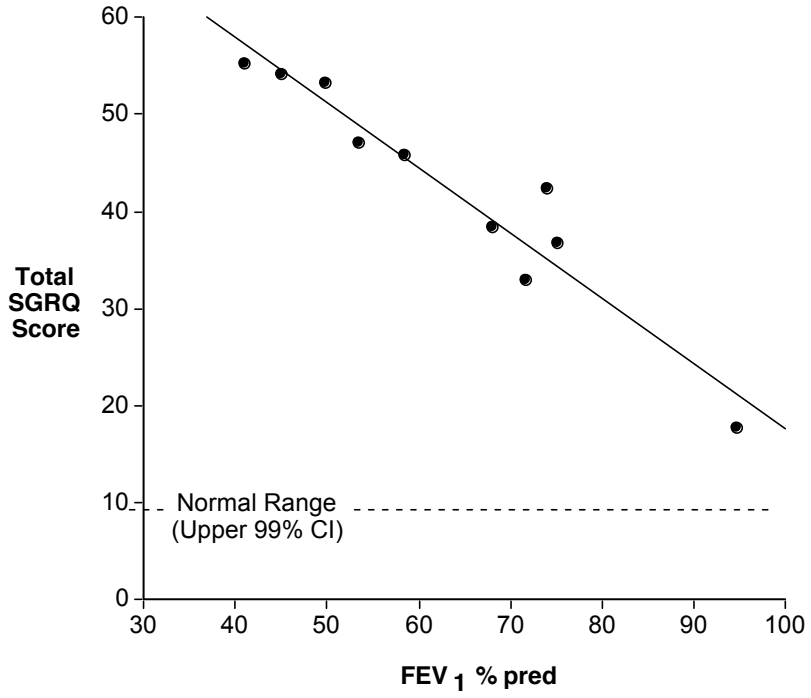
Means (95% confidence intervals) for SGRQ scores in normal subjects with no history of respiratory disease

N	Age - years	FEV1 as % predicted	Symptoms Score	Activity Score	Impacts Score	Total Score
74	46 range 17-80	95 (91-99)	12 (9-15)	9 (7-12)	2 (1-3)	6 (5-7)

A full range of normative values for a general population studied in Spain can be found in Reference 26 in the Bibliography

6. DATA FROM PREVIOUS STUDIES

SGRQ SCORES AND FEV_1 FROM 10 STUDIES IN COPD AND ASTHMA
(Total n - 1900)



7. ITEM WEIGHTS

Note:

1. *This is given for information only. The Excel-based system and other computerised scoring systems use these weights.*
2. *The wording of the item may not correspond exactly with the wording in the current version of the questionnaire.*

PART 1

1) Over the last year, I have coughed:
Most 80.6
Several 63.2
A few 29.3
Only 28.1
Not 0.0

2) Over the last year, I have brought up phlegm (sputum):
Most 76.8
Several 60.0
A few 34.0
Only 30.2
Not 0.0

3) Over the last year, I have had shortness of breath:
Most 87.2
Several 71.4
A few 43.7
Only 35.7
Not 0.0

4) Over the last year, I have had attacks of wheezing:
Most 86.2
Several 71.0
A few 45.6
Only 36.4
Not 0.0

5) During the last year, how many severe or very bad unpleasant attacks of chest trouble have you had?
More than three 86.7
3 attacks 73.5
2 attacks 60.3
1 attack 44.2
None 0.0

6) How long did the worst attack of chest trouble last?
a week or more 89.7
3 or more days 73.5
1 or 2 days 58.8
less than a day 41.9

7) Over the last year, in an average week, how many good days (with little chest trouble) have you had?
None 93.3
1 or 2 76.6
3 or 4 61.5
nearly every day 15.4
every day 0.0

8) If you have a wheeze, is it worse in the morning?
No 0.0
Yes 62.0

PART 2

9) How would you describe your chest condition?

The most important problem I have 83 .2

Causes me quite a lot of problems 82.5

Causes me a few problems 34.6

Causes no problem 0.0

10) If you have ever had paid employment?

My chest trouble made me stop work 88.9

My chest trouble interferes with my work or made me change my work 77.6

My chest trouble does not affect my work 0.0

11) Questions about what activities usually make you feel breathless.

Sitting or lying still 90.6

Getting washed or dressed 82.8

Walking around the home 80.2

Walking outside on the level 81.4

Walking up a flight of stairs 76.1

Walking up hills 75.1

Playing sports or games 72.1

12) More questions about your cough and breathlessness.

My cough hurts 81.1

My cough makes me tired 79.1

I get breathless when I talk 84.5

I get breathless when I bend over 76.8

My cough or breathing disturbs my sleep 87.9

I get exhausted easily 84.0

13) Questions about other effects your chest trouble may have on you.

My cough or breathing is embarrassing in public 74.1

My chest trouble is a nuisance to my family, friends or neighbours 79.1

I get afraid or panic when I cannot get my breath 87.7

I feel that I am not in control of my chest problem 90.1

I do not expect my chest to get any better 82.3

I have become frail or an invalid because of my chest 89.9

Exercise is not safe for me 75.7

Everything seems too much of an effort 84.5

14) Questions about your medication.

My medication does not help me very much 88.2

I get embarrassed using my medication in public 53.9

I have unpleasant side effects from my medication 81.1

My medication interferes with my life a lot 70.3

15) Questions about how activities may be affected by your breathing.

I take a long time to get washed or dressed 74.2

I cannot take a bath or shower, or I take a long time 81.0

I walk more slowly than other people, or I stop for rests 71.7

Jobs such as housework take a long time, or I have to stop for rests 70.6

If I walk up one flight of stairs, I have to go slowly or stop 71.6

If I hurry or walk fast, I have to stop or slow down 72.3

My breathing makes it difficult to do things such as walk up hills, carry things up stairs, light gardening such as weeding, dance, play bowls or play golf 74.5

My breathing makes it difficult to do things such as carry heavy loads, dig the garden or shovel snow, jog or walk at 5 miles per hour, play tennis or swim 71.4

My breathing makes it difficult to do things such as very heavy manual work, run, cycle, swim fast or play competitive sports 63.5

16) We would like to know how your chest trouble usually affects your daily life.

I cannot play sports or games 64.8

I cannot go out for entertainment or recreation 79.8

I cannot go out of the house to do the shopping 81.0

I cannot do housework 79.1

I cannot move far from my bed or chair 94.0

17) Tick the statement which you think best describes how your chest affects you.

It does not stop me doing anything I would like to do 0.0 It stops me doing one or two things I would like to do 42.0

It stops me doing most of the things I would like to do 84.2

It stops me doing everything I would like to do 96.7

8. OUTLINE OF SCORING ALGORITHM

Note: This is given for information only. The Excel-based system and other computerised scoring systems use these principles.

SUMMARY

Three component scores are calculated: **Symptoms; Activity; Impacts**

One **Total** score is also calculated.

PRINCIPLE OF CALCULATION

Each questionnaire response has a unique empirically derived 'weight'. The lowest possible weight is zero and the highest is 100.

Each component of the questionnaire is scored separately in three steps:

i. The weights for all items with a positive responses are summed.

ii The weights for missed items are deducted from the maximum possible weight for each component. The weights for all missed items are deducted from the maximum possible weight for the Total score.

iii. The score is calculated by dividing the summed weights by the adjusted maximum possible weight for that component and expressing the result as a percentage :

$$\text{Score} = 100 \times \frac{\text{Summed weights from positive items in that component}}{\text{Sum of weights for all items in that component}}$$

The Total score is calculated in similar way:

$$\text{Score} = 100 \times \frac{\text{Summed weights from positive items in the questionnaire}}{\text{Sum of weights for all items in the questionnaire}}$$

Sum of maximum possible weights for each component and Total:

Symptoms	662.5
Activity	1209.1
Impacts	2117.8
Total	3989.4

(Note: these are the maximum possible weights that could be obtained for the worst possible state of the patient).

It will be noted that the questionnaire requests a single response to questions 1-7, 9-10 and 17. If multiple responses are given to one of these questions then averaging the weights for the positive responses for that question are acceptable. We feel that this is a better approach than losing an entire data set and have used this technique in calculating the results used in our validation studies. (Clearly a better approach is to prevent such multiple response occurring, but it is difficult to prevent occasional accidents). This method is used in the Excel calculator

SYMPTOMS COMPONENT

This is calculated from the summed weights for the positive responses to questions 1-8.

ACTIVITY COMPONENT

This is calculated from the summed weights for the positive responses to questions 11 and 15.

IMPACTS COMPONENT

This is calculated from the summed weights for the positive responses to questions 9-10, 12-14 and 16-17.

TOTAL SCORE

The Total score is calculated by summing all positive responses in the questionnaire and expressing the result as a percentage of the total weight for the questionnaire (as shown on previous page).

HANDLING MISSED ITEMS

It is better not to miss items and any missing items are the fault of the experimenter, not the patient. We have examined the effect of missing items and recommend the following methods:

Symptoms

The Symptoms component will tolerate a maximum of 2 missed items. The weight for the missed item is subtracted from the total possible weight for the Symptoms component (662.5) and from the Total weight (3989.4).

Activity

The Activity component will tolerate a maximum of 4 missed items. The weight for the missed item is subtracted from the total possible weight for the Activity component (1209.1) and from the Total weight (3989.4).

Impacts

The Impacts component will tolerate a maximum of 6 missed items. The weight for the missed item is subtracted from the total possible weight for the Impacts component (2117.8) and from the Total weight (3989.4).

APPENDIX D. Validation of SGRQ in Normal Population

Table 3.–Mean St George's Respiratory Questionnaire scale scores by demographical and clinical characteristics in the general population weighted sample

	Symptoms	Activity	Impacts	Overall
Sex				
M	11.62	12.17	5.23	8.60
F	7.82	14.58	4.26	8.23
p-value	<0.001	0.043	0.15	0.63
Age yrs				
39–49	7.97	9.33	2.69	5.78
50–59	8.74	13.48	4.55	8.19
60–69	12.54	17.95	7.23	11.61
p-value	<0.001	<0.001	<0.001	<0.001
Education				
High school or more	8.54	9.26	3.10	6.05
Primary school or no education	10.45	16.53	6.02	10.20
p-value	0.03	<0.001	<0.001	<0.001
Social class (occupations)#				
I-II (professional/ intermediate)	9.55	9.46	2.96	6.23
III (skilled nonmanual)	7.92	10.19	3.14	6.27
IV–V (manual)	10.29	15.93	5.64	9.79
p-value	0.07	<0.001	<0.001	<0.001
Smoking behaviour				
Never smoker	7.49	13.63	4.16	7.81
Former smoker	9.58	13.19	5.50	8.69
Smoker ⩽20 pack-yrs	12.99	11.58	3.38	7.76
Smoker >20 pack-yrs	16.12	14.20	6.59	10.76
p-value	<0.001	0.74	0.04	0.09
FEV_1 % over pred				
FEV_1 % ⩾100	5.39	9.33	2.33	5.14
90⩽ FEV_1 % <100	8.23	9.17	2.80	6.01
80⩽ FEV_1 % <90	9.12	13.94	4.68	8.47
FEV_1 % <80	16.20	21.14	9.27	14.30
p-value	<0.001	<0.001	<0.001	<0.001

M: male; F: female; FEV_1: forced expiratory volume in one second. n=862. #: social class based on an adaptation of the British Registrar General's Classification [26].

Ferrer, M., et al. "Interpretation of quality of life scores from the St George's Respiratory Questionnaire." *European Respiratory Journal* 19.3 (2002): 405-413.

APPENDIX E. Residual analysis and model diagnostics: NTM cases