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Comparing the Non-Cystic Fibrosis Bronchiectasis Patients with Non-Tuberculous Mycobacteria (NTM) and Non-NTM Infections

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Comparing the Non-Cystic Fibrosis Bronchiectasis Patients with Non-Tuberculous Mycobacteria (NTM) and Non-NTM Infections

Capstone Project Paper

A paper submitted in partial fulfillment of the requirement for the degree of Master of Public Health in the University Of Kentucky College Of Public Health

By

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Abstract

Objective

The objective of the study is to compare the Non-Cystic Fibrosis Bronchiectasis patients with Non Tubercular Mycobacteria (NTM) and Non-NTM infection and determine if the NTM and Non-NTM groups are different.

Methods

Data from the COPD Foundation's Bronchiectasis Research Registry (BRR) was used in the study (n=1660).Logistic regression, Cox proportional hazards regression, and Kaplan Meier survival analysis were used to analyze the data.

Results.

The study found odds ratio for having NTM infection for age to be 1.02 and for gender to be 2.34, after adjusting for all other variables in the multivariate logistic regression, with the p-value of <0.001. The study found the Log rank test for the Kaplan Meier survival to be 0.7656, which is greater than p-value of 0.05, and hence found that we did not have strong enough statistical evidence to say that the two groups have different survival.

Conclusion

This study, one of the first study done using the BRR's database found age and gender to be significantly associated with NTM infection, but did not found any difference in survival among patients of the two groups. Further studies need to be done to expand the horizon of this less researched topic.

Introduction

Bronchiectasis is defined as the abnormal dilatation of the airways, caused by the destruction of the muscular and elastic components of their walls, due to recurrent infection and inflammation. The term “Bronchiectasis” is derived from the Greek words “bronchia”, which means branches of the main bronchi and “ektasis” which means stretching, thereby making bronchiectasis as the stretching of the branches of the main bronchi. Bronchiectasis was first described by Laennec in 1819. [1]

“This affection of bronchia is always produced by chronic catarrh, or by some other disease attended by long, violent, and often repeated fits of coughing.”

R. T. H. Laennec. [2]

Bronchiectasis was later explained by Sir William Osler in the late 19th century, who himself was one of the famous patient with non-cystic fibrosis bronchiectasis. He had severe chest infections for many years suggesting underlying bronchiectasis and died in 1919 as a result of lung abscess and empyema, which were complications of pneumonia. [3] The introduction of contrast bronchoscopy by Jean Sicard, which permitted the precise imaging of the destructive changes in airways, was another landmark in the history of bronchiectasis. Further work on Bronchiectasis was done by Reid in 1950,s, when he correlated the bronchography with pathological specimens. [4]

Bronchiectasis, which has lost its relevance in the late 20th century in the developed world and was once thought to be decreasing in prevalence, is now being diagnosed with increasing frequency in United States as well as around the world.

Prevalence

The prevalence of Bronchiectasis is increasing in United States of America. According to a study by Seitz and colleagues, who analyzed the 5% sample of the Medicare part –B outpatient databases for bronchiectasis ICD-9 codes, bronchiectasis prevalence increased 8.74% annually from 2000 to 2007. Prevalence was also shown to increase with age, peaking at ages 80-84 years, and was higher in females, even after the logistic regression controlling for race and CT scans (OR=1.36). The prevalence of bronchiectasis was also found to be highest in the Asian population. [5]

According to a study done by Weycker et al, based on the insurance claim database, it is estimated that in the United States at least 110,000 patients are currently being treated for non- cystic fibrosis bronchiectasis. They further reported that, among person aged 18 to 34 years in United States, the prevalence rate of non-cystic fibrosis bronchiectasis is 4.2 per 100,000, and for those greater than 75 years of age 272 per 100,000. [6] According to Tsang and Tipoe the prevalence rate of non-cystic fibrosis bronchiectasis is about 16.67 per 100,000 person in Aukland, New Zealand and the rate is 16.4 per 100,000 population among children and hospital admissions in Hong Kong. [7] There is a great burden caused by non-cystic fibrosis bronchiectasis on the patients as they require more frequent outpatient visits, longer hospital stays and more extensive therapy as compared to matched controls .According to study done

by Weycker et al in 2001, patients with bronchiectasis averaged two additional days in the hospital, 6.1 additional outpatient encounters, and 27.2 more days of antibiotic therapy than those without the disorder. The study also found that total medical expenditures were $5681 higher for bronchiectasis patients. Non-cystic fibrosis bronchiectasis is a great financial burden with annual costs of approximately $630 million for the United States. [6] A study done by Joish et al, found first year total medical care expenditure after diagnosis increased by $2319 per person per year. [8] The mortality rate for bronchiectasis ranged from 10-16% for the observation period of approximately 4 years. The low Forced Expiratory Volume in one second ($FEV_{1)}$ values and advanced dyspnea scores were found to be closely related to mortality. [9] An association between the etiology of bronchiectasis and mortality rate has not been definitely established, but a recent study done by Geommine and colleagues showed that idiopathic bronchiectasis has the lowest death rate among all causes of bronchiectasis. [10]

Pathophysiology

Bronchiectasis can affect just a section of one lung, or a complete lung, or both of the lungs. The development of bronchiectasis is a complex process, and the initial damage that can lead to development of bronchiectasis usually occurs in childhood, symptoms of bronchiectasis however are usually delayed for months or years. In developing countries the main cause of bronchiectasis is childhood infections such as measles and whooping cough, but in United States these causes have decreased due to the childhood vaccines and development of antibiotics. [11] [9] [4]

Cole's Vicious Cycle model is the generally accepted explanation for development of bronchiectasis.[9] Cole's model explains that pulmonary infections or tissue injury develop an exaggerated inflammatory response in the individuals predisposed to bronchiectasis. This inflammatory response in turn is responsible for the structural damage of the airways, which can lead to further infection. The structural abnormalities lead to stasis of mucus, which in turn leads to chronic continuous infection and the cycle persists. The mucus itself is often abnormal, more complex and the tracheobronchial clearance also has been shown to be slower in patients with bronchiectasis, thereby leading to increased chances of infection and airway damage. This retained mucus can overtime lead to formation of plugs and airway obstruction, thereby further leading to more advanced bronchiectasis.

Regardless of the underlying cause, bronchiectasis results when the bronchial and bronchiolar wall damage due to inflammation and infection leads to vicious cycle of airway injury. Mikaemi et al, showed increased chemotactic activity of sputum in the patients with bronchiectasis. Studies show that the some systemic markers of inflammation are also increased in patients with bronchiectasis. There are studies showing that the anatomic factors, chronic infection and inflammation, and host defense all play an important role in the development of bronchiectasis, but these roles are poorly understood, especially for non-cystic fibrosis bronchiectasis. [12]

Signs and Symptoms

The clinical course and symptoms of non-cystic fibrosis bronchiectasis vary to a great extent from one patient to another. Some patients have minor or no symptoms at all, or only during

exacerbations, whereas some patients have them regularly. The most common sign and symptoms of non-cystic fibrosis bronchiectasis includes cough that occurs for months or years, daily production of large amounts of sputum, which may contain mucus, trapped particles and pus, dyspnea or shortness of breath, chest pain, wheezing, clubbing of the fingers, hemoptysis, weight loss, and decreased exercise tolerance. [13]

A large number of patients with non-cystic fibrosis bronchiectasis have frequent exacerbations of their symptoms, which is defined as having at least four of the following symptoms: increased cough and dyspnea, change in sputum production, increased wheezing, fever over 38^0 C, decreased tolerance to exercise, fatigue, lethargy, decrease in pulmonary function, changes in chest sounds or radiographic changes consistent with new infectious process. [10] The rate of these exacerbations were found to be 1.5 per year in the countries of Ireland, United Kingdom and North America. The studies have shown that in the patients with non-smoking non-cystic fibrosis bronchiectasis there is loss of lung function with an average decline in the forced expiratory volume in one second (FEV_1) of about 50 ml per year. [12] The various signs and symptoms associated with bronchiectasis worsens as the disease progress, and hence leads to the decreased quality of life.

Etiology

Based on the etiology, the major cause of bronchiectasis in the developed world is the genetic disease of cystic fibrosis. So based on this etiology, we can widely divide bronchiectasis into two major categories:

1. Cystic Fibrosis Bronchiectasis

2. Non-Cystic Fibrosis Bronchiectasis

There is a renewed interest in the non-cystic fibrosis bronchiectasis, mainly due to the fact that we may be able to decrease its incidence or improve the quality of life for bronchiectasis patients by the use of different vaccinations and modern antibiotics. There are various causes that can lead to development of non-cystic fibrosis bronchiectasis.

Table showing etiologies for non-cystic fibrosis bronchiectasis :[9] [10]

Post infections: • Viral • Bacterial • Fungal • Atypical Mycobacterial
Idiopathic
Traction: •Post-tuberculosis fibrosis • Post-radiation fibrosis • Collagen vascular disease • Twisting or displacement of airways after lobar resection
Cilia abnormalities: Primary ciliary dyskinesia
Immune deficiency: •Immunoglobulin deficiency • HIV infection • Job's syndrome
Injury: • Pneumonia/childhood infections • Aspiration • Smoke inhalation
Obstruction: • Tumor • Foreign body • Lymphadenopathy
Autoimmune disease: • Rheumatoid arthritis • Sjogren's syndrome
Connective tissue disorder: • Tracheobronchomegaly (Mounier-Kuhn syndrome) • Marfan's syndrome • Cartilage deficiency (William Campbell Syndrome)
Hypersensitivity: •Allergic Bronchopulmonary Aspergillosis
Inflammatory bowel disease: • Ulcerative colitis • Crohn's disease

Malignancy: • Chronic lymphocytic lymphoma •Stem cell transplantation, graft versus host reaction
α-1 antitrypsin deficiency
Yellow nail syndrome
Young's syndrome

According to an extensive study by Pasteur and colleagues in 2000, 53% of the cases of non-cystic fibrosis bronchiectasis are idiopathic. [14] Another study showed that only 26% of the cases remained idiopathic. [15] Both studies, however concluded that the most common etiology was post-infectious, contributing to about 1/3 of the cases. Research has thus shown that there is a significant relationship between NTM infection and bronchiectasis.

Non Tuberculous Mycobacteria consists of mycobacteria other than Mycobacterium tuberculosis and Mycobacterium leprae. Almost 160 different species have been isolated, many of which may cause disease in humans. NTM are ubiquitous in the environment and have been isolated from the soil and water, which are presumed source of infection. The route of contact with NTM is most likely by inhalation of aerosols from natural surface water and hot water systems. Some studies showed that patients with gastroesophageal reflux disease (GERD) associated bronchiectasis might be more predisposed to NTM infection, but the study done by Mirsaeidi et al. found no difference with regard to GERD for patients with non-cystic fibrosis bronchiectasis in relation to NTM infection. [16] Despite the fact that NTM are ubiquitous, relatively few individuals develop NTM infection, thereby

leading to speculation that there may be a predisposition to develop NTM infection. Non Tuberculous Mycobacteria pulmonary disease is most common in elderly women with bronchiectasis and low body mass index, a condition known as “Lady Windermere Syndrome”, which was first used by Reich and Johnson to describe the pattern of NTM infection in elderly white women without underlying lung disease. Non Tuberculous Mycobacteria infection is also commonly associated with conditions such as scoliosis, pectus excavatum, mitral valve prolapse and cystic fibrosis transmembrane conductance regulator mutation. [17]

There is no evidence of transmission of NTM from human to human or from animals , but recent studies have shown some possibility of indirect human to human transmission. A recent case report from United Kingdom demonstrated infection by identified strains of Mycobacterium kansasii in a couple in London, where no common source of infection was identified. [18] [19]

There is no mandatory reporting of NTM disease, and it is difficult to differentiate between colonization and active infection, thus it is difficult to estimate the exact prevalence of NTM. Due to improved diagnostic techniques and increased focus on NTM infection in non-cystic fibrosis bronchiectasis patients, the rates of isolation of NTM are increasing in the recent years. From 2004 to 2006 the prevalence of NTM infection in the United States of America increased from 1.4 to 6.6 per 100,000 persons. [20] The rate of all NTM reports increased from 0.9 per 100,000 in 1995 to 2.9 per 100,000 in 2006, in Northern Ireland, Wales and England. [21] According to the American Thoracic Society criteria, the rate of NTM infection in patients with bronchiectasis varies from under to 30%.

[16] A recent meta-analysis found the overall prevalence of NTM in bronchiectasis patients to be 9.3%. [21] A study done by Mirsaeidi and colleagues found that MAC is the most frequent species isolated in the bronchiectasis patients, accounting for 50% to 80% of all NTM infection. The study also found that NTM is more frequently isolated from female patients with age 65 years or more. In addition, the study also found that one of the most important risk factor for acquiring NTM infection is childhood pulmonary infection. [16] A study done by Han and colleagues showed that MAC infection increases with increasing postmenopausal years, but is rare in women younger than 50 , suggesting that estrogen has a protective effect.[22]

Non Tuberculous Mycobacteria infection is commonly associated with co-infections with other NTM species and microorganisms. According to a study by Wickremasinghe and colleagues, P. aeruginosa was the most common copathogen isolated (52% of patients). The second most common copathogen was *S. aureus* with a percentage of 28%, followed by *H.influenza*(12%), *A.fumigatus*(4%), *C.albicans* (8%), and *S.maetophila*(4%). [23]

Most bacteria involved in bronchiectasis form biofilms, which makes the effective antimicrobial therapy more challenging, as a hydrated matrix of extracellular polysaccharides and proteins protect them from the host environment. [9]

DIAGNOSIS

Diagnosis of bronchiectasis is accomplished using wide range of different tests to rule in or rule out certain conditions. The various procedures and tests used to diagnose Non-cystic fibrosis bronchiectasis are;[24] [23] [25]

- **Chest CT scan**: It is the most common test used for the diagnosis of bronchiectasis. It is a painless test that creates a precise picture of a patient's airways and shows the exact location and extent of damage to the lungs.
- **Blood Tests**: Various types of blood tests are used to detect an underlying condition that can lead to bronchiectasis, such as immunodeficiency.
- **Sputum culture**: Sputum culture is the standard test for evaluating airway colonization and infection in non-cystic fibrosis bronchiectasis. Sputum culture can grow a causative organism, which is very helpful in choosing a treatment antibiotic.
- **Lung function tests**: Various lung function tests, such as forced expiratory volume in one second (FEV_1), are used in the diagnosis of non-cystic fibrosis bronchiectasis. These tests measure the amount of air a patient can inhale or exhale, and also check the flow of air, thereby revealing the extent of damage to the lungs.
- **Sweat test**: A sweat test is used to rule out the diagnosis of cystic fibrosis related bronchiectasis.
- **Bronchoscopy:** In the patients who are unable to expectorate, or if the sputum culture is negative but the patient has unfavorable clinical outcome, a bronchoscopy is indicated. During bronchoscopy a flexible tube with a video camera called the bronchoscope, is passed through the nose or mouth of the patient after anesthesia, and it gives a video image of the airway and to help in diagnosis.

PREVENTION

Widespread use of vaccination programs in childhood, especially for whooping cough and measles, has likely reduced the prevalence of bronchiectasis but, in addition to universal childhood vaccination, appropriate and careful treatment of childhood pneumonia is also important.

Due to a lack of early symptoms, a diagnosis of bronchiectasis may be delayed or initially diagnosed as a lower respiratory infection. Among those with cystic fibrosis there is good evidence that prognosis of bronchiectasis can be improved through antibiotic therapy and other drugs that improve mucociliary clearance, but more studies are needed for the non-cystic fibrosis bronchiectasis. [14]

METHODS AND MATERIAL

This study analyzed the secondary data obtained from the Bronchiectasis Research Registry (BRR) to compare the characteristics and survival of the non-cystic fibrosis bronchiectasis patients with Non- Tuberculous Mycobacteria (NTM) and non-NTM infections. Despite the significant impact of non-cystic fibrosis bronchiectasis in the terms of morbidity, quality of life, and financial burden, there are limited data sources for examining characteristics of patients with non- cystic fibrosis bronchiectasis. In order to better understand the characteristics of patients with non-cystic fibrosis bronchiectasis, the BRR was established within the COPD Foundation in 2008. The BRR gathers data from the patients aged 18 or older with non-cystic fibrosis bronchiectasis. The BRR collects data from patients at 13 sites in the United States, located in the states of Colorado, Connecticut, Florida, Minnesota, New York, North Carolina, Pennsylvania, Texas, Washington D.C. and the Washington state

with the special focus on bronchiectasis and NTM disease. Some states have more than one center. The data is collected with the help of different forms at individual level and is stored in form of 13 different data sets. In Bronchiectasis Research Registry, the baseline data sets includes variables related to demographics, microbiologic, medical history and therapeutic information etc., and is stored in a central web based database. We merged these different data sets to create a single data set to analyze the characteristics of the patients with non-cystic fibrosis bronchiectasis. Patients in the BRR database are classified by the presence or absence of NTM infection, therefore the BRR contains the patients with NCFB classified by the presence or absence of NTM infection.

Inclusion and Exclusion Criteria-

Adult patients with a diagnosis of non-cystic fibrosis bronchiectasis established by a physician were eligible for inclusion in the database.

Patients diagnosed with cystic fibrosis, based on the clinical history, sweat chloride test results, and/ or genetic testing results at the time of enrollment into the BRR were excluded from the database.

In this study we used the BRR to compare the characteristics and survival of the non-cystic fibrosis bronchiectasis patients with Non-Tubercular Mycobacteria (NTM) and non-NTM infections. Patients were divided into two groups - NTM and non-NTM, and the patients missing information on their NTM status were excluded. The two groups were compared in terms of age, gender, smoking status, education level and mortality status. Age was coded as a continuous variable, whereas other variables were categorical. Gender was coded as 1

for the females and 0 for males, with males used as the reference. Smoking status was categorized as current smoker (1), past smoker (2) and never smoker (3), with never smoker used as the reference. Educational status, based on the highest level of education attained was categorized as high school or less (1), some college or associate degree (2), and college degree or post graduate (3). Since many patients had information missing on education (n= 505, 30.42%), we created a missing category (4), to prevent exclusion and increase the power of the study. The category high school or less (1) was used as the reference.

Mortality status was divided into 3 categories; Alive (1), Dead (2), and lost to follow up (3). Alive was used as the reference. In this study we used the logistic regression to compare characteristics of two groups, cox proportional hazard regression to examine risk of death and Kaplan Meier survival curve to compare survival times of two groups. March 31, 2015 was used as the end of the study date for censoring.

Statistical Analysis:

Logistic regression: Analysis was performed to determine crude estimates as well as estimates after adjustment for other factors. Exploratory analysis included use of descriptive statistics. Mean and standard deviation were calculated for continuous variable of age. Frequencies and percentages were calculated for categorical variables: smoking status, gender, mortality status, and education level. The descriptive statistics are presented in the Table 1. The effects of individual factors were first estimated by including each variable separately in a logistic regression model to investigate the unadjusted association between the independent variable and outcome (NTM infection). Odds ratios, 95%

confidence intervals and p-values were calculated for each variable. The results are presented in the Table 2. A multivariate logistic regression was used to estimate the adjusted odds ratio, 95% confidence interval, and p-value for the observed association between NTM status and other risk factors. The results for the multiivariate logistic regression are presented in the Table 3.

For Cox proportional hazard regression, we calculated the hazard ratio and 95% confidence interval to compare hazards of death for the NTM and non-NTM group, when comparing for the different variables. The results for the cox proportional hazard regression are presented in the Table 4.

Kaplan Meier survival analysis was used to compare the survival for the patients in the NTM and non-NTM groups. Survival time was defined as the difference between the time of the death and the time of diagnosis. Patients who were alive or lost to follow up were censored. March 31, 2015 was used as the date for the end of the study, and therefore to censor patients who were alive until that date. A log rank test was used to check the statistical significance of the survival curve. SAS v 9.3 was used for all the statistical analysis in the study. The significance level used in the analysis was $p<0.05$

RESULTS:

Table 1 presents the distribution of demographic and other characteristics of the total sample (n=1660) and according to the presence or absence of NTM infection; NTM (n=902) and non-NTM (n=758). The mean age of all the participants was 64.16 years with the standard deviation of 14.24. (64.16 ± 14.24). The mean age for the NTM group was 66.00

years with the standard deviation of 11.81 (66.00±11.81), and the mean age for the non-NTM group was 61.96 years with a standard deviation of 16.42 (61.96±16.42).

Smoking status data was available for 1652 participants, including 899 NTM and 753 non-NTM patients. Among all participants, 24(1.45%) patients were current smokers, while 633(38.32%) were past smokers, and 995(60.23%) were never smokers. In the NTM group (n=899), 15(1.67%) participants were current smokers, 341(37.93%) were past smokers, and 543(60.40%) were never smokers. In the non-NTM group (n=753), 9(1.20%) were current smokers, 292(38.78%) were past smokers, and 452(60.03%) were never smokers.

Gender was available for 1659 participants. There were 345(20.80%) male participants and 1314(79.20%) female participants. In the NTM group (n=902), 130(14.41%) participants were males, and 772(85.59%) were females. In the non-NTM group (n=757), 215(28.40%) participants were males, while 542(71.60%) participants were females.

Mortality status data was available for 1653 patients, including 896 NTM and 757 non-NTM participants. Among all participants, 1502(90.87%) were alive, 80(4.84%) were dead and 71(4.30%) were lost to follow up. In the NTM group (n=896), 823(91.85%) patients were alive, 46(5.13%) were dead and 27(3.01%) were lost to follow up. In the non-NTM group (n=757), 679(89.70%) of the participants were alive, 34(4.49%) were dead and 44(5.81%) were lost to follow up.

Education level was available for only 1155 participants, so a category for the missing observations was created, so as to retain them in the study. For education level (n=1660), 902 participants were in the NTM group and 758 were in the non-NTM group. Among all

participants (n=1660), 218(13.13%) were in the high school or less category, while 252(15.18%) had some college or 2 year associate degree. 685(41.27%) had college or post grad, and 505(30.42%) were missing information on education. In the NTM group (n=902), 118(13.08%) had high school or less, 135(14.97%) were in some college category, 374(41.46%) had college or post grad and 275(30.49%) were missing. In the non-NTM group (n=758), 100(13.19%) had the highest level of education as high school or less, 117(15.44%) had some college, 311(41.03%) were in the college or post grad category, and 230(30.34%) were missing.

Univariate Analysis:

Table 2 presents the results from the univariate logistic regression. Age and gender were found to be significantly associated with the NTM disease in the patients with non-cystic fibrosis bronchiectasis. The various variables were associated with NTM disease in the model at the significance level of $p<0.05$. The analysis shows that for one year increase in age, the odds of having the NTM disease increases by 2.0%, when age is the only variable adjusted for in the model (OR, 1.02; 95% CI, 1.01-1.03,$p < 0.001$). The data also shows that when considering the gender, the odds of having NTM disease are 2.36 times higher for the females as compared to the males (OR, 2.36;95% CI, 1.84-3.00, $p <0.001$).

While considering the smoking status, the “never smoker” category was used as the reference. The data shows that that the odds of having NTM disease in the current smoker category are 1.39 times the odds for the never smoker category, but the result is not statistically significant (OR, 1.39; 95%CI, 0.60-3.20, p=0.4426). The data also shows that the

odds of having NTM disease in the past smoker are 0.97 times the odds in the never smoker, but the result is not statistically significant (OR, 0.97; 95%CI, 0.80-1.19, p=0.7815).

While considering the mortality status, the "Alive" category was used as the reference. The data shows that the odds of having NTM infection in the patient who died are 1.12 times the odds in the patient who are alive, but results are not significant (OR, 1.12; 95%CI, 0.71-1.76; p=0.6356). The analyses also shows that the odds of having NTM infection in the patients who are lost to follow up are 0.51 times the odds for the patients who are alive (OR, 0.51; 95%CI, 0.31-0.83;p=0.0065)While considering the highest level of education attained, the level of high school or less was used as the reference. The analyses of the data shows that for the patients with some college, the odds for having the NTM infection are 0.98 times the odds for the patients with high school or less, but the result is not statistically significant (OR,0.98; 95%CI,0.68-1.41;p=0.9037). The data also shows that the odds of having the NTM infection in the patients with college or post grad level of education are 1.02 times the odds for the patient with high school or less (OR,1.02; 95%CI,0.75-1.39;p=0.9034). the data further shows that the odds of having NTM infection in the patients in whom in whom the information on education is missing are 1.01 times the odds for the patient with high school or less (OR<1.01; 95%CI, 0.74-1.40;p=0.9353).

Multivariate Analysis;

We obtained adjusted odds ratio for all the variables by including them together in the multivariate logistic regression model. Table 3. Presents the results of the multivariate logistic regression. The analysis of the data shows that while controlling for all other

variables in model, with each year increase in the age the odds of having NTM infection increase by 2.0% (OR,1.02; 95%CI,1.01-1.03;p<0.001)

The data also shows that while considering the gender, the odds of having the NTM disease in females 2. 34 times the odds for having disease in males, while controlling for all other variables in the model (OR, 2.34; 95%CI, 1.82-3.02; p<0.001), and since the p-value is less than 0.05, therefore the results are statistically significant. The data analyses further shows that while considering the smoking status, in the multivariate regression model, the odds of current smoker having the NTM infection are 1.99 times compared to the odds of NTM infection in the patients who are never smoker, while controlling for all other variables in the model (OR,1.99; 95%CI, 0.84-4.76;p=0.1189). The data further shows that the odds of having NTM infection in the past smoker compared to the odds in the never smoker are 0.89, while controlling for all other variables in the model, but the results are not statistically significant (OR, 0.89; 95%CI, 0.72-1.10; p=0.2689).

While considering the mortality status, the data analysis found that the odds of having NTM infection in the patient who died are 1.15 times the odds for the patient ,who are alive, while controlling for all other variables in the model (OR, 1.15; 95%CI, 0.71-1.86;p-0.5691). The data analysis also showed that the odds of having NTM disease in a patient who was lost to follow up are 0.53 times the odds for the patient who are alive, while controlling for all other variables in the model (OR,0.53; 95%CI,0.32-0.89;p=0.0162)

While considering the highest level of the education attained, the analysis of the data found that the odds for having the NTM infection for the patients who have some college are 1.04

times the odds for the patients who have high school or less, while controlling for all other variables in the model (OR, 1.04; 95%CI, 0.71-1.52; p=0.8298), but the results are not statistically significant. The data also shows that odds of having NTM infection in the patient with college or post grad are 1.17 times the odds for the patients with high school or less, while controlling for all other variables in the model (OR,1.17; 95%CI, 0.85-1.61; p=0.3343). The data also shows that odds of having NTM infection in the patient whom the education status is missing are 1.10 times the odds for the patients with high school or less, while controlling for all other variables in the model.(OR,1.10; 95% CI, 0.79-1.53; p=0.58340, but the results are not statistically significant.

Cox proportional hazard regression;

Table 4. Presents the results from the cox proportional hazards regression.

The data analysis for the NTM group shows that, while controlling for all other variables in the model, with each year increase in the age at diagnosis of bronchiectasis, the hazards of death increased by 7.0%(HR,1.07;95%CI,1.04-1.11). The data further shows that the hazards of death for those who are current smoker are 7.63 times the hazards for those who are never smokers, while adjusting for other variables in the model (HR,7.63;95%CI,1.58-36.85), but the result is not significant. The confidence interval is very large, which can be explained by the fact that there are very few observations for this category. The data analysis further found that the hazards of death for those who were past smoker are 1.56 times the hazards for those who are never smoker (HR, 1.56; 95%CI,0.71-

3.43), after adjusting for all other variables in the model, but the results are not statistically significant.

While considering for gender, the data analysis found that the females in the NTM group has 58% less hazards on time to death than the males, after controlling for all other variables in the model (HR, 0.42;95%CI,0.17-1.02), but since the confidence interval includes 1, the results are not statistically significant .

The analysis further found that while considering the highest level of education attained , the hazards of death for the patient who has some college are 0.64 times or 36% less than those who has high school or less, while adjusting for all other variables in the model (HR, 0.64;95%CI,0.22-1.86). The data also showed that hazards of death in the patient who have college or post grad are 0.34 times or 66% less than the hazards in the patient with high school or less, while adjusting for all other variables in the model(HR, 0.34;95%CI,0.13-0.93). The data also shows that the hazards of death in the patient with missing education level are 0.37 times the hazards of death in a patient with high school or less, while adjusting for all other variables in the model, but the results are not statistically significant (HR,0.37;95%CI,0.12-1.13)

For the non-NTM group, the data analyses shows that, while controlling for all other variables in the model, with each year increase in the age at diagnosis of bronchiectasis, the hazards of death increased by 10.0%(HR,1.10;95%CI,1.05-1.14). The data further showed that the hazards of death in the patients who are past smokers are 2.28 times the hazards of death, compared to the patients who are never smokers., while adjusting for all other

variables in the model (HR,2.28;95%CI,0.88-5.90).While considering for gender the analyses of the data showed that the hazards of death in the female patients are 0.45 times or 55% less than the hazards for the male patients, while controlling for all other variables in the model, but the data is not statistically significant (HR,0.45; 95%CI, 0.19-1.03)

While considering for level of education attained the data showed that hazards of death in the patient with some college are 1.40 times the hazards for patients with high school or less, while controlling for all other variables in the model (HR,1.40;95%CI, 0.47-4.14). The data also showed that the hazards of death in a patient with college or post grad are 0.39 times the hazards of death for the patient with high school or less, while controlling for all other variables in the model, but the results are not statistically significant (HR,0.39;95%CI,0.11-1.30). The data also showed that the hazards for death in a person with education in missing category are 0.67 times the hazards for death for the patient with high school or less, while adjusting for all other variables in the model, but the results are not statistically significant (HR,0.67;95%CI, 0.21-2.11).

Kaplan Meier Survival Analysis:

Kaplan Meier survival analysis was done to check the difference in the survival of the two groups i.e. non- cystic fibrosis patients with NTM and non-NTM infection. We used data from 1415 patients for the survival analysis as the patients who had the “age at diagnosis” missing were not included in the Kaplan Meier survival and the Kaplan Meier curve shows that the two groups are similar on survival. The Log rank test has a p-value of 0.7656, which

is greater than 0.05, thereby again showing that there is not enough statistical evidence to say that the two groups are different on survival.

DISCUSSION

We explored the comparison of the non-cystic fibrosis bronchiectasis patients with Non Tubercular Mycobacteria (NTM) and non-NTM infections, using the data from the COPD Foundation's Bronchiectasis Research Registry. The study has found that the odds of having NTM infection increases with age, and that the two groups are different with respect to age as the mean age for the patients in the NTM group is 66.00, while the mean age for the patients in the non-NTM group is 61.96, which shows that the NTM group has significantly more participants with higher age. This finding may be explained by the fact that as the age advances, the symptoms of the bronchiectasis disease worsens, thereby making it more difficult for the patient to avoid the NTM infection or may be the possibility that the biofilm on the NTM bacteria helps them to establish themselves in the elderly patients, in whom the immune defense is decreased.

The study also found that the females are more likely to have NTM infection. The study shows that 85% of the patients with NTM infection were females compared to 71% in the non-NTM group. The study also found that females are 2.34 times more likely to have NTM infection. This may be explained by the fact that sex hormones may plays a role in defense against NTM infection. There have been studies, which showed the differential effect of sex hormones on the NTM infection and showed that NTM infection increases in females with increasing age and the increase was phenomenal after the menopause and since most

participants in the NTM group are elderly females, therefore they are more likely to have NTM infection.[16] The study did not found any difference between the groups with regard to smoking, which may be explained by the fact that very low percentage of the patients are current smokers, with current smokers constituting 1.67% and 1.20% of the NTM and non-NTM group respectively, which may have led to no difference between the groups .The study did not found any major difference in survival of the two groups on the Cox proportional hazards regression even though the observations in the NTM group are little better as compared to the Non-NTM group. The study did not found any difference between the two groups with respect to survival, while using Kaplan Meier, which may be due to the fact that data of the Bronchiectasis Research Registry is from the tertiary practice centers. All patients who are in the tertiary practice center gets proper care. With sputum culture and treatment specific for the culture, which may be controlling the symptoms and survival in these patients, thereby leading to no difference in survival. Similarly, level of education may have an impact on the delay of diagnosis, due to proper education and exposure, but once the person is in the tertiary practice center, the care is of the same high level, which may have led to no difference in the survival within two groups.

There are several limitations to the study. Since this study analyzes the data from the Bronchiectasis Research Registry, rather than the population based sample, therefore there may be potential bias in the demographic information, which may be reflective of the demographics of the patients frequently seen in the tertiary practice centers participating in the registry. The most of the tertiary centers participating in the study are located in the eastern United States, which may further lead to bias.

CONCLUSION

The study analyzed the 1660 patients with non-cystic fibrosis bronchiectasis with the basis of NTM infection and found that the 2 groups differ on age and gender characteristics but had the similar survival (n=1415 for Kaplan Meier). There are not many studies done on the patients with non-cystic fibrosis bronchiectasis. This is one of the first study done on the data from bronchiectasis research registry, so there are not many resources to compare the results of this study. Further studies need to be done to enhance our knowledge of the non-cystic fibrosis comparing NTM and non-NTM groups.

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Table 1: Descriptive statistics showing all participants and NTM and Non-NTM groups. Mean and Standard deviation are given for continuous variables, while frequency and percentages (in parenthesis) are given for categorical variables.

Variable	**All Participants** **1660**	**Non Tubercular Mycobacteria (NTM)** **902**	**Non-NTM** **758**
AGE **Mean ± SD**	64.16 ± 14.24	66.00 ± 11.81	61.96 ± 16.42
Smoking Status (1) Smoker (2) Past Smoker **(3)** Never Smoker	1652 24 (1.45) 633 (38.32) 995 (60.23)	899 15(1.67) 341(37.93) 543(60.40)	753 9 (1.20) 292(38.78) 452(60.03)
Gender Male Female	1659 345 (20.80) 1314 (79.20)	902 130(14.41) 772(85.59)	757 215(28.40) 542(71.60)
Mortality Status (1) Alive (2) Dead (3) Lost to follow up	1653 1502(90.87) 80 (4.84) 71 (4.30)	896 823(91.85) 46(5.13) 27(3.01)	757 679(89.70) 34(4.49) 44(5.81)
Education Level (1) High School or less (2) Some College (3) College of Post Grad (4) Missing	1660 218(13.13) 252(15.18) 685(41.27) 505(30.42)	902 118(13.08) 135(14.97) 374(41.46) 275(30.49)	758 100(13.19) 117(15.44) 311(41.03) 230(30.34)

Table 2: Univariate logistic regression results for unadjusted association of variables and NTM infection as an outcome

Variable	Odds Ratio	95% Confidence Interval	P-Value
Age	1.02	(1.01), (1.03)	<.0001
Smoking Status			
(1)Current Smoker	1.39	(0.60), (3.20)	0.4426
(2)Past Smoker	0.97	(0.80), (1.19)	0.7815
(3)Never Smoker	Reference		
Gender			
M	Reference		
F	2.36	(1.84), (3.00)	<.0001
Mortality Status			
(1) Alive	Reference		
(2) Dead	1.12	(0.71), (1.76)	0.6356
(3) Lost to Follow up	0.51	(0.31), (0.83)	0.0065
Education			
(1) High School or Less	Reference		
(2) Some College	0.98	(0.68), (1.41)	0.9037
(3) College of Post Grad	1.02	(0.75), (1.38)	0.9034
(4) Missing	1.01	(0.74), (1.40)	0.9353

Table 3: Multivariate logistic regression results for adjusted association of variables with NTM infection as outcome.

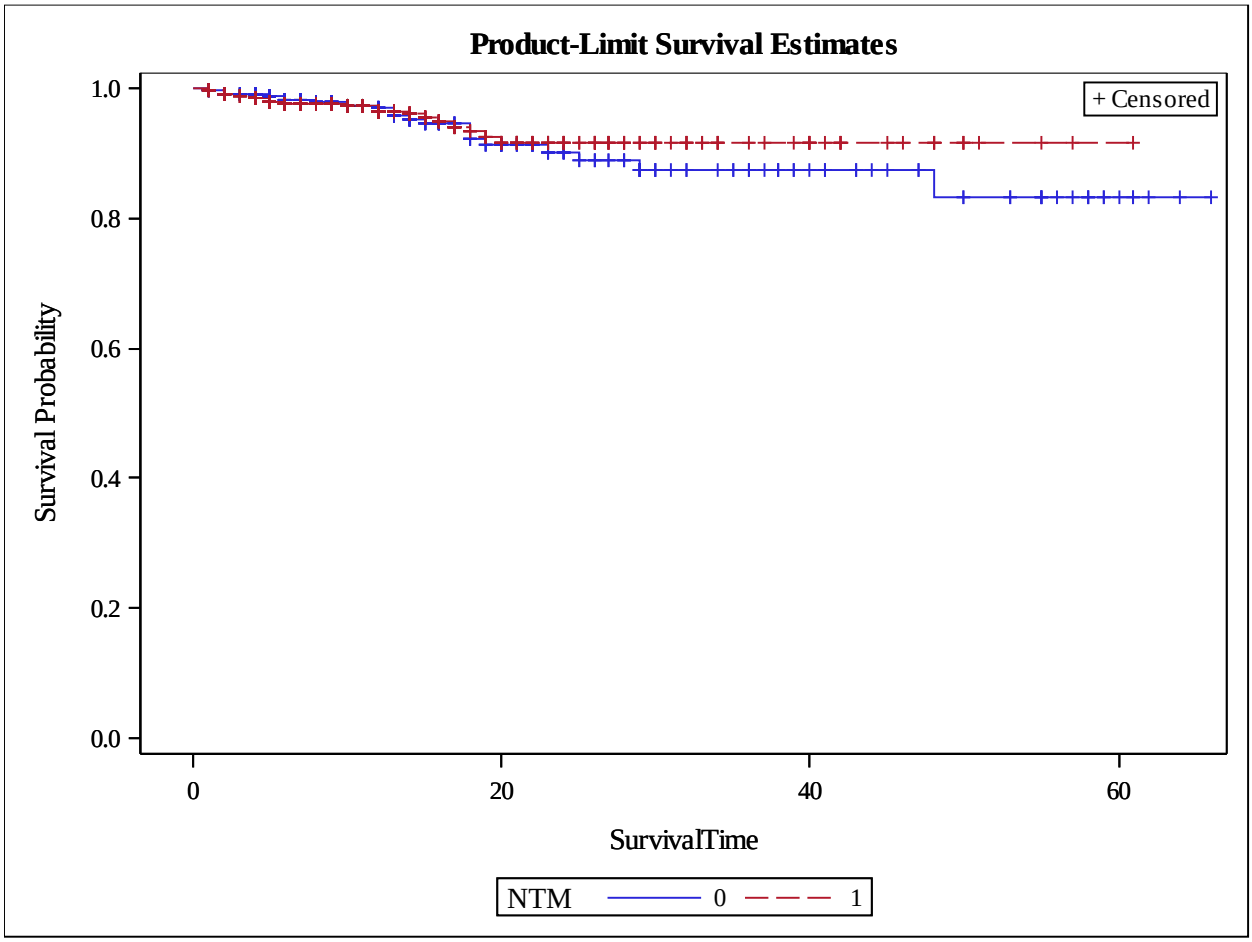
Variable	Odds Ratio	95% Confidence Interval	P Value
Age	1.02	(1.01), (1.03)	<.0001
Smoking Status			
(1)Current Smoker	1.99	(0.84), (4.76)	0.1189
(2) Past Smoker	0.89	(0.72),(1.10)	0.2689
(3) Never Smoker	Reference		
Gender			
M	Reference		
F	2.34	(1.82) ,(3.02)	<.0001
Mortality Status			
(1)Alive	Reference		
(2) Dead	1.15	(0.71), (1.89)	0.5691
(3) Lost to Follow up	0.53	(0.31), (0.89)	0.0162
Education			
(1)High School or less	Reference		
(2) Some College	1.04	(0.71), (1.52)	0.8298
(3) College or Post Grad	1.17	(0.85), (1.61)	0.3343
(4) Missing	1.10	(0.79), (1.53)	0.5834

Table 4: Results for Cox proportional hazard regression

Variable	Non-Tubercular Mycobacteria (NTM)		Non-NTM	
	Hazard Ratio	95% Confidence Interval	Hazard Ratio	95% Confidence Interval
Age at Diagnosis	1.07	(1.04),(1.11)	1.10	(1.05), (1.14)
Smoking Status				
1.Current Smoker	7.63	(1.58), (36.85)[#]	*	*
2. Past Smoker	1.56	(0.71), (3.43)	2.28	(0.88), (5.90)
3. Never Smoker	Reference		Reference	
Gender				
1. Male	Reference		Reference	(0.19), (1.03)
2. Female	0.42	(0.17),(1.02)	0.45	
Education Level				
1. High School or less	Reference		Reference	
2. Some College	0.64	(0.22), (1.86)	1.40	(0.47), (4.14)
3. College or post grad	0.34	(0.13), (0.93)	0.39	(0.11), (1.30)
4. Missing	0.37	(0.12), (1.13)	0.67	(0.21), (2.11)

Very few observations in the category. * No observations in the category

Graph 1: Kaplan Meier survival curve comparing NTM and Non-NTM groups



Survival time in years

NTM 0= No NTM infection and NTM 1= NTM infection

LOG RANK= 0.7656

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