2019

ESTIMATING DISEASE SEVERITY, SYMPTOM BURDEN AND HEALTH-RELATED BEHAVIORS IN PATIENTS WITH CHRONIC PULMONARY DISEASES

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Digital Object Identifier: https://doi.org/10.13023/etd.2019.059

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ESTIMATING DISEASE SEVERITY, SYMPTOM BURDEN AND HEALTH-RELATED BEHAVIORS IN PATIENTS WITH CHRONIC PULMONARY DISEASES

DISSERTATION

A dissertation submitted in partial fulfillment of the
requirements for the degree of Doctor of Philosophy in the
College of Public Health
at the University of Kentucky

By
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2019

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ABSTRACT OF DISSERTATION

ESTIMATING DISEASE SEVERITY, SYMPTOM BURDEN AND HEALTH-RELATED BEHAVIORS IN PATIENTS WITH CHRONIC PULMONARY DISEASES

Chronic pulmonary diseases include a wide range of illnesses that differ in etiology, prevalence, symptomatology and available therapy. A common link among these illnesses is their impact on patients' vital function of breathing, high symptom burden and significantly impaired quality of life.

This dissertation research evaluates disease severity, symptom burden and health behaviors of patients with three different chronic pulmonary conditions. First, alpha-1 antitrypsin deficiency (AATD) is an inherited condition that typically is associated with an increased risk of early onset pulmonary emphysema. This study examines differences in demographic, health, and behavioral characteristics and compares clinical outcomes and health related behaviors and attitudes between two severe genotypes of AATD - ZZ and SZ. The findings of the study suggest that patients with SZ genotype and less severe form of deficiency report higher number of exacerbations, comorbidities, as well as unhealthy behaviors such as lack of exercise and current smoking. In addition, individuals with the more severely deficient ZZ genotype are more adherent to disease management and prevention program recommendations and maintain a healthier lifestyle than individuals with SZ genotype.

Second chronic lung disease examined in this research was chronic obstructive pulmonary disease (COPD), the fourth leading cause of death and second leading cause of disability in the United States. Prevalence and burden of cough and phlegm, two of the most common symptoms of the COPD, were assessed among participants of the COPD Foundation's Patient-Powered Research Network (COPD PPRN). In addition, association between patient-reported levels of phlegm and cough, clinical outcomes and patients' quality of life were evaluated. Participants' quality of life was assessed using Patient Reported Outcome Measurement Information System instrument PROMIS-29. Association between changes in symptom severity over time and patient-reported quality of life were examined. Findings of this study indicated that severity of cough and phlegm were associated with higher number of exacerbations, greater dyspnea, and worsened

patient-reported quality of life including physical and social functioning. Improvement in cough and phlegm severity over time was associated with better patient-reported quality of life.

Third pulmonary illness described in this dissertation is non-cystic fibrosis bronchiectasis (NCFB), a rare and etiologically diverse condition characterized by dilated bronchi, poor mucus clearance and susceptibility to bacterial infection. Association between presence of Pseudomonas aeruginosa (PA), one of the most frequently isolated pathogens in patients with NCFFB, and disease severity was assessed utilizing enrollment data from the Bronchiectasis and NTM Research Registry (BRR). NCFB disease severity was evaluated using modified versions of validated in large international cohorts instruments, the Bronchiectasis Severity Index (BSI) and FACED. The findings of this study indicate that PA infection is common in NCFB patients, and presence of PA in patients' sputum is associated with having moderate and high severity of bronchiectasis. In addition, the results of this study suggest that the two severity assessment instruments classify patients with NCFB differently which may be attributed to a greater number of severity markers utilized in the calculation of the BSI compared to FACED.

In conclusion, the proposed dissertation aims to enhance understanding of differences in health outcomes between genotypes of AATD within AlphaNet registry, and to guide future health-promoting behaviors. It highlights the burden of common symptoms such as cough and phlegm in patients with COPD within COPD PPRN and their association with patients' quality of life. In addition, it introduces modified indices of NCFB severity and emphasizes high burden of the disease in patients with presence of PA within US BRR.

KEYWORDS: Lung disease, Symptom burden, Disease severity, COPD, Bronchiectasis, Alpha1-antitrypsin deficiency.

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03/04/2019

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DEDICATION

To my beloved son Ben who has inspired me to pursue my dreams and to complete this dissertation research

ACKNOWLEDGMENTS

This dissertation research would not have been possible without the guidance and efforts of my Dissertation Committee. I would like to express my deepest appreciation to my dissertation advisor and chair, Dr. Erin Abner, for the continuous support, motivation and immense knowledge. My sincere thanks goes to Dr. Steve Browning, the DGS for the Epi/Bio PhD and my dissertation committee member, for his endless support and guidance throughout this research and the entire PhD program journey. My deepest gratitude goes to Dr. David Mannino, my mentor and committee member, who has introduced me to the world of chronic pulmonary diseases and provided clinical expertise and support in the development of this dissertation research. I would also like to thank my committee member, Dr. Phil Westgate, for being a great source of knowledge and for sharing his constructive suggestions for this dissertation. Finally, I would like to thank my outside examiner, Dr. Patricia Freeman, for agreeing to serve on my committee and for her insightful feedback related to this research. I also would like to acknowledge and thank AlphaNet and Dr. Robert Sandhaus, the COPD Foundation and Dr. Barbara Yawn, the BRR and Dr. Timothy Aksamit, as well as Ms. Malanga, Ms. Pasquale, Ms. Prieto, and many other collaborators for their continued support and for allowing me to utilize their data for my dissertation research. I would like to extend my gratitude to the participants of AlphaNet, the COPD PPRN, and the BRR for their participation that made this research possible.

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CHAPTER 1. INTRODUCTION

Chronic pulmonary diseases, which include a wide range of illnesses of various lung structures, represent a growing public health problem and affect over a billion of people of all ages throughout the world.[1,2] In the United States, chronic lower respiratory diseases are the fourth leading cause of death.[3] Some of these illnesses are preventable and curable, while others still have no treatment available.[4]

Despite the heterogeneity in their etiology, prevalence and presentation, all chronic pulmonary diseases affect individuals' lungs and hence the vital act of breathing.[4] The burden of these conditions on people's daily lives, as well as the economic burden to society in view of lost productivity, disability and healthcare costs is immense. Exacerbations, or acute flare-ups of symptoms, are common in people with chronic respiratory diseases, and associate with decreases in health-related quality of life (HRQOL) and increases in disease-associated mortality.[5]

Many respiratory diseases, such as Chronic Obstructive Pulmonary Disease (COPD) remain highly prevalent in the United States (US) and worldwide. In 2015, over 15 million adults in the US reported ever receiving a COPD diagnosis.[6] In fact, the actual prevalence might be significantly higher considering that over 12 million adults may have undiagnosed COPD due to variations in diagnostic criteria.[7,8] COPD is a heterogeneous group of conditions that include chronic bronchitis, emphysema, and asthma components.[9] It is characterized by symptoms related to airflow obstruction, such as chronic cough and production of sputum, dyspnea on exertion and wheezing.[7] Presence of these symptoms along with the recurrent lower respiratory tract infections, history of risk factors such as smoking, environmental and genetic factors, and family history of

COPD, in an individual over age of 40 may indicate COPD and requires spirometry to establish a diagnosis.[10]

In COPD patients, burden of the disease is high. COPD patients suffer from chronic respiratory symptoms, fatigue, and often experience flare-ups of their symptoms that require physician or emergency room visits, change in therapy regimen, or even hospital admissions. Some of the main goals of COPD treatment are relief of symptoms and prevention of future excerbations.[11] Previous research consistently found decreased HRQOL in patients with COPD, and its association with disease severity.[11,12] Recent studies suggest symptom burden to be an appropriate marker for COPD disease severity.[11] Thus, patient-perceived and reported symptom burden should be emphasized in COPD patient evaluation. HRQOL in patients with COPD is a composite measure that accounts for many psychological factors and other self-perceived patient experiences.[13] Patient-reported outcome measurement tools, such as Patient Reported Outcome Measurement Information System (PROMIS-29) have been validated and utilized to assess and incorporate COPD patients' subjective experience in their disease severity assessment.

Some illnesses under the umbrella of chronic pulmonary diseases are less common or even rare. In the US, a disease is considered rare if its prevalence does not exceed 200,000 individuals, or if it affects a greater number of people, but drug development and availability costs for the disease might not be potentially recovered from sales.[14,15] Approximately 7,000 rare conditions affect estimated 30 million people in the US and lead to significant morbidity and mortality.[16] Over 80% of rare diseases are genetically based and many are chronically debilitating.[16] Alpha-1 antitrypsin deficiency

(AATD) is an autosomal codominant genetic condition that results in the production of defective Alpha-1 antitrypsin (AAT) protein.[17] There are over 200 genetic variants of AAT. The two most frequent deficient alleles are PiZ and PiS.[17] PiZZ genotype results in very low (below the protective threshold of 50 mg/dL) and PiSZ in below normal (less than 90 mg/dL) serum concentrations of AAT.[18,19] Some researchers consider AATD not a rare but a rarely diagnosed illness.[20] Lung disease in patients with AATD often presents with symptoms of COPD, and most commonly emphysema, and, thus is often misdiagnosed. AATD is considered one of the most common metabolic disorders among individuals of northern European descent.[21] Low serum concentration of AAT and detection of genetic mutation assist in establishing the cause of patients' COPD symptoms. AATD is estimated to affect one in 5,000-7,000 individuals in North America. Smoking, along with other environmental and occupational exposures, is one of the main factors influencing development of the lung disease regardless of genotype.[21] Early diagnosis, healthy lifestyle, standard therapy for obstructive lung disease and, if indicated, periodic augmentation therapy to replace the deficient protein are the main disease management options in patients with AATD-related lung disease.[21]

Another rarely diagnosed chronic pulmonary disease, non-cystic fibrosis bronchiectasis (NCFB), is inherently heterogeneous and is characterized by progressive and irreversible airway damage.[22] Due to a complex pathophysiology involving infective, immune and inflammatory mechanisms, which chronically destruct bronchi in a so called "vicious cycle", bronchiectasis patients require specific and long-term management.[22,23] Prevalence of NCFB continues to increase which may be explained by a greater awareness of the disease among clinicians and radiological advancements that aid in

accurate diagnosis.[22] Some of the main presentations of bronchiectasis include chronic cough with sputum production, fatigue, hemoptysis, COPD symptoms in non-smokers, frequent respiratory infections and isolation of sputum pathogens such as *Pseudomonas aeruginosa* (PA) or Non-tuberculous mycobacterium (NTM).[24] High resolution CT scan confirms the diagnosis of bronchiectasis.[24]

Due to the complexity of various symptoms, recurrent exacerbations and hospitalizations, doctors' visits, and frequent sputum microbiology and imaging testing, the burden of bronchiectasis on patients' lives and healthcare systems is substantial.[23,24] Bronchiectasis severity is a multidimensional concept and use of multiple parameters is needed to capture the complexity of the disease burden and prognosis. The Bronchiectasis Severity Index (BSI) and the FACED have been developed and validated to improve the identification of high-risk NCFB patients and to guide therapy decisions.[25,26]

The chapters that follow present studies that estimate disease severity, symptom burden and health-related behaviors in patients with the described above three chronic pulmonary conditions. In Chapter Two, "Comparing Patients with ZZ versus SZ Alpha-1 Antitrypsin Deficiency within AlphaNet's Disease Management Program", demographic, clinical characteristics and health-related behaviors of patients with two most prevalent AATD genotypes, PiZZ and PiSZ, are evaluated. The major findings from this study identified that patients with ZZ and SZ genotypes in AlphaNet's disease management program differ in health outcomes and health-related behaviors.[27] Patients with SZ genotype had more comorbidities and were not as engaged in health-promoting behaviors compared to patients with ZZ genotype. ZZ patients were found to be more adherent to

the recommendations of the disease management program and maintained a healthier lifestyle than SZs.

The study presented in Chapter Three, "The Burden of Cough and Phlegm in Chronic Obstructive Pulmonary Disease (COPD) Patients within the COPD Patient-Powered Research Network (PPRN)" addresses the association between severity of cough and phlegm and quality of life in patients with self-reported physician-diagnosed COPD. The findings of this study identified that cough and phlegm severity levels were associated with higher number of exacerbations, greater dyspnea, and worsened patient-reported quality of life including physical and social functioning and mood. The study results indicated that improvement in cough and phlegm severity over time were associated with better patient-reported quality of life. Exploration of new treatments aimed at improvement of cough and phlegm severity in this patient population were recommended.

Findings presented in Chapter Four, "*Pseudomonas aeruginosa* Associated with Severity of Non-cystic Fibrosis Bronchiectasis Measured by the Modified Bronchiectasis Severity Score (BSI) and the FACED: the US Bronchiectasis and NTM Research Registry (BRR) Study", supports previous research that PA infection is common in patients with NCFB. The study identified that the severity of bronchiectasis is significantly greater in patients with PA, which emphasizes the high burden of the disease. This chapter concludes that further collaborative work in this area are needed including exploration of new management options aimed at the improvement of patient outcomes and prognosis in PA infected NCFB patients.

Chapter Five of this dissertation provides summaries of major findings, discusses strengths and limitations, and suggests future research recommendations.

CHAPTER 2. COMPARING PATIENTS WITH ZZ VERSUS SZ ALPHA-1 ANTITRYPSIN DEFICIENCY WITHIN ALPHANET'S DISEASE MANAGEMENT PROGRAM

Abstract

Background: The aim of this study was to examine differences in demographic, health, and behavioral characteristics in individuals with ZZ and SZ genotypes of alpha-1 antitrypsin deficiency (AATD) within AlphaNet's Disease Management and Prevention Program (ADMAPP).

Methods: Self-reported data from 3,535 patients with AATD, including 3,031 (85.7%) patients with ZZ, ZNull, and NullNull genotypes (referred to here as ZZ), and 504 (14.3%) with the SZ genotype were analyzed using t-tests, ANOVAs, and Chi-squared tests.

Results: The average age of the cohort was 56.3±10.6 years. The majority of respondents were males (51.2%), Caucasians (98.2%), and married (65.2%). SZs reported having more frequent exacerbations ($p<0.001$) and hospitalizations ($p=0.012$) than ZZs. A higher proportion of SZs than ZZs had been diagnosed with high blood pressure, diabetes, congestive heart failure, and other comorbid conditions. SZs were more likely than ZZs to report "poor" health ($p=0.005$). Over a third (38.4%) of SZs do not exercise compared to 27.1% of ZZs ($p<0.001$). A greater proportion of SZs compared to ZZs view themselves as being overweight ($p<0.001$) or "out of shape" ($p=0.001$). A higher proportion of SZs than ZZs reported any history of smoking and current smoking ($p<0.001$).

Conclusions: In patients with AATD and lung disease participating in a disease management program, a higher proportion of SZs than ZZs report exacerbations, comorbidities, and overall poor health, as well as unhealthy behaviors such as lack of exercise and current smoking. Future work should consider the extent to which genotype-specific health promotion interventions would be useful.

2.1 Introduction

Alpha-1 antitrypsin deficiency (AATD) is an autosomal co-dominant disorder that results from mutations of the SERPINA1 gene and typically is associated with the elevated risk of early onset pulmonary emphysema[28] in adults, liver disease in children and adults and, more rarely, necrotizing panniculitis.[29]

SERPINA1 is considered a polymorphic gene.[30] The PiM-allele represents the normal genotype. The two most common mutations of the gene associated with AATD are the PiZ and PiS mutations, where Pi stands for "protease inhibitor".[31] Homozygous PiZZ is the most commonly identified severely deficient genotype while the PiS-allele leads to a milder plasma deficiency of AAT.[30] Over 200 mutations of the gene have been discovered, with approximately one third of these mutations leading to clinically significant deficiency.[31] Serum levels of AAT between 85 and 215 mg/dL are considered normal,[32] although normal ranges vary by laboratory. Individuals with a ZZ genotype rarely have levels above 57 mg/dL, and levels below this value are presumed to provide inadequate lung protection.[31]

Both Z and S mutations are believed to have originated among populations of European (Caucasian) descent.[33] The Z-gene is associated with the Scandinavian/Baltic region,[34] and the S-gene is considered to derive from the Iberian peninsula.[35] AATD can be found in all major racial subgroups in the world, although often at a very low frequency.[36]

Previous studies that compared clinical features of SZ and ZZ patients have found significantly fewer respiratory symptoms, less severe airflow obstruction, and fewer radiographic lung abnormalities in SZ patients.[37] Similarly, a study using the Spanish AATD registry (REDAAT) determined that ZZs have greater lung function impairment than SZs.[35] The results of a large study in the UK demonstrated similar disease progression between SZs and ZZs although SZs had better baseline characteristics.[38] These findings were explained by the greater importance of AAT levels rather than genotype.[38] Other studies have demonstrated a correlation of serum AAT levels with the severity of emphysema.[39] Smoking is the major risk factor for development of lung disease in patients with AATD regardless of genotype.[40,41]

It is important to know whether genotype is associated with health outcomes and health behaviors, in order to determine whether individuals with the SZ genotype have differing needs from ZZs with regard to health education and behavioral interventions such as smoking cessation. The primary aim of this study was to examine differences in demographic, health, and behavioral characteristics in individuals with ZZ and SZ genotypes among individuals who are participating in a disease management program designed for patients with AATD and lung disease.

2.2 Methods

The study population consisted of participants of AlphaNet, a not-for-profit health management organization that coordinates management and treatment of individuals with AATD and lung disease in the US.[42] Enrollment in ADMAPP is offered when an individual is prescribed plasma-derived, intravenous AAT for the treatment of lung disease due to AATD (augmentation therapy). Analyses were conducted on de-identified data collected by AlphaNet. The study was approved by the University of Kentucky Institutional Review Board (IRB).

The inclusion criteria were that the participants were members of AlphaNet and had either a ZZ, ZNull, NullNull (analyzed in combination with ZZ) or SZ genotype of AATD. The final sample included 3,535 respondents (Figure 1). Of these, 3,031 (85.7%) were identified as ZZs. The ZZs can be broken down as follows: ZZ (n=2,979, 98.3%), ZNull (n=38, 1.2%), and NullNull (n=14, 0.5%). The present study analyses compared baseline characteristics of AATD patients with the ZZ genotype to those with the SZ genotype. All data were collected using questionnaires administered via a telephone interview.

Statistical analyses

Descriptive statistics were computed for baseline characteristics for the overall sample and stratified by genotype (ZZ vs. SZ). The results for continuous variables were reported as mean (SD), and for categorical variables by frequencies and proportions. Values between the groups were compared using t-test/ANOVA, and Chi-squared test respectively. Post-hoc comparison of adjusted standardized residuals was used to determine the source of the statistically significant Chi-square for categorical variables.

Negative binomial (NB) regression models were fit for frequency of exacerbations and visits to a primary care physician in the past year adjusting for age, sex, smoking status and Charlson Comorbidity Index (CCI). A zero-inflated negative binomial (ZINB) model was fit for frequency of hospitalizations adjusting for the same covariates. The significance level for all analyses was set at 0.05. False discovery rate control was used to correct for multiple univariate testing.[43] SAS 9.4 and SPSS version 22 were used to conduct analyses.

2.3 Results

Table 2.1 demonstrates the baseline demographic characteristics of the overall sample (n=3,535) and stratified by genotype: ZZ (n=3,031, 85.7%) and SZ (n=504, 14.3%). Average age of the study population was 56.3±10.6 years. Patients with the ZZ genotype were slightly younger than SZs (55.9 years vs. 58.6 years, $p<0.001$), and a greater proportion of ZZs were Caucasians (98.4% vs. 96.8%, $p=0.012$), and reported being married (66.1% vs. 59.3%, $p=0.004$). The majority of respondents were male (51.2%) with no significant differences by genotype. Over ninety percent of all the respondents (92.7%) were on augmentation therapy with a greater proportion of ZZs than SZs (93.5% vs. 87.1%, $p<0.001$). The CCI score (which accounts for number and complexity of comorbidities) was significantly higher among SZs than ZZs ($p<0.0001$)[44].

A total of 3,274 (97.6%) patients reported ever having lung disease, with no significant difference between the genotypes. Emphysema/chronic bronchitis/COPD (96.8%) and asthma (37.7%) were the most frequent types of lung disease reported by the respondents.

Among those who reported ever having lung disease, significant differences were found in exacerbation frequency between ZZ and SZ patients ($p<0.001$, Table 2.2). Based on post-hoc analysis using standardized residuals, a significantly greater proportion of SZs than ZZs reported having monthly (20.2% vs. 13.9%) and quarterly (21.3% vs. 16.2%) exacerbations, while ZZs reported more semi-annual exacerbations (13.9% vs. 9.6%). SZs did not differ from ZZs with regard to percent that used oxygen regularly, number of hours oxygen was used per day, or coughing up sputum regularly.

The average number of visits to the primary care physician over the past year among all the respondents was 3.2±1.9, and to the lung specialist was 2.9±1.7. The mean number of hospitalizations was 0.7±1.3. SZs reported more primary physician visits ($p<0.001$), lung specialists visits ($p<0.001$) and hospitalizations ($p=0.012$) than ZZs.

Table 2.3 presents the frequencies of the comorbidities within the overall study sample and stratified by genotype. The most frequent comorbidities were high blood pressure (40.3%), gastroesophageal reflux (34.8%), sinus disease (16.1%), heart rhythm problems (12.9%) and any tumor/cancer (11.9%). This study found that a statistically significantly greater proportion of SZs in the cohort were diagnosed with the six most prevalent comorbidities.

Table 2.4 presents the results of self-reported health behaviors and fitness characteristics of ZZs and SZs. The majority of respondents reported having ever smoked (73.1%), and a significantly greater proportion of SZs than ZZs reported having ever smoked ($p<0.001$). In addition, SZs are more likely to continue to smoke ($p<0.001$), have been smoking longer ($p<0.001$), and report smoking more packs per day ($p<0.001$). Contrary to the findings for smoking, a higher proportion of ZZs report that they

consume alcohol (p=.009), and ZZs consume more drinks per week on average than SZs (p=.030).

In view of self-perceived health and fitness, a significantly greater proportion of SZs than ZZs perceive themselves as being overweight (p<0.001), out of shape (p=0.001) and in "poor health" (p=0.005). More ZZs report that they exercise regularly compared to SZs, and 38.4% of SZs do not exercise at all compared to 27.1% ZZs (p<0.001).

The majority of patients reported that they follow the guidelines of ADMAPP (53.5%), and a significantly greater proportion of ZZs report following the program compared to SZs (p=0.026). Almost a half of the participants (49.2%) reported ever reading the BFRG with no difference by genotype.

Most patients reported being very comfortable with their knowledge about AATD (51.1%). However, significant differences were found between the genotypes (p<0.001). Specifically, a greater proportion of SZs, when compared to ZZs, reported being either "not comfortable" (9.8% vs. 4.0%) or "somewhat comfortable" (55.0% vs. 42.2%) with knowledge about their condition.

Table 2.5 presents results of the adjusted NB and ZINB models. The criteria for assessing goodness of fit of each of the regression models showed adequate fit: deviance (scaled deviance) value/DF and Pearson Chi-Square (Scaled Pearson) value/DF were reasonably close to 1 (between 0.95 and 1.18) which indicates adequate fit of the models to the data. The selected regression models showed superior fit using Vuong test and AIC, AICC, and BIC criteria, when compared to other types of count models.

As demonstrated in Table 2.5, genotype was associated with the number of exacerbations and visits to a primary care physician after adjusting for age, gender, current smoking status, and CCI score. SZs had 1.21 times the rate of pulmonary exacerbations (IRR=1.21, 95% CI: 1.05-1.40) and visits to a primary care physician (IRR=1.21, 95%CI: 1.12-1.30) in the past year compared to ZZs.

2.4 Discussion

Earlier work by Turino et al.[37] described clinical features of a relatively small number of patients with the SZ genotype of AATD and AAT concentrations above or below 11 μM (~57 mg/dL), including the effects of smoking on development of lung disease in SZs. More recent studies comparing characteristics of individuals with the ZZ and SZ genotypes were mainly carried out in Europe[35,38,45] as the prevalence of S-allele is the highest in the general population of Spain and Portugal (17.3 and 13.8 per 1,000, respectively).[46]

Although any individual with AATD can enroll in AlphaNet's disease management program, the vast majority of individuals entered because of a prescription for augmentation therapy for lung disease due to AATD. Individuals not receiving augmentation therapy are moved to a different program within AlphaNet that focuses on risk reduction: Risk Evaluation to Ensure Continued Health (REACH). Thus, the population described here is greatly enriched for individuals with lung disease due to AATD. Since individuals with the SZ genotype are considerably less likely to develop lung disease than ZZs,[37] many of the differences reported in this study may be reflective of the subpopulation of SZs with risk factor exposure sufficient to have led to clinically significant lung disease. Risk for development of lung disease is associated with the

interaction between genetic factors and various environmental exposures such as smoking.[40]

Prior studies have noted higher mean smoking consumption of SZs compared to ZZs.[47] This study findings complement these observations by showing that when compared to ZZs, SZs had a significantly longer smoking history with greater number of packs smoked per day. Further, the SZs in our sample were more likely to continue smoking after being diagnosed with lung disease. These results reflect the importance of emphasizing behavioral interventions and health education including smoking cessation, especially among SZs, as well as early diagnosis of AATD prior to the development of heavy smoking habits.[47]

Exacerbations commonly occur among patients with AATD-related lung disease[48] and, in previous research, were demonstrated to be associated with a decline in lung function.[48] In our sample, SZs reported more frequent exacerbations than ZZs, even after adjusting for age, sex, current smoking status and CCI score. Possible explanations include greater prior exposure to smoking, and lower adherence to healthy lifestyle recommendations, including adherence to AlphaNet's disease management program. However, lack of pulmonary function data limited our ability to compare lung disease severity between genotypes.

Previous research has demonstrated an association between AATD and certain comorbidities, such as ulcerative colitis and hypothyroidism[49] among ZZs. Other studies demonstrated associations between ZZ and MZ genotypes of AATD and reduced blood pressure, as well as MZ and reduced risk of ischemic cerebrovascular and ischemic heart disease.[50,51] This study results show a significantly higher prevalence of cardiovascular

comorbidities, including hypertension, cerebrovascular disease, congestive heart failure, and arrhythmia among SZs compared with ZZs. The reasons for this association with SZ genotype are not well understood, nor sufficiently investigated previously. It should be noted that SZs in our cohort are slightly older than ZZs; also, the diagnosis of AATD may prompt a more thorough assessment for other health problems among SZs. Additionally, our findings of unhealthy lifestyle of the majority of SZs in this study population, may have contributed to the greater prevalence of cardiovascular comorbidities among patients with this genotype.

Previous research has explored the effects of genetic information on health behaviors of patients and their families.[52-56] These studies have found inconsistent results with regard to the effect of genetic information on smoking cessation and motivation to improve diet and physical activity. The present study demonstrated that ZZs and SZs significantly differ in their perception of health and fitness as well as their health behaviors. A greater proportion of SZs viewed themselves as overweight, out of shape and in poor health, and they also exercise less and report heavier and longer history of smoking compared with ZZs in our study. These findings may be explained by the perception that the SZ genotype presents a lower risk of the disease in view of the higher AAT levels in plasma. Our findings with regard to alcohol consumption suggest that, regardless of genotype, additional education about moderation of alcohol consumption should be considered due to the increased risk of liver disease among individuals with AATD.

ADMAPP is a vital part of AlphaNet's commitment to improve patients' health outcomes.[42,57] The present study shows that a significantly lower proportion of SZs report

following the guidelines of ADMAPP compared to ZZs. This lower adherence to the program may be due to the earlier mentioned concept of the low self-perceived seriousness of their condition. It should also be noted that SZs are less comfortable with the level of their knowledge about AATD compared to ZZs.

Our results suggest that, among individuals with AATD who have developed lung disease, people with a less severe genotype who develop lung disease have worse health outcomes and health behaviors. Thus, the people who are less at risk (from a genetic standpoint) to develop lung disease may actually do worse once they have developed lung disease. While prevention efforts may need to be targeted to ZZs (since they are most at risk to develop disease) it is possible that disease management may be even more vital to SZs.

Understanding differences and similarities between various genotypes of AATD is of great importance from the public health perspective. Early knowledge and awareness of AATD allows for timely testing, smoking prevention and cessation, and initiation of augmentation therapy when indicated.[58]

Strengths and limitations

The main strengths of the present study include a large number of patients with AATD-related lung diseases enrolled in the disease management program, as well as unique data on multiple health-related behaviors collected by AlphaNet.

Several limitations must be acknowledged. First, a considerably larger fraction of ZZs develop lung disease compared with SZs. Since only patients with lung disease were invited to participate in ADMAPP, this may have introduced ascertainment bias into the

study. Although, both SZs and ZZs were enrolled based on the presence of lung disease. This study provides no information about the comparative characteristics of SZs and ZZs without lung disease. Second, causality cannot be inferred due to the cross-sectional design of this study. Third, objective data were not available to provide more specifics on clinical phenotyping of lung disease, including CT findings and lung function measurements. Another limitation of this study is unavailability of the actual date of AATD diagnosis in most patients, which limits our ability to account for the length of time since diagnosis. The benefits of earlier age at diagnosis might be reflected in behavior modifications such as smoking cessation or improved exercise habits, which might contribute to better outcomes.

2.5 Conclusion

In summary, the results of this study document that ZZ and SZ patients in AlphaNet's disease management program differ with regard to health outcomes and health behaviors. Individuals with the SZ genotype report more comorbidities and are less likely to engage in health-promoting behaviors such as exercise and smoking cessation. It appears that individuals with the more severely deficient ZZ genotype are more adherent to ADMAPP recommendations and maintain a healthier lifestyle than individuals with the less severely deficient SZ genotype. As such, improvements in education efforts may be especially beneficial for individuals with the SZ genotype who have lung disease, even though their underlying AATD is considered to be less severe.

Funding Support: This study was funded by an unrestricted research grant from AlphaNet.

Table 2.1 Select demographic and clinical characteristics of the overall sample and stratified by genotype

	Data available	Total (N=3,535)	ZZ (N=3,031)	SZ (N=504)	*P*-value
Age, *mean (SD)*	3,535	56.3 (10.6)	55.9 (10.5)	58.6 (11.2)	<.001
Male	3,535	1,808 (51.2)	1,535 (50.6)	273 (54.2)	.143
Race/ Ethnicity	3,475				.012
Non-Hispanic White[a]		3,412 (98.2)	2,935 (98.4)	477 (96.8)	
African-American		14 (0.4)	13 (0.4)	1 (0.2)	
Hispanic[a]		29 (0.8)	20 (0.7)	9 (1.8)	
Other[a]		20 (0.6)	14 (0.5)	6 (1.2)	
Married	3,417	2,227 (65.2)	1,938 (66.1)	289 (59.3)	.004
Employed	3,135	1,118 (35.7)	997 (36.8)	121 (28.5)	.002
Augmentation use	2,842	2,634 (92.7)	2,330 (93.5)	304 (87.1)	<.001
History of any lung disease	3,354	3,274 (97.6)	2,819 (97.7)	455 (96.8)	.336
Emphysema/ Chronic Bronchitis/ COPD	3,204	3,100 (96.8)	2,681 (96.9)	419 (95.7)	.165
Asthma	3,031	1,144 (37.7)	993 (37.8)	151 (37.2)	.806
Pneumonia	2,995	520 (17.4)	453 (17.4)	670(17.0)	.822
Bronchiectasis	2,999	292 (9.7)	263 (10.1)	29 (7.29)	.077
Charlson Comorbidity Index, *mean (SD)*	3,352	0.68 (1.31)	0.63 (1.25)	0.97 (1.59)	<.0001

Note: All statistics are reported as frequency (percentage) unless otherwise indicated.
[a] denotes statistically significant difference based on post hoc analysis using standardized residuals

Table 2.2 Exacerbations, hospitalizations, oxygen use and physician visits in the overall sample and stratified by genotype

	Data available	Total (N=3,535)	ZZ (N=3,031)	SZ (N=504)	P-value
Exacerbation frequency of lung problems over the past year[a]	2,903				<.001
Every Month [c]		427 (14.7)	351 (13.9)	76 (20.2)	
Every 3 Months [c]		489 (16.8)	409 (16.2)	80 (21.3)	
Every 4 Months		285 (9.8)	252 (10.0)	33 (8.8)	
Every 6 Months [c]		387 (13.3)	351 (13.9)	36 (9.6)	
Once		615 (21.2)	546 (21.6)	69 (18.4)	
Never		700 (24.1)	618 (24.5)	82 (21.8)	
Number of exacerbations of lung problems over the past year, *mean (SD)*	2,903	3.2 (3.9)	3.1 (3.8)	3.9 (4.3)	<.001
Regular oxygen use[a]	2,943	1,515 (51.5)	1,333 (52.2)	182 (46.9)	.053
Regular Oxygen use[a], average hours per day, *mean (SD)*	1,470	15.5 (7.9)	15.6 (7.9)	15.3 (7.9)	.740
Regular[b] coughing up sputum from lungs over the past 2 years[a]	2,863	1,228 (42.9)	1,056 (42.3)	172 (46.9)	.099
Primary physician visits over the past year, *mean (SD)*	3,380	3.2 (1.9)	3.1 (1.9)	3.7 (1.9)	<.001
Lung specialist visits over the past year, *mean (SD)*	3,382	2.9 (1.7)	2.9 (1.7)	3.2 (1.7)	<.001
Hospitalizations over the past year, *mean (SD)*	3,362	0.7 (1.3)	0.6 (1.2)	0.8 (1.3)	.012

Note: All statistics are reported as frequency (percentage) unless otherwise indicated.
[a] denotes frequency among patients with any type of lung disease, [b] denotes frequency of at least three months per year over the past two years, [c] denotes statistically significant difference based on post hoc analysis using standardized residuals

Table 2.3 Frequencies of the comorbidities reported by the respondents in the overall sample and stratified by genotype

	Total (N=3,535)	ZZ (N=3,031)	SZ (N=504)	P-value
Data available	N=3,099	N=2,668	N=431	
High Blood Pressure	1,248 (40.3)	1,024 (38.4)	224 (52.0)	<.001 [a]
Gastroesophageal reflux (GERD, heartburn)	1,077 (34.8)	903 (33.9)	174 (40.4)	.008 [a]
Sinus disease	499 (16.1)	411 (15.4)	88 (20.4)	.009 [a]
Heart rhythm problem	399 (12.9)	319 (12.0)	80 (18.6)	.001 [a]
Any tumor or cancer	369 (11.9)	299 (11.2)	70 (16.2)	.003 [a]
Diabetes	268 (8.7)	195 (7.3)	73 (17.0)	<.001 [a]
Skin problems (such as panniculitis)	258 (8.3)	228 (8.6)	30 (7.0)	.269
Pulmonary hypertension	204 (6.6)	169 (6.3)	35 (8.1)	.165
Peripheral vascular disease	199 (6.4)	169 (6.3)	30 (7.0)	.623
Connective tissue disease	192 (6.2)	160 (6.0)	32 (7.4)	.254
Mild liver disease	183 (5.9)	155 (5.8)	28 (6.5)	.580
Ulcer Disease	172 (5.6)	137 (5.1)	35 (8.1)	.012 [a]
Inflammatory bowel disease	169 (5.5)	138 (5.2)	31 (7.2)	.087
Severe eye problems	136 (4.4)	111 (4.2)	25 (5.8)	.123
Congestive heart failure	119 (3.8)	89 (3.3)	30 (7.0)	<.001 [a]
Myocardial infarction	108 (3.5)	80 (3.0)	28 (6.5)	<.001 [a]
Hepatitis	103 (3.3)	83 (3.1)	20 (4.6)	.100

Table 2.3 Continued

	Total (N=3,535)	ZZ (N=3,031)	SZ (N=504)	P-value
Moderate or severe liver disease	95 (3.1)	80 (3.0)	15 (3.5)	.590
Cerebrovascular disease	91 (2.9)	66 (2.5)	25 (5.8)	<.001 [a]
Mild kidney disease	72 (2.3)	63 (2.4)	9 (2.1)	.864
Moderate or severe kidney disease	59 (1.9)	44 (1.7)	15 (3.5)	.010 [a]
Granulomatosis with polyangiitis	38 (1.2)	34 (1.3)	4 (0.9)	.812
Paralysis of arms and/or legs	24 (0.8)	16 (0.6)	8 (1.9)	.012 [a]
Dementia or Alzheimer's	16 (0.5)	14 (0.5)	2 (0.5)	.999
Metastatic cancer	13 (0.4)	12 (0.5)	1 (0.2)	.999
Lymphoma	11 (0.4)	11 (0.4)	--	--
Leukemia	7 (0.2)	4 (0.2)	3 (0.7)	.061
AIDS	2 (0.1)	1 (0.1)	1 (0.2)	.259

Note: All statistics are reported as frequency (percentage) unless otherwise indicated. [a] - significant results after false discovery rate control

Table 2.4 Self-reported health behaviors and fitness characteristics in the overall sample and by genotype

	Data available	Total (N=3,535)	ZZ (N=3,031)	SZ (N=504)	P-value
Ever smoking history	3,105	2,270 (73.1)	1,937 (72.0)	333 (80.6)	<.001
Still smoking	2,257	106 (4.7)	68 (3.5)	38 (11.5)	<.001
Max number of packs/ day	2,197				
Mean (SD)		1.4 (0.8)	1.4 (0.8)	1.7 (0.9)	<.001
Years of smoking	2,162				
Mean (SD)		19.9 (9.9)	18.4 (8.7)	28.5 (11.9)	<.001
Consume alcohol	3,027	1,372 (45.3)	1,216 (46.4)	156 (38.6)	.009
Number of drinks/week	1,328				
Mean (SD)		5.4 (6.3)	5.5 (6.5)	4.3 (4.8)	.030
Do you exercise	3,103				<.001
No [a]		888 (28.6)	729 (27.1)	159 (38.4)	
Irregularly		1,071 (34.5)	945 (35.1)	126 (30.4)	
Regularly [a]		1,144 (36.9)	1,015 (37.8)	129 (31.2)	
Perception of weight	3,077				<.001
Underweight		349 (11.3)	299 (11.2)	50 (12.2)	
About Right [a]		1,249 (40.6)	1,123 (42.1)	126 (30.7)	
Overweight [a]		1,479 (48.1)	1,244 (46.7)	235 (57.2)	
Perception of fitness	3,054				.001
Out of Shape [a]		1,396 (45.7)	1,179 (44.5)	217 (53.7)	
Getting Fit		606 (19.8)	525 (19.8)	81 (20.1)	
Pretty Fit [a]		957 (31.3)	860 (32.5)	97 (24.0)	
Very Fit		95 (3.1)	86 (3.3)	9 (2.2)	
Perception of health	3,069				.005
Poor [a]		529 (17.2)	436 (16.4)	93 (22.6)	
Fair		1,272 (41.5)	1,112 (41.8)	160 (38.9)	
Good		1,136 (37.0)	988 (37.2)	148 (36.0)	
Excellent [a]		132 (4.3)	122 (4.6)	10 (2.4)	
Follow ADMAPP	2,412	1,291 (53.5)	1,154 (54.4)	137 (47.4)	.026

Table 2.4 Continued

	Data available	Total (N=3,535)	ZZ (N=3,031)	SZ (N=504)	P-value
Ever read BFRG	3027	1,488 (49.2)	1,300 (49.6)	188 (46.3)	0.22
Comfortable with Alpha1 knowledge	3438				<.001
No [a]		167 (4.9)	119 (4.0)	48 (9.8)	
Somewhat [a]		1,513 (44.0)	1,244 (42.2)	269 (55.0)	
Very [a]		1,758 (51.1)	1,586 (53.8)	172 (35.2)	

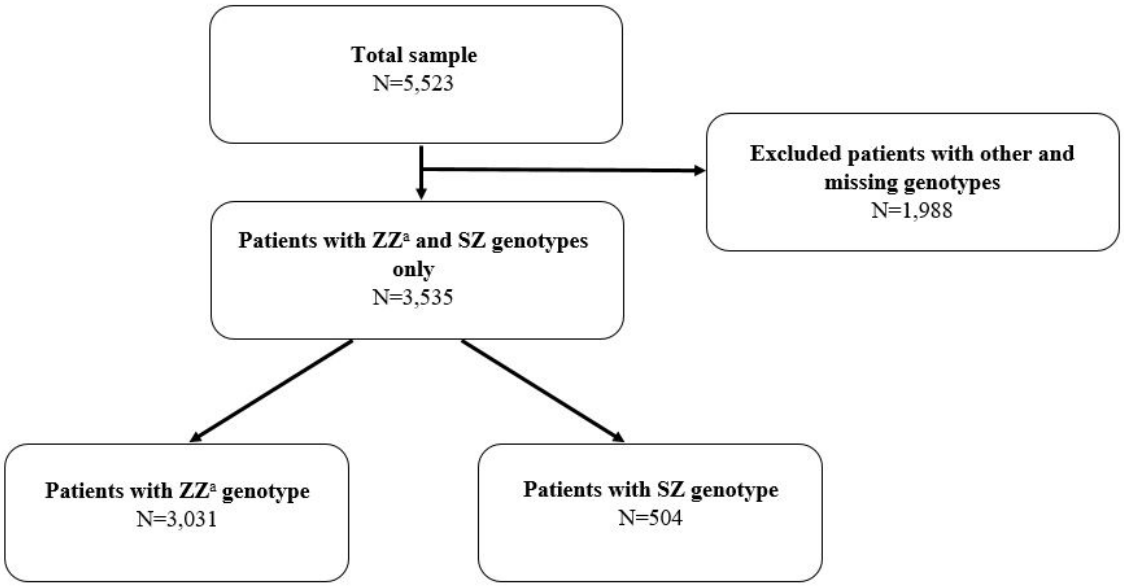
Note: All statistics are reported as frequency (percentage) unless otherwise indicated.
[a] denotes statistically significant difference based on post hoc analysis using standardized residuals, BFRG- Big Fat Reference Guide, ADMAPP- Alphanet's Disease Management and Prevention Program

Table 2.5 Results of adjusted[a] analyses comparing patients with SZ versus ZZ genotype

Outcome	Parameter Estimate[b] (SE)	P-value	Rate Ratio	95% CI
Frequency of pulmonary exacerbations in the past year[c]	0.20 (0.07)	0.0074	1.21	(1.05-1.40)
Frequency of hospitalizations in the past year[d]	0.21 (0.11)	0.0564	1.23	(0.99-1.52)
Frequency of visits to a primary care physician in the past year[c]	0.19 (0.04)	<.0001	1.21	(1.12-1.30)

[a] adjusted for age, gender, current smoking status, and CCI score, [b]Parameter Estimate (SE) for SZ genotype, [c]results of negative binomial regression, [d]results of zero-inflated negative binomial regression

Figure 2.1 Study sample flow diagram



[a] Combination of ZZ, ZNull and NullNull genotypes

CHAPTER 3. THE BURDEN OF COUGH AND PHLEGM IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) PATIENTS WITHIN THE COPD PATIENT-POWERED RESEARCH NETWORK (PPRN)

Abstract

Rationale: Cough and phlegm are common in patients with COPD and significantly affect the quality of their day-to-day lives. The main objectives of this study were to estimate the prevalence and assess the burden of cough and phlegm among patients with a self-reported physician-diagnosed COPD, and to determine if an association is present among reported levels of phlegm and cough, clinical outcomes and patients' quality of life.

Methods: Patient-reported data from the COPD Foundation's Patient-Powered Research Network (COPD PPRN) were used for this study. Severity of cough and phlegm were assessed according to patients' responses on COPD Assessment Test. Burden of cough and phlegm on patients' quality of life was evaluated using the Patient-Reported Outcome Measurement Information System (PROMIS-29) instrument. Associations between the seven domains of PROMIS-29 and the severity of cough and phlegm were examined using MANOVAs. PROMIS-29 domain scores at follow-up were evaluated stratified by changes in self-reported cough and phlegm severity levels between baseline and follow-up.

Results: The average age of the study participants (n=5,286) was 64.4 years (SD=11.5), 95.3% white, 60.4% female, 51.2% married, and 42.2% had caregivers. Patients with moderate/high cough (73.1%) or phlegm (67.9%) had significantly worse dyspnea ($p<.0001$), greater number of exacerbations in the past 1 year ($p<.0001$), and worse quality of life compared to those with no/low cough and phlegm. PROMIS-29 scores at

follow-up were significantly associated with changes in cough and phlegm severity over time.

Conclusions: In patients with COPD, severity of cough and phlegm were associated with greater number of exacerbations, greater dyspnea, and worsened patient-reported quality of life including physical and social functioning. Improvement in cough and phlegm severity over time was associated with improvement of patient-reported quality of life.

3.1 Introduction

Chronic obstructive pulmonary disease (COPD) affects between 15 and 25 million adults in the United States (US), and is the fourth leading cause of death and the second leading cause of disability.[8,59,60] In the US, COPD is estimated to be responsible for over 10 million physician office visits, 1.5 million emergency room department visits, and approximately 700,000 hospitalizations annually.[8,61] The direct and indirect cost burden of COPD in the US are estimated at over $50 billion.[8,62] Actual burden of COPD is significantly higher considering that patients with COPD often have multiple comorbid conditions.[7]

COPD assessment includes several criteria such as symptom burden, exacerbation history, and airflow obstruction.[8,63] The most recent Global initiative for chronic Obstructive Lung Disease (GOLD) guidelines emphasizes focus on patients' symptoms in evaluating disease severity.[63] Some of the most commonly reported symptoms of COPD are cough, dyspnea, sputum production, and wheezing, which largely depend on the stage of the disease. Cough, along with mucus production, is frequently among the first reasons for seeking help from medical professionals among patients with COPD.[64]

The association between COPD symptom severity and health-related quality of life (HRQOL), including its physical, social function and psychological aspects, was highlighted in published literature and attributed to the "humanistic" burden of the disease.[65] Additionally, the burden of nighttime COPD symptoms, especially cough and production of mucus, on patients' quality of life and sleep further contributes to increased mortality and morbidity in this patient population.[66] COPD symptom experience was identified as closely related to patient health outcomes.[67,68]

However, little research has been conducted to specifically address patient-reported burden of cough and phlegm on functional status, role fulfillment abilities and impact on mood and sleep. Symptom severity perception as a subjective patient experience is best evaluated using patient-reported data and patient-reported outcome instruments.[69]

The main objectives of this study were to estimate the prevalence and assess the burden of cough and phlegm among patients with a diagnosis of COPD within COPD Foundation's Patient-Powered Research Network (COPD PPRN) community, and to determine if an association is present between reported levels of phlegm and cough, clinical outcomes and patients' quality of life. Secondary objectives of the study were to evaluate associations between changes in cough and phlegm severity levels over time and patients' self-reported quality of life.

3.2 Methods

Our study used data from the patient-reported information collected by the COPD PPRN. This secure online interactive patient registry maintained by the COPD Foundation (COPDF) and funded by Patient-Centered Outcomes Research Institute

(PCORI) and the COPDF, enrolls patients with self-reported physician diagnosed COPD or risk factors for COPD. The COPD PPRN data used for the present study included only individuals with a self-reported physician-diagnosed COPD, and excluded patients with risk factors for but no diagnosis of COPD. Demographic information such as age, gender, race, and ethnicity, COPD-related clinical information including COPD Assessment Test (CAT) scores, frequency of exacerbations, dyspnea severity, as well as presence of various comorbid conditions, smoking status, and other patient characteristics were collected at the time of enrollment and completion of eConsent. Severity of symptoms, burden of the disease and comorbidities as well as patient-reported outcomes are reported for all patients at time of enrollment, and for a smaller subset of enrollees who have completed baseline and follow-up surveys.

CAT was used to assess the frequency and severity of patients' cough and phlegm.[70] CAT is a well-validated patient-completed questionnaire that measures eight various symptoms of COPD (cough, phlegm, chest tightness, breathlessness going up hills and stairs, activity limitation at home, confidence leaving home, sleep, and energy) on a 0 - 5 point Likert-type scale.[70] CAT was designed to assist health professionals in quantifying burden of COPD symptoms on patients' health status.[71] Question 1 assesses frequency of cough and is anchored by "I never cough" and "I cough all the time" questions. Question 2 assesses severity of phlegm and is anchored by questions "I have no phlegm (mucus) in my chest at all" and "My chest is completely full of phlegm (mucus)" (Figure 3.1). Scoring range of CAT inclusive of all eight questions is 0-40 with higher scores reflecting more severe burden of COPD symptoms. Suggested scoring interpretation is low impact <10, moderate impact 10-20, high impact 21-30, and very

high impact >30. Considering that our study is assessing the burden of only two COPD symptoms, for the purposes of the present analyses, frequency and severity of cough and phlegm levels were stratified into three categories according to the responses on questions 1 and 2 of CAT: 1) 0-1 no/low, 2) 2-3 moderate and 3) 4-5 high. Additionally, for some of the descriptive analyses, cough and phlegm severity levels were dichotomized according to CAT scores of the respective components: 1) 0-1 no/low, and b) 2-5 moderate/high. The joint effect across severity levels of cough and phlegm was calculated and classified into four categories: 1) no or low cough/no or low phlegm, 2) no or low cough/moderate or high phlegm, 3) moderate or high cough/no or low phlegm and 4) moderate or high cough/ moderate or high phlegm.

Modified Medical Research Council (mMRC) Dyspnea Scale items were collected and used to measure functional impairment due to shortness of breath in patients with COPD. mMRC rates patient-reported perception of dyspnea severity on a 0-4 Likert-type scale.[72,73]

Patient Reported Outcome Measurement Information System (PROMIS-29) instrument was used to evaluate burden of cough and phlegm on patients' quality of life and specific functional abilities such as social and physical role functioning.[74,75] Specifically, the PROMIS-29 profile instrument was designed to be used in people with chronic conditions and encompasses 7 domains (Depression, Anxiety, Physical Function, Pain Interference, Fatigue, Sleep Disturbance, and Ability to Participate in Social Roles and Activities), with 4 questions for each domain.[76,77] Data were collected at enrollment and 12 months later at follow-up. Each of the questions had five response options scored 1-5. The total raw score of each domain ranged between 4 and 20 and was calculated as a

sum of score values for each question. Scoring of the PROMIS-29 domains requires all questions within a specific domain to be answered. Raw scores for each domain were then converted to standardized T-scores with a mean of 50 (SD=10) using scoring tables specific to each of the domains. Per PROMIS-29 scoring guidelines, for 5 out of 7 domains, a score of 50 represented the average for the general US population, and for Ability to Participate in Social Roles and Activities, and Sleep Disturbance, a score of 50 represented the average of a calibration sample enriched for chronic morbidities.[76] For negatively worded concepts, such as Depression or Fatigue, higher PROMIS-29 T-score (above 50) was worse as it represented more of the negative concept being measured. Whereas, for positively worded concepts such as Ability to Participate in Social Roles and Activities, higher PROMIS-29 T-score (above 50) was better.

Charlson Age-Comorbidity Index (CACI) was calculated using information on self-reported illnesses to measure the burden of comorbidities. CACI is a validated tool designed to predict patient outcomes according to age and comorbid conditions.[78] It incorporates 19 medical conditions weighted 1-6 points, and scores also receive an additional point for every decade increase above the age of 50 years.

One year after completion of the baseline survey, patients were eligible to participate in the follow-up survey. Among various follow-up characteristics of the patients, data on CAT and PROMIS-29 scores were collected. PROMIS-29 follow-up scores were computed and standardized according to the same scoring guidelines as baseline scores. According to the changes in severity levels of cough and phlegm between baseline and follow-up patients were stratified into four categories: 1) improved - patients with moderate/high severity levels at baseline and no/low severity at follow-up;

2) worsened - patients with no/low severity levels at baseline and moderate/high severity at follow-up; 3) patients who maintained no/low severity at baseline and follow-up, 4) patients who maintained moderate/high severity at baseline and follow-up.

Statistical Analyses

Descriptive statistics were computed and reported as mean (SD) for continuous variables, and frequencies and proportions for categorical variables. Stratified analyses of main demographic (age, gender, race/ethnicity, smoking status) and clinical characteristics (CAT, mMRC, CACI, exacerbation frequency, 7 domains of PROMIS-29) were performed by severity levels of cough and phlegm. Values between the strata were compared using Chi-square tests for categorical variables and t-tests for continuous variables. Correlations between cough and phlegm severity levels, and the correlation between current cough and phlegm severity levels and presence or absence of cough or phlegm for at least three months per year in the past two years were evaluated using Kendall's tau-b. Standardized scores of PROMIS-29 domains were calculated and reported as mean (SD) in the overall sample and stratified by cough and phlegm severity levels.

Correlations between seven domains of PROMIS-29 were assessed using Pearson correlation coefficients. Joint effect of severity of both symptoms was calculated across cough and phlegm severity levels. One-way multivariate analysis of variance (MANOVA)[79] was conducted to identify mean differences between joint severity levels of cough and phlegm and standardized scores of seven PROMIS-29 domains. Follow-up ANOVAs and a series of post-hoc Fisher's LSD tests were performed to examine individual mean difference comparisons across all levels of the combined symptoms

severity and all seven PROMIS-29 domains' scores. Adjusted associations between PROMIS-29 domains and severity levels of both cough and phlegm were evaluated controlling for age, gender, and smoking history.

Associations between seven PROMIS-29 domain scores at follow-up and the four categories of changes in cough and phlegm severity levels between baseline and follow-up were examined using MANOVA. Missing data analyses were performed to compare select baseline characteristics of the patients included in the follow-up data analyses versus those with missing follow-up data. The significance level was set at 0.05. All statistical analyses were performed using SAS 9.4.

3.3 Results

Of the 5,314 respondents with self-reported physician-diagnosed COPD who participated in the survey, 5,286 respondents had data to assess the severity of cough and phlegm and were included in the baseline analyses (Figure 3.2). The majority of the patients were women (60.4%) with a mean age of 64.4 years (SD=11.5), predominantly white (87.9%), approximately half of them were married (51.2%), and 42.2% had caregivers. Most of the respondents (88.2%) reported a history of ever smoking with an average of 45.5 packs/year, and 17.8% of them were current smokers.

Moderate/high levels of cough were reported by 73.1% of the patients and moderate/high levels of phlegm by 67.9% of the patients. Respondents with moderate/high cough and phlegm severity were younger compared to those with no/low levels of these symptoms ($p<.0001$). No statistically significant differences were found in other demographic characteristics between the strata by cough or phlegm severity (Table

3.1). A significantly greater proportion of patients with moderate/high levels of cough (19.0%) and phlegm (19.8%) reported being current smokers compared to those with no/low cough and phlegm (5.7% and 6.5%, respectively, p<.0001). Those with moderate/high cough and phlegm had significantly worse self-reported dyspnea as measured by mMRC (p<.0001), and greater number of exacerbations in the past 1 year compared to those with no/low cough and phlegm (p<.0001). Four and greater exacerbations per year were reported by 25.9% of patients with moderate to high cough and 27.1% with moderate to high phlegm compared to those with no/low severity levels of cough and phlegm (11.0% for both).

Cough and phlegm severity levels at baseline were strongly and positively correlated with presence or absence of cough or phlegm for at least three months per year in the past two years ($\tau_b = 0.607$, $p = 0.01$). Among those respondents who reported bringing up phlegm from their chest at least three months per year in the past 2 years (68.5%), 87.1% had moderate/high phlegm levels. Similarly, of those who reported having cough for at least three months per year in the past 2 years (63.1%), 92.7% had moderate/high cough levels.

There was a strong, positive correlation between cough and phlegm levels as measured by Kendall's tau-b, which was statistically significant ($\tau_b = 0.599$, $p < 0.01$) (Table 3.2). Joint effects of cough and phlegm severity levels were, therefore, an appropriate measure of combining the severity of these two symptoms. Over 60% of the patients had moderate to severe levels of both cough and phlegm (62.0%), and 21.1% had no or low severity of both cough and phlegm. The remaining 16.9% of the study sample had combinations of no/low and moderate/high levels of each of the symptoms.

A total of 4,752 patients had complete data on all items in seven domains of PROMIS-29 and were included in the analyses of quality of life. Analysis of missing data (n=534, 10.1%) did not reveal any obvious patterns. Pearson correlations among the seven domains of PROMIS-29 were significant ($p<.0001$) and ranged from $r = -0.27$ to $r = 0.77$. The strongest correlations were identified between Physical Function and Ability to Participate in Social Roles and Activities ($r=0.77$, $p<.0001$), Anxiety and Depression ($r=0.75$, $p<.0001$), and Fatigue and Ability to participate in social roles and activities ($r=-0.67$, $p<.0001$) (Table 3.3).

Mean scores of PROMIS-29 domains differed by levels of severity of cough and phlegm ($p<.0001$) (Table 3.4). Figure 3.3 demonstrates the burden of severity of cough and phlegm on patients' quality of life in relation to the average scores for the general US population within the seven domains of PROMIS-29 (mean=50, SD=10). Anxiety, depression, fatigue, sleep disturbance, and pain interference scores increased in a stepwise fashion as the severity levels of cough and phlegm increased from no/low to moderate and high. Scores for these domains were on average one standard deviation higher in patients with high cough and phlegm compared to the standard US population. Similarly, scores for positively worded domains, such as Physical Function and Ability to Participate in Social Roles and Activities decreased as the severity of cough and phlegm increased. Patients with high levels of cough and phlegm scored on average 1 to 1.5 standard deviations lower on these domains compared to the average US population.

The results of the one-way multivariate analysis of variance (MANOVA)[79] identified significant mean differences between the joint levels of cough and phlegm and standardized scores of the seven PROMIS-29 domains (Pillai's Trace=0.12, F (21,

14232) =27.96, p<.0001). Follow-up one-way ANOVAs on each of the seven dependent variables were performed, and all were found to be statistically significant (p<.0001). A series of post-hoc tests (Fisher's Least Significant Difference (LSD)) were conducted to assess individual mean difference comparisons across the four levels of the joint cough and phlegm severity levels and all seven PROMIS-29 domains. The results were significant at the 0.0001 level except for no significant difference in Physical Functioning and Social ability scores between groups with moderate to high levels of both cough and phlegm and a group with low or no cough and moderate to high levels of phlegm. Additionally, no significant difference in Anxiety, Depression and Fatigue scores were found between no or low cough/moderate or high phlegm, and moderate or high cough/ no or low phlegm categories.

Adjusted association between severity levels of both cough and phlegm and PROMIS-29 scores from all seven domains were significant controlling for age, gender and smoking history (Pillai's Trace=0.12, F (21, 13974) =26.91, p<.0001).

Overall, 2,696 participants qualified for the annual follow-up and 869 (32.2%) of them completed the follow-up survey. Of those, 863 had data on cough and phlegm severity, and 803 had complete data on PROMIS-29 and were included in the longitudinal analysis. At baseline, the majority of these patients reported moderate/high levels of cough and phlegm (66.9% and 64.4%, respectively), and only 33.1% and 35.6% reported no or low levels of cough and phlegm, respectively. At follow-up survey completion, 12.8-12.0% reported improved cough or phlegm and 9.3-10.2% reported worsened cough or phlegm (Table 3.5). The majority of the patients continued having

moderate/high levels of cough (54.1%) and phlegm (52.3%), and approximately a quarter of the participants still had no/low cough (23.8%) or phlegm (25.4%).

Figure 3.4 demonstrates PROMIS-29 scores at follow up by severity changes in cough and phlegm between baseline and follow-up in relation to the average scores for the general US population within the seven domains of PROMIS-29 (mean=50, (SD=10)). Patients who continued having moderate to high severity levels of cough and phlegm reported having approximately half of a standard deviation greater scores for anxiety, fatigue, depression, pain interference followed by patients whose levels worsened from being no/low at baseline to moderate/high at follow-up. Scores for physical function and social ability at follow-up were significantly lower for those who continued having moderate to high severity levels of cough and phlegm and those whose cough and phlegm worsened, compared to patients with lessened severity or remaining with no/low cough and phlegm. Physical function scores were one standard deviation or greater than average scores for US population among all severity levels.

PROMIS-29 domains scores at follow-up were significantly associated with changes in cough and phlegm severity over time. The results of the one-way MANOVA identified significant mean differences (one or more) between the cough severity changes and standardized scores of the seven PROMIS-29 domains (Pillai's Trace=0.16, $F(21, 2385) = 6.54$, $p<.0001$). MANOVAs between the phlegm severity changes and seven PROMIS-29 domain scores demonstrated similar results (Pillai's Trace=0.09, $F(21, 2385) = 3.68$, $p<.0001$). Follow-up one-way ANOVAs on each of the seven dependent variables were found to be statistically significant (cough severity changes: $p<.0001$ for

all domains, phlegm severity changes: p=0.0061 for depression, p<0.001 for anxiety and p<.0001 for all other domains).

Missing data analyses compared select baseline characteristics of those patients who qualified for one year follow-up and completed the survey ("responders", n=869) and those who qualified but did not respond to the invitation ("non-responders", n=1,827). The "responders" were on average three years older (64.7 years vs 61.5 years), greater proportion of them were males (44.1% vs 32.2%, p<0.001), married (55.3% vs 49.7%, p<0.001), had college degree or higher (42.8% vs 32.1%), reported no or low levels of phlegm (35.3% vs 30.7%, p=0.02) or cough (32.6% vs 25.6%, p<0.001). Additionally, we compared select baseline characteristics of the participants included in the follow-up analyses to those of the rest of the patients in the baseline cohort with similar findings except for no significant difference in mean age.

3.4 Discussion

This study of the association between severity of cough and phlegm and patient-reported outcomes in individuals within COPD PPRN community who self-reported physician-diagnosed COPD yields several important findings. First, the burden of cough and phlegm was high, with approximately three-quarters of the patients reporting moderate to high levels of cough and/or phlegm. Our findings support previously reported data on the frequency of cough (70%) and phlegm (60%) in patients with COPD in a large international survey.[64,80] Recent Global initiative for chronic Obstructive Lung Disease (GOLD) statement acknowledged that cough and sputum production in the

COPD population may be underreported.[81] This further underlines the importance of symptom burden estimates based on patient-reported data.

Previous research related to the burden of cough and phlegm on patients' health outcomes and their quality of life is limited.[64] In earlier work, the major focus on cough and phlegm was to define chronic bronchitis, which specifically uses frequent and persistent cough and sputum production to define the phenotype.[82-84] A pan-European study highlighted the importance of patient-perceived daily variability of the symptoms and related impact on quality of life and activities.[85] The results of this study showed that overall COPD symptoms are most troublesome in the mornings compared to other times of the day. Specifically, among other symptoms, the greatest proportion of patients reported morning difficulties with cough (60.1%) and phlegm (70.9%). Washing and dressing were among the most affected by their symptoms morning activities reported by the study participants (41.0% and 40.7% respectively). Moreover, other researchers suggested that COPD patients with early-morning and nighttime symptoms are significantly more likely to have worse HRQOL.[82,86,87]

Lindberg et al. in their recent work indicated that productive cough in patients with COPD was associated with exacerbations and risk for death.[88] Previous work also identified cough to be significantly associated with decline in patients with airflow obstruction and independently associated with disability in COPD.[64] In a large longitudinal study of Danish men, cough was found to have the highest predictive value for subsequent hospitalization due to pulmonary disease, and for treatment for airflow obstruction.[89] Narrowing the focus to cough and phlegm particularly is important since currently only a few pharmacotherapies directly address either of these symptoms.[63,81]

In their recent narrative review, Miravitlles and Ribera described the impact of COPD symptoms on disease burden and HRQOL of the patients.[82] They highlighted the association between burden of COPD symptoms and high levels of anxiety and depression as well as greater risk of exacerbations and worse patient outcomes. However, they did not specifically focus on cough and phlegm, and association between these symptoms and patients' functional status, and other various aspects of quality of life. Our study findings indicate significant association between severity of cough and phlegm and patient-reported quality of life as measured by PROMIS-29. In our study cohort, increased cough and phlegm levels were associated with higher levels of fatigue, anxiety, and depression, greater pain interference and sleep disturbance, and lower social abilities and physical function.

The NIH-developed PROMIS-29 has been shown to be a valuable instrument to assess several domains of quality of life across a range of chronic morbidities and various clinical populations.[77,90] In 2009, a longitudinal study assessed the validity of PROMIS with COPD exacerbations, and evaluated responsiveness of the instrument with a known change in the underlying COPD, i.e., acute and stable conditions.[91] Recent study by Irwin et al. examined the performance of PROMIS instrument in patients with COPD according to their exacerbation status.[92] It has identified that stable patients had significantly better PROMIS scores in all domains. Similarly to our study, study by Irwin et al. used self-reported COPD status and did not include other clinical assessments.[92]

Findings of a multi-center cross-sectional study (CONCERT) supported the validity of PROMIS in patients with COPD and identified that among all domains, physical functioning was most negatively affected compared to the general population

across all COPD severity grades.[93] Consistent with these findings, our study results also indicate the worst standardized scores in Physical Function (over 1 SD worse than the average scores for the general US population) among all seven PROMIS-29 domains across all cough and phlegm severity levels.

Recent research by Schalet et al. evaluated longitudinal performance of Physical Function domain of PROMIS in six chronic health conditions including COPD.[94] No significant change in physical function over time was detected in patients with COPD exacerbations which may be attributed to only minor improvements in physical function during 12 weeks of follow-up and considerably small sample size of subgroups (under 20 patients).[94] In the longitudinal portion of our study, patient-reported improvements in cough and phlegm severity over time (improved scores on those questions in the CAT) was associated with better quality of life at the follow-up timepoint as measured by PROMIS-29.

The significance of patient-reported outcomes and particularly PROMIS-29 in comparative effectiveness research was highlighted in the recent research by Craig et al.[95] The authors identify the importance of patient-reported outcomes in assessing cost-effectiveness of various treatment options.[95] The findings of our study highlight the needs to review and renew the search for therapies designed to reduce either cough or phlegm. No new and effective cough medication has been developed by the pharmaceutical industry in over a century.[64] Only about a third of the patients in our study had either no or low severity of cough or phlegm. Higher severity of cough and phlegm were found to be associated with worse mood, pain, sleep, and physical and social functioning. The levels of cough and phlegm might also be explored as a proxy for COPD disease severity.

The consistent association between high levels of cough and phlegm burden and worse quality of life suggests the need for further research in this area.

Strengths and Limitations

The main strengths of our study include a large number of patients enrolled in the COPD PPRN as well as unique and rich data collected by the COPD PPRN. These data include seldom-addressed patient-reported outcomes such as patient-perceived ability to participate in social roles and activities, physical function, anxiety, depression, and sleep disturbance. Some of the limitations of the study include potential selection bias in view of the self-reported nature of physician-diagnosed COPD. Patient-reported clinical information including presence of comorbidities, frequency of physician, ER visits and hospitalizations are subject to potential recall bias. Also, classification of cough and phlegm severity levels for the purposes of this study was performed according to the respective CAT scores and is not a widely used classification. Additionally, many participants were excluded from the follow-up analyses due to not qualifying, not responding to the follow-up survey or missing data. Missing data analysis identified that those included in the follow-up analyses differed from those excluded in several demographic and clinical characteristics that may have introduced potential selection bias.

3.5 Conclusion

In this population of people with self-reported physician-diagnosed COPD, severity of cough and phlegm are associated with higher number of exacerbations, greater dyspnea, and worsened patient-reported quality of life including physical and social functioning. Improvement in cough and phlegm severity over time is associated with

improvement of patient-reported quality of life. Further work in this area is needed including exploration of new treatments aimed at improvement of cough and phlegm severity in this patient population.

Funding Support: This study was funded through a Patient-Centered Outcomes Research Institute® (PCORI®) Award (PPRN-1306-04748 Phase II) for the development of the National Patient-Centered Clinical Research Network, known as PCORnet® and through the COPD Foundation, Washington DC. The statements presented in this publication are solely the responsibility of the authors and do not necessarily represent the views of the Patient-Centered Outcomes Research Institute® (PCORI®), its Board of Governors or Methodology Committee or other participants in PCORnet®.

Table 3.1 Select demographic and clinical characteristics of the study participants, n = 5,286

	Overall cohort	**Phlegm Severity Levels**		**Cough Severity Levels**	
	N=5,286	**No/ Low** (CAT 0-1) N = 1,699 (32.1%)	**Moderate/ High** (CAT 2-5) N= 3,587 (67.9%)	**No/ Low** (CAT 0-1) N = 1,424 (26.9%)	**Moderate/ High** (CAT 2-5) N = 3,862 (73.1%)
Age					
Mean (SD)	64.4 (11.4)	65.2 (11.3)‡	64.0 (11.5)‡	65.8 (11.1)†	63.8 (11.5)†
Median [Q1-Q3]	65 [57-72]	67 [59-73]	65 [57-72]	67 [60-73]	65 [57-72]
Race, n (%)					
White	4,644 (87.9)	1,538 (90.5)	3,106 (86.6)	1,304 (91.6)	3,340 (86.4)
Black	269 (5.1)	68 (4.0)	201 (5.6)	48 (3.4)	221 (5.7)
Asian	16 (0.3)	8 (0.5)	8 (0.2)	8 (0.6)	8 (0.2)
Other*	58 (1.1)	12 (0.7)	46 (1.3)	9 (0.6)	49 (1.3)
Multiple races	207 (3.9)	42 (2.5)	165 (4.6)	27 (1.9)	180 (4.7)
Unknown/missing	92 (1.7)	31 (1.8)	61 (1.7)	28 (2.0)	64 (1.7)
Gender, n (%)					
Female	3,180 (60.4)	1,086 (64.2)	2,094 (58.6)	848 (59.7)	2,332 (60.6)
Male	2,086 (39.6)	606 (35.8)	1480 (41.4)	572 (40.3)	1,514 (39.4)
Ethnicity, n (%)					
Hispanic	141 (2.7)	48 (2.9)	93 (2.7)	34 (2.4)	107 (2.8)
BMI, mean (SD)	28.2 (7.6)	28.0 (7.1)	28.5 (7.7)	27.4 (6.7)	28.7 (7.8)
Never smoker, n (%)	620 (11.7)	230 (13.6)‡	390 (10.9)‡	153 (10.8)	467 (12.1)
Current smoker, n (%) †	815 (15.4)	110 (6.5)	705 (19.7)	80 (5.7)	735 (19.0)

Table 3.1 Continued

	Overall cohort	Phlegm Severity Levels		Cough Severity Levels	
	N=5,286	**No/ Low** (CAT 0-1) N = 1,699 (32.1%)	**Moderate/ High** (CAT 2-5) N= 3,587 (67.9%)	**No/ Low** (CAT 0-1) N = 1,424 (26.9%)	**Moderate/ High** (CAT 2-5) N = 3,862 (73.1%)
Pack/year among ever smokers	N=4,525	N=1,432	N=3,093	N=1,232	N=3,293
Mean (SD)	45.5 (28.3)	45.5 (28.0)	45.6 (28.4)	47.9 (28.6)‡	44.7 (28.2)‡
Median [Q1-Q3]	41 [25-62]	42 [25.5-62]	41 [24.5-63]	44 [27.9-66]	40 [24-61.5]
mMRC***, n (%)†					
0	448 (8.5)	228 (13.6)	220 (6.2)	207 (14.7)	241 (6.3)
1	1,529 (29.2)	591 (35.2)	938 (26.3)	484 (34.3)	1,045 (27.3)
2	1,635 (31.2)	472 (28.1)	1,163 (32.6)	373 (26.4)	1,262 (32.9)
3	991 (18.9)	262 (15.6)	729 (20.4)	228 (16.2)	763 (19.9)
4	642 (12.2)	125 (7.5)	517 (14.5)	119 (8.4)	523 (13.6)
CACI					
Mean (SD)	3.9 (2.3)	3.7 (2.0)	4.0 (2.4)	3.8 (1.8)	4.0 (2.4)
Exacerbations in the past 1 year**† , n (%)					
0	1,189 (22.8)	601 (36.0)	588 (16.6)	519 (37.3)	670 (17.6)
1	1,164 (22.4)	473 (28.3)	691 (19.6)	385 (27.6)	779 (20.4)
2	953 (18.3)	252 (15.1)	701 (19.8)	206 (14.8)	747 (19.6)
3	758 (14.6)	161 (9.6)	597 (16.9)	130 (9.3)	628 (16.5)
4+	1,141 (21.9)	184 (11.0)	957 (27.1)	153 (11.0)	988 (25.9)

Table 3.1 Continued

	Overall cohort	Phlegm Severity Levels		Cough Severity Levels	
	N=5,286	No/ Low (CAT 0-1) N = 1,699 (32.1%)	Moderate/ High (CAT 2-5) N= 3,587 (67.9%)	No/ Low (CAT 0-1) N = 1,424 (26.9%)	Moderate/ High (CAT 2-5) N = 3,862 (73.1%)
History of cough for at least 3 months per year for the last 2 years†, n (%)					
Yes	3,308 (63.1)	506 (30.0)	2,802 (78.9)	243 (17.2)	3,065 (90.1)
No	1,932 (36.9)	1,181 (70.0)	751 (21.1)	1,168 (82.8)	764 (20.0)
History of phlegm for at least 3 months per year for the last 2 years†, n (%)					
Yes	3,564 (68.5)	459 (27.5)	3,105 (87.9)	475 (33.9)	3,089 (81.3)
No	1,638 (31.5)	1,211 (72.5)	427 (12.1)	925 (66.1)	713 (18.8)
Phlegm Severity Levels†, n (%)					
No/Low	1,699 (32.1)			1,114 (78.2)	585 (15.2)
Moderate/High	3,587 (67.9)			310 (21.8)	3,277 (84.9)
Cough Severity Levels†, n (%)					
No/Low	1,424 (26.9)	1,114 (65.8)	310 (8.6)		
Moderate/High	3,862 (73.1)	585 (34.4)	3,277 (91.4)		

Table 3.1 Continued

†p<0.0001; ‡p<0.001; *- Other races include Native Hawaiian/Pacific Islander and American Indian/ Alaska Native; **-defined as a max number of antibiotic/prednisone/ER visit/ hospital, **CACI**- Charlson Age-Comorbidity Index, **mMRC**- (Modified Medical Research Council) Dyspnea Scale

mMRC*:**

0: "I only get breathless with strenuous exercise"

1: "I get short of breath when hurrying on the level or walking up a slight hill"

2: "I walk slower than people of the same age on the level because of breathlessness or have to stop for breath when walking at my own pace on the level"

3: "I stop for breath after walking about 100 yards or after a few minutes on the level"

4: "I am too breathless to leave the house" or "I am breathless when dressing or undressing"

Table 3.2 Cross-tabulation of cough and phlegm severity categories, n=5,286

Cough Categories	Phlegm Categories		
	High	**Moderate**	**No/Low**
High	708 (64.1)	498 (20.1)	48 (2.8)
Moderate	365 (33.0)	1,706 (68.7)	537 (31.6)
No/Low	32 (2.9)	278 (11.2)	1,114 (65.6)

Note: $\tau_b = 0.599$, $p < 0.01$

Table 3.3 Pearson correlations, means and standard deviations associated with the PROMIS-29 domains, n=4,752

	PF	SA	SD	AN	DE	FA	PI	Mean	Stand. Dev.
Physical Function	1.0							37.14	7.33
Social Ability	0.77	1.0						42.78	9.13
Sleep Disturbance	-0.27	-0.36	1.0					52.55	8.88
Anxiety	-0.36	-0.47	0.43	1.0				56.10	10.34
Depression	-0.39	-0.51	0.41	0.75	1.0			54.66	10.09
Fatigue	-0.57	-0.67	0.50	0.54	0.59	1.0		57.11	9.79
Pain Interference	-0.35	-0.43	0.43	0.42	0.42	0.51	1.0	54.33	10.83

Note: all correlations were statistically significant, p<.0001; PF-Physical Function; SA-Social Ability; SD-Sleep Disturbance; AN- Anxiety; DE-depression; FA- Fatigue; PI-Pain Interference; Stand. Dev. - Standard Deviation;

Table 3.4 PROMIS-29 T-scores in the overall sample and stratified by cough and phlegm severity levels at baseline, n=4,752

		Phlegm Severity Levels			Cough Severity Levels		
	Overall (n=4,752)	**No/Low** (CAT 0-1) N =1,526 (32.1%)	**Moderate** (CAT 2-3) N=2,222 (46.8%)	**High** (CAT 4-5) N=1,004 (21.1%)	**No/Low** (CAT 0-1) N =1,282 (27.0%)	**Moderate** (CAT 2-3) N= 2,325 (48.9%)	**High** (CAT 4-5) N=1,145 (24.1%)
Physical Function	37.1 (7.3)	39.6 (8.2)	36.6 (6.7)	34.4 (6.0)	39.3 (8.3)	36.9 (7.0)	35.1 (6.2)
Ability to Participate in Social Roles and Activities	42.8 (9.1)	45.8 (9.9)	42.3 (8.4)	39.2 (7.9)	45.4 (10.0)	42.7 (8.7)	40.0 (8.0)
Sleep Disturbance	52.5 (8.9)	49.8 (8.6)	52.8 (8.5)	56.1 (8.7)	49.1 (8.5)	52.4 (8.3)	56.7 (8.8)
Anxiety	56.1 (10.3)	53.4 (10.0)	56.2 (10.2)	60.0 (10.0)	53.3 (9.9)	56.0 (10.0)	59.5 (10.5)
Depression	54.7 (10.1)	52.3 (9.7)	54.6 (9.7)	58.4 (10.3)	52.2 (9.7)	54.3 (9.7)	58.1 (10.4)
Fatigue	57.1 (9.8)	53.6 (10.0)	57.6 (9.1)	61.5 (8.9)	53.3 (10.2)	57.1 (8.9)	61.4 (9.4)
Pain Interference	54.3 (10.8)	51.2 (10.3)	54.7 (10.6)	58.1 (10.8)	50.3 (10.0)	54.4 (10.5)	58.6 (10.8)

Note: All statistics are reported as mean (SD) unless otherwise indicated. For negatively worded concepts -Sleep Disturbance, Anxiety, Depression, Fatigue and Pain Interference- higher PROMIS-29 T-score (above 50) reflects worse outcome. For positively worded concepts -Physical Function and Ability to Participate in Social Roles and Activities- higher PROMIS-29 T-score (above 50) reflects better outcome.

Table 3.5 Changes in severity levels of cough and phlegm between baseline and follow-up, n=803

	Cough	**Phlegm**
Improved (Mod/High to No/Low)	103 (12.8)	97 (12.1)
Remained Mod/High	434 (54.1)	420 (52.3)
Remained No/Low	191 (23.8)	204 (25.4)
Worsened (No/Low to Mod/High)	75 (9.3)	82 (10.2)

Note: All statistics are reported as n (%)

Figure 3.1 Cough and phlegm CAT scales

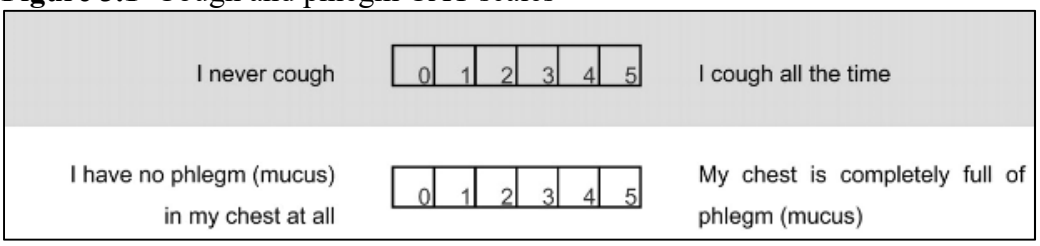


Figure 3.2 Study Flow Diagram

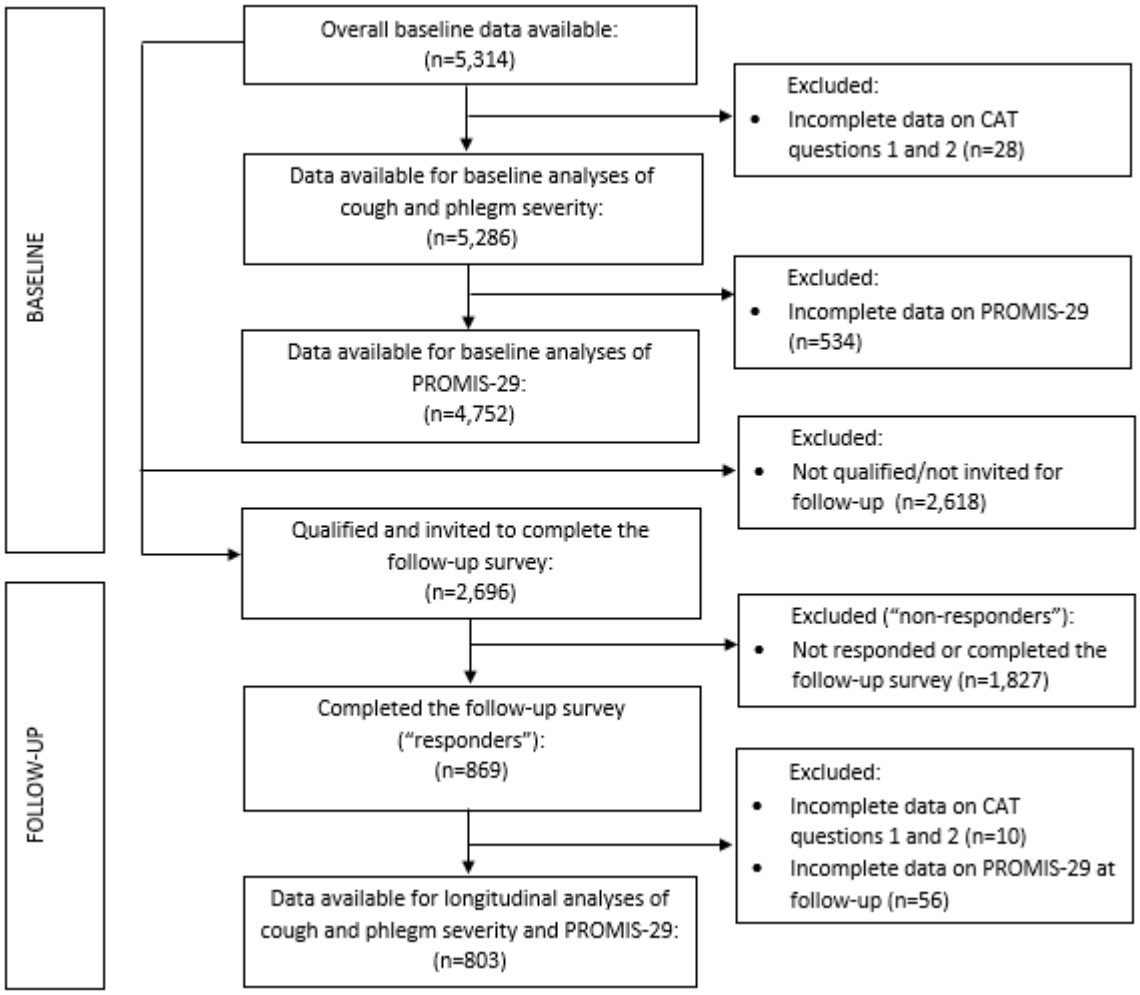
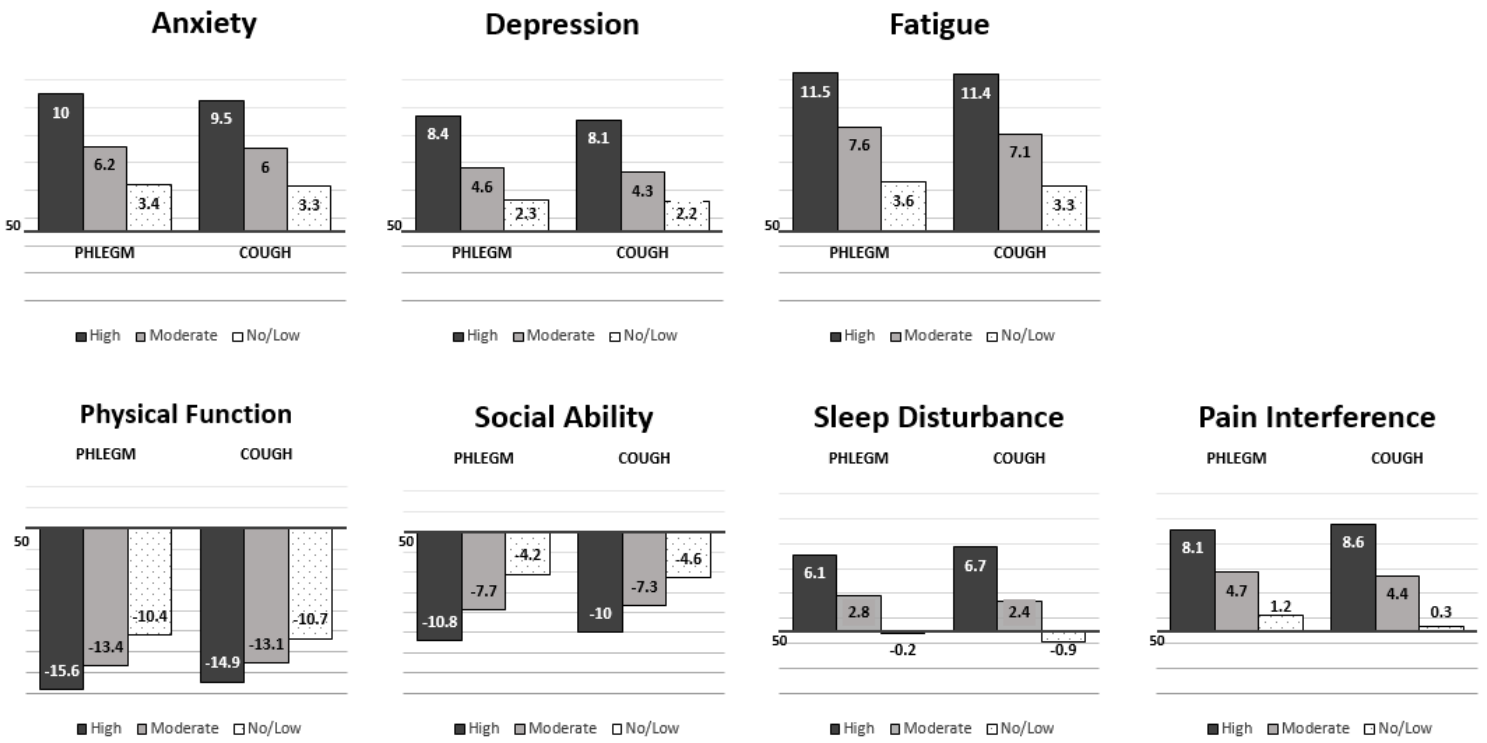
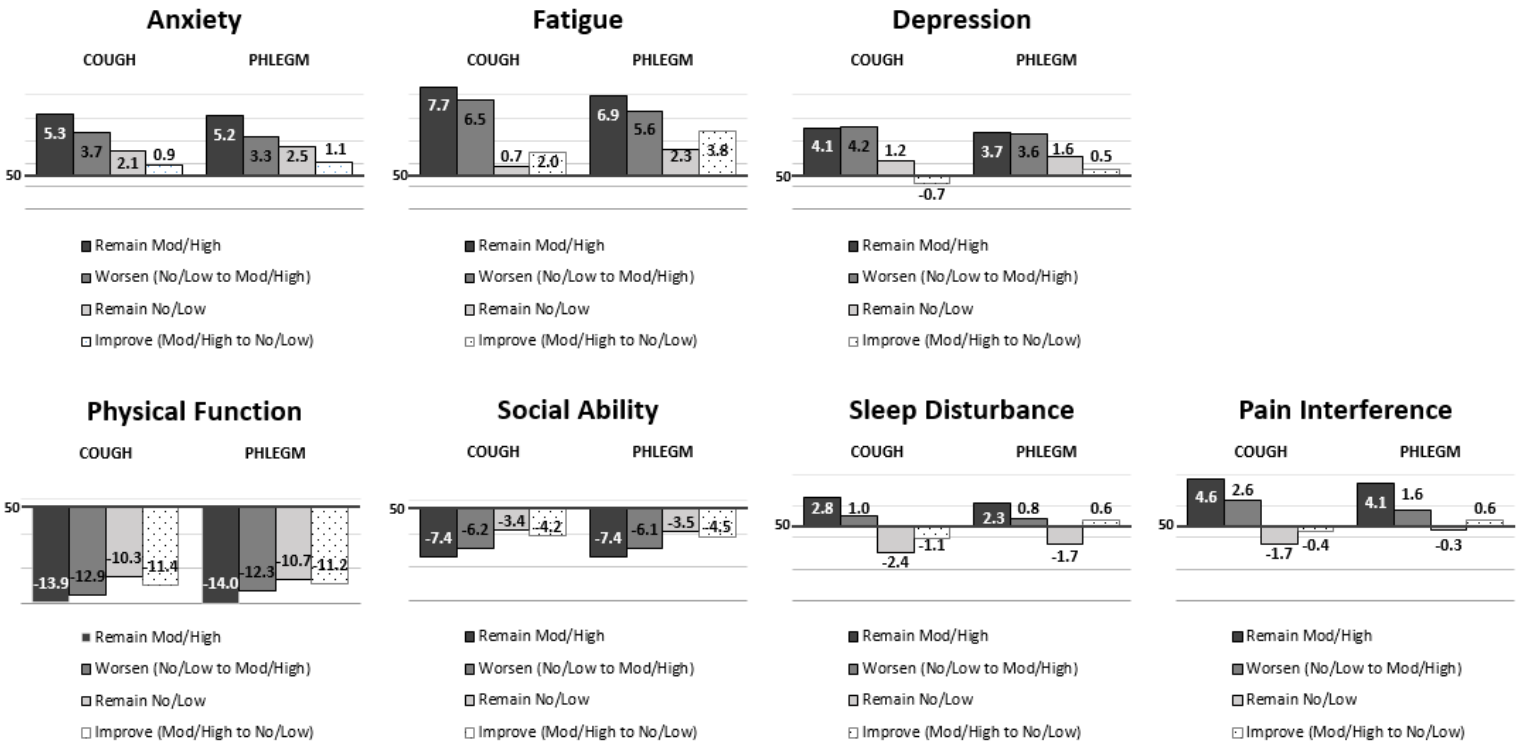


Figure 3.3 PROMIS-29 T-scores at baseline by severity of cough and phlegm, n=4,752



Note: PROMIS-29 T-scores above 50 (average for the US population) indicate worse outcomes for Anxiety, Depression, Fatigue, Sleep Disturbance and Pain Interference, and better outcomes for Physical Function and Social Ability.

Figure 3.4 . PROMIS-29 T-scores at follow-up by severity changes in cough and phlegm between baseline and follow-up, n=803



Note: PROMIS-29 T-scores above 50 (average for the US population) indicate worse outcomes for Anxiety, Depression, Fatigue, Sleep Disturbance and Pain Interference, and better outcomes for Physical Function and Social Ability.

CHAPTER 4. PSEUDOMONAS AERUGINOSA ASSOCIATED WITH SEVERITY OF NON-CYSTIC FIBROSIS BRONCHIECTASIS MEASURED BY THE BRONCHIECTASIS SEVERITY SCORE (BSI) AND THE FACED: THE US BRONCHIECTASIS AND NTM RESEARCH REGISTRY (BRR) STUDY

Abstract

Rationale: Non-cystic fibrosis bronchiectasis (NCFB) is characterized by dilated bronchi, poor mucus clearance and susceptibility to bacterial infection. *Pseudomonas aeruginosa* (PA) is one of the most frequently isolated pathogens in patients with NCFB. The purpose of the present study was to evaluate the association between presence of PA and disease severity in patients with NCFB within the US Bronchiectasis and Nontuberculous mycobacteria (NTM) Research Registry (BRR).

Methods: Baseline US BRR data from adult patients with NCFB collected between 2008 and 2018 was used for this study. Presence of PA was defined as one or more, and chronic colonization as two or more positive PA cultures within two years prior to enrollment. Descriptive statistics were computed for the overall study sample and stratified by presence of PA. Values between the strata were compared using t-tests for continuous variables, and Chi-square tests for categorical variables. Modified Bronchiectasis Severity Index (m-BSI) and modified FACED (m-FACED) were computed to evaluate severity of bronchiectasis. Unadjusted and multivariable multinomial regression models were used to assess the association between presence of PA and severity of bronchiectasis.

Results: Average age of the study participants (n=1,831) was 63.7 years (SD=14.1), 91.5% white, 78.8% female, 41.0% reported history of smoking, and 48.3% had history of NTM. Presence of PA was identified in 25.4%, and chronic colonization in 13.6% of the patients. Patients with presence of PA had significantly lower mean pre-

bronchodilator Forced Expiratory Volume in the first second (FEV1) % predicted compared to those without PA (62.8% vs. 73.7%, p<.0001). In multivariate analyses, patients in PA group had significantly greater odds for having high (OR_{adj}=6.41 (95%CI: 4.15-9.89) and intermediate (OR_{adj}=2.11 (95%CI: 1.40-3.16) severity vs. low severity on m-BSI. The sensitivity analyses after excluding PA severity marker from calculation of m-BSI and m-FACED showed the same direction of the association as in the main analyses.

Conclusion: PA infection is common in patients with NCFB within the Bronchiectasis and NTM Research Registry. Severity of bronchiectasis is significantly greater in patients with PA which emphasizes high burden of the disease. Future longitudinal studies are recommended to assess clinical outcomes and prognosis over time.

4.1 Introduction

Non-cystic fibrosis bronchiectasis (NCFB) is an etiologically diverse, irreversible, and chronic disease associated with significant morbidity in adults.[22,24] NCFB is characterized by dilated bronchi, poor mucus clearance and susceptibility to bacterial infection leading to productive cough, recurrent infections, and exacerbations.[96,97] Prevalence of NCFB in the United States is increasing, especially with age, and has been estimated between 230,000 and 430,000 cases using three large US healthcare databases.[98] Bronchiectasis was shown to be more expensive to treat compared to many other chronic diseases.[99] Annual burden of bronchiectasis to the healthcare system has been estimated at approximately $630 million.[97]

According to the "vicious circle" theory of bronchiectasis pathogenesis, airway inflammation in response to pulmonary infection results in airway damage, mucus collection, and further infections.[24,79] Among the most prevalent gram-negative bacteria responsible for pulmonary infections in patients with NCFB, *Pseudomonas aeruginosa* (PA), an opportunistic pathogen, possesses natural resistance to antibiotics that makes these infections particularly challenging to treat.[100] PA colonization is associated with worse lung function, higher mortality, hospitalizations, exacerbations, and decreased quality of life.[24,101] To date it remains unclear whether infection with PA is the result or the cause of severe NCFB.[102]

The overall significance of PA in the natural course of bronchiectasis has been reflected by inclusion of PA as a key marker in the calculation of several severity assessment instruments. The Bronchiectasis Severity Index (BSI) is a disease-specific clinical predictive tool derived in the United Kingdom and validated in several European cohorts.[25] This instrument was designed to identify bronchiectasis patients with future risk for mortality, hospitalizations, exacerbations, and poor quality of life.[25] Independently, Spanish researchers derived another severity assessment tool, FACED, which utilizes only five dichotomized variables in its calculation and was validated for 5-year mortality.[26]

A wide range of NCFB and PA management strategies exists among clinicians both in the US and internationally, which highlights the need and importance of collaborative research to improve patient outcomes.[96] Findings from bronchiectasis registry-based studies assist in guiding future clinical trials to enhance treatment options in this patient population.

The two main objectives of the present study were to estimate the prevalence of PA and to evaluate the association between the PA and disease severity measured by the bronchiectasis severity assessment instruments in patients with NCFB within the US bronchiectasis registry.

4.2 Methods

This study used baseline data from the Bronchiectasis and NTM Research Registry (BRR). The BRR is a centralized database of adult patients with physician-diagnosed NCFB or NTM from 16 clinical institutions across the United States.[103] After obtaining informed consent, patients' medical records are queried by trained site study coordinators using standardized data collection forms. Data collection includes demographic information, medical history and procedures, respiratory symptoms, therapies and treatment, imaging, microbiology results, and other detailed clinical information. Data entry is done through a centralized Internet-based entry system managed by the data coordinating center. At the time of enrollment, patients with primary Cystic Fibrosis bronchiectasis are excluded based on clinical history, previous sweat chloride or genetic testing results. After enrollment, follow-up data is collected annually from participants' electronic medical records as it becomes available. As of October 2018, the BRR contained data on over 3,000 patients with up to 10 years of participant follow-up. BRR obtains institutional review board (IRB) approvals for each BRR participating site.

Baseline data utilized in the present study included data abstracted from patients' records during the registry baseline period, which is defined as the interval between the

two years prior to and 90 days after patients' enrollment.[103] Microbiological evaluation at baseline consisted of a maximum of three respiratory culture results for each of the bacterial, fungal and mycobacterial growth. Bacterial cultures included available data on numerous microorganisms such as PA, *Haemophilus influenza*, *Staphylococcus aureus,* and other pathogens. For the purposes of the present study, "presence" of a microorganism was defined as one or more, and "chronic colonization" as two or more positive cultures available at baseline. Patients with presence of PA at baseline were identified as a "PA group," and those without presence of PA at baseline as a "non-PA group." NTM status of patients in this study was defined as a reported history of NTMLD prior to enrollment or one or more NTM positive cultures within the baseline period, or both.[103] Baseline data also contained information on number of hospital admissions and exacerbations within the preceding two years prior to enrollment.

Severity of bronchiectasis was evaluated using the BSI, which was derived and validated in the United Kingdom to identify bronchiectasis patients with future risk of mortality, hospitalizations, exacerbations, and poor quality of life.[25] The BSI is a multidimensional instrument that consists of nine severity markers that have been identified by the authors as common variables that predict mortality and hospitalizations.[25] These severity markers include age, BMI, Forced Expiratory Volume in the first second (FEV1) % predicted, prior hospitalizations, history of exacerbations in the previous year, Medical Research Council (MRC) dyspnea score, PA colonization, colonization with other microorganisms, and radiological severity. For the purposes of the present study, the BSI was modified according to the structure of the BRR data collection, and modified BSI (m-BSI) was computed to evaluate the severity of NCFB.

Specifically, modifications to the BSI were made to accommodate alternate measurement of dyspnea in the BRR data collection forms that identifies presence or absence of dyspnea when active or when at rest. The original BSI uses the MRC dyspnea scale that rates patients' perception of dyspnea severity on a 1-5 Likert-type scale.[73,104] In addition, BRR collects data on frequency of exacerbations and hospitalizations in the previous two years at enrollment, and the BSI measures frequency of these markers in the past one year (Table 4.2). Using the BSI scoring guidelines, the m-BSI (range 0-26 points) scores were derived as sums of the score points for each of the nine severity markers. Using the same guidelines, the patients were classified into three bronchiectasis severity categories according to the total m-BSI score value: 1) low, 0-4 points, 2) intermediate, 5-8 points, and 3) high, 9 or more points.

FACED, our second bronchiectasis severity assessment instrument, was derived and validated by Spanish researchers independently from the BSI.[26] It utilizes only five dichotomized variables in the calculation the severity score- **F**EV1 % predicted, **A**ge, **C**hronic colonization, **E**xtension (radiological), and **D**yspnea. Similar to the BSI, this instrument was also modified to accommodate the alternate dyspnea measurement scale and modified FACED (m-FACED) was calculated for study participants (Table 4.3). The m-FACED (range 0-7 points) was computed as a sum of the score points for each of the five dichotomized variables. According to the FACED scoring guidelines, bronchiectasis was classified into three severity classes according to the total m-FACED score: 1) mild, 0-2 points, 2) moderate, 3-4 points, and 3) severe, 5-7 points.

Statistical Analyses

Descriptive statistics were computed for the overall study sample and stratified by presence of PA at baseline. All results were reported as frequencies and proportions for categorical variables, and as means (± SD) for continuous variables. m-BSI and m-FACED severity levels were calculated for the overall cohort and analyzed stratified by PA presence at baseline. Values between the strata were compared using t-tests for continuous variables, and Chi-square tests for categorical variables. To assess the influence of the variable identifying chronic colonization by PA on the severity of bronchiectasis, m-BSI and m-FACED were also computed after excluding chronic colonization by PA from the severity markers.

Ordinal regression models were initially considered for the analyses, but the proportional odds assumption assessed using score test was found not to be supported by the data for either m-BSI or m-FACED: m-BSI: $\chi^2_{(DF=6)} = 43.46$, $p < .0001$; m-FACED: $\chi^2_{(DF=5)} = 59.81$, $p < .0001$). Thus, multinomial logistic regression models were used to examine the association between presence of PA and severity categories of bronchiectasis on m-BSI and m-FACED. Both unadjusted and adjusted results were obtained. In the adjusted regression models, we controlled for variables that had clinical importance, statistically significant difference between the PA groups in the bivariate analyses, and either not included in the calculation of severity indices or used in a different form. The final models included age as a continuous variable, gender, NTM status, and FEV1 % predicted as a continuous variable.

Sensitivity analyses were performed by excluding the PA severity item from the m-BSI and m-FACED scoring prior to fitting multinomial regression models. Cohen's kappa

statistic was used to measure the agreement between the m-BSI and FACED severity classification. Missing data analyses compared the included study population with those who were excluded from the analyses due to missing or incomplete data. Significance level was set at 0.05. Statistical analyses were performed using SAS version 9.4.

4.3 Results

Of 3,008 participants in the BRR as of October 2018, 1,831 had data available on variables needed for calculation of m-BSI and m-FACED and were included in the present study. Demographic characteristics of the study population at baseline are displayed in Table 4.1. The average age of the study participants was 63.7 years (SD=14.1), 91.5% white, 78.8% female, 41.0% reported history of smoking. Presence of PA was identified in 25.4%, and chronic colonization in 13.6%, of the patients.

Patients in the PA group had significantly lower mean pre-bronchodilator FEV1% predicted (62.8% vs. 73.7%, p<.0001) and FVC% predicted (74.4% vs. 81.8%, p<.0001) compared to those without PA. A significantly greater proportion of patients with presence of PA at baseline reported three or more exacerbations (30.5%) and history of hospital admissions (32.0%) in the previous two years prior to enrollment compared to those without PA (17.2% and 17.1% respectively, p<.0001). Approximately half of the respondents (48.3%) had a history of NTM with significantly greater proportion among those in non-PA group (51.7% vs. 38.5%, p<.0001). There was no significant difference in age, race, ethnicity or smoking history between the two groups.

Tables 4.2 and 4.3 contain data on frequencies of individual components of m-BSI and m-FACED in the overall study sample and stratified by PA group. Statistically significant differences were found between the PA groups in age, FEV1% predicted, hospital admissions, number of exacerbations, dyspnea, and radiological severity for m-BSI (Table 4.2). Similarly, the two groups differed in FEV1% predicted, age, and dyspnea for m-FACED (Table 4.3).

Table 4.4 demonstrates bronchiectasis severity categories using m-BSI and m-FACED computed for the overall study sample and stratified by presence of PA at baseline. According to m-BSI, a majority of the respondents were classified as intermediate (41.2%) and high (35.5%) severity of bronchiectasis. In comparison, m-FACED classified over half of the patients (52.5%) as mild disease severity, followed by moderate (37.4%) and high severity (10.1%) of bronchiectasis. Table 4.5 demonstrates comparison of bronchiectasis severity classification by both instruments and agreement rates (kappa= 0.2632 (95% CI: 0.2334-0.2930)). There was fair agreement between the two instruments in classifying severity of NCFB.[105]

For disease severity, a significantly greater proportion of patients with PA were classified as having high severity of bronchiectasis using both m-BSI (60.9% vs. 26.9%, p<.0001) and m-FACED (25.8% vs. 4.8%, p<.0001) compared to those without PA. Likewise, both m-BSI and m-FACED classified greater proportion of patients without PA as having low and mild severity of the disease (m-BSI: 27.9% vs. 9.7%, m-FACED: 58.9% vs. 33.8%, p<.0001) (Figure 1).

Table 4.4 presents the results of the sensitivity analyses demonstrating the distribution of the m-BSI and m-FACED severity categories after excluding PA severity

marker from the scores' calculations. Removing chronic colonization by PA variable, that is weighted as 3 points in the calculation of the m-BSI and 1 point in m-FACED, resulted in a greater proportion of the participants to be re-classified as low or moderate severity by m-BSI and m-FACED. We compared disease severity between the PA strata after removing PA variable from the scores' calculations. The proportion of PA-positive patients who were classified as high severity of bronchiectasis on m-BSI and FACED remained significantly greater compared to those without PA (m-BSI: 45.8% vs. 26.9%, p<.0001; m-FACED: 11.8% vs. 4.8%, p<.0001).

Results of the unadjusted and adjusted multinomial regression models are presented in Table 4.6. The multinomial regression estimated the log-odds: 1) comparing high severity of bronchiectasis vs low, and 2) comparing intermediate severity vs low. First, we fit the unadjusted multinomial regression model with m-BSI as an outcome variable. Patients in PA group had 6.53 times the odds for having high severity vs. low (95% CI: 4.62-9.23), and 1.88 times the odds for having intermediate severity vs. low (95% CI: 1.31-2.69).

The adjusted multinomial regression fit the two equations below, with each comparison having its own intercept and set of coefficients:

1) $\text{Log}\left(\frac{P(y=\text{High})}{P(y=\text{Low})}\right) = \beta_0 + \beta_1\,(\text{PA}=1) + \beta_2\,(\text{Age}) + \beta_3(\text{Female}=1) + \beta_4\,(\text{FEV1\%predicted}) + \beta_5\,(\text{Exacerbations in the past 2 years}=1) + \beta_6\,(\text{NTM history}=1)$

2) $\text{Log}\left(\frac{P(y=\text{Intemediate})}{P(y=\text{Low})}\right) = \beta_0^* + \beta_1^*\,(\text{PA}=1) + \beta_2^*\,(\text{Age}) + \beta_3^*\,(\text{Female}=1) + \beta_4^*\,(\text{FEV1\%predicted}) + \beta_5^*\,(\text{Exacerbations in the past 2 years}=1) + \beta_6^*\,(\text{NTM history}=1)$

Results of the adjusted multinomial regression model are presented in Table 4.6. Controlling for other covariates in the model, participants in PA group had 6.15 times the odds of being classified as high severity of bronchiectasis versus low severity on m-BSI (95% CI 3.98-9.50), and 2.06 times the odds of being classified as intermediate severity of bronchiectasis versus low severity on m-BSI (95% CI 1.37-3.09).

Similarly, we found a significant association between presence of PA at baseline and severity of bronchiectasis calculated using m-FACED. Table 4.6 presents the results of unadjusted and adjusted multinomial regressions using m-FACED as an outcome variable. In unadjusted analyses, participants with PA had 9.47 times the odds (95% CI: 6.69-13.39) for having severe bronchiectasis on m-FACED versus mild, and 1.94 times the odds (95% CI: 1.53-2.47) for having moderate bronchiectasis vs. mild.

Results of the adjusted analyses demonstrated that controlling for other covariates in the model, the participants with PA had 14.59 times the odds (95% CI: 8.53-24.94) for having severe bronchiectasis versus low, and 2.15 times the odds (95% CI: 1.59-2.91) for having moderate bronchiectasis vs. mild.

Results of the sensitivity analyses after excluding PA severity marker from calculation of m-BSI and m-FACED showed the same direction of the association as in the main analyses, although the effect size was attenuated in unadjusted analyses and failed to reach statistical significance at $\alpha=0.05$ in most adjusted analyses for both m-BSI and m-FACED (Table 4.6).

Missing data analyses did not reveal any significant differences between the patients included in the present study and those excluded from the analyses due to

incomplete data in gender, ethnicity, and smoking status. However, we identified a greater proportion of white patients among those included in the study (91.53% vs. 88.81%, p=0.02). In addition, our study participants were on average over two years younger (63.7 vs. 66.0 years, p<.0001), and had lower FEV1%predicted (70.9 (±22.2) vs. 77.7 (±21.6), p<.0001) and FVC % predicted (79.9 (±19.7) vs. 87.6 (±20.2), p<.0001) compared to excluded patients.

4.4 Discussion

Our study of patients with NCFB utilizes baseline data from the BRR (n=1831) to assess the prevalence of PA presence in sputum of patients with NCFB and evaluates the association between the presence of PA and disease severity using two bronchiectasis severity assessment instruments.

Our analyses indicate that over a quarter of patients in our study (25.4%) showed presence of PA in their sputum culture at baseline, and 13.6 % of the participants had chronic colonization by PA. This is in agreement with previously reported PA prevalence in the earlier BRR cohort[103] as well as other studies of patients with NCFB including a Spanish cohort with 19.7% of patients with chronic PA colonization.[106] Our findings also support the recent report of chronic PA infection in 15% of patients within the European FRIENDS bronchiectasis cohort.[107] Notably, the lower prevalence of PA presence of only 12% was reported by researchers in a longitudinal study in Australia.[108] Significantly higher prevalence of PA presence (47%) and colonization (30%) were reported by authors of a recent study in England.[109] The authors suggest that the high prevalence of PA among their patients might be attributed to longer follow-up periods or cross-infection.[109]

Our review of reported PA prevalence in various bronchiectasis cohorts reflects a wide variety of prevalence estimates of presence as well as chronic colonization of PA in patients with NCFB in different geographic areas. In some cohorts, including our study population, PA is identified as the most prevalent microorganism[103] while others report *Haemophilus influenza* was the most prevalent pathogen.[108,110] Identification of prevalent microorganisms and treatment selection according to the culture results is highly important in patients with NCFB. According to the vicious cycle hypothesis, pathogenic microorganisms such as PA may potentially play a role in the development of bronchiectasis.[24,79] Hence, early identification of PA presence and prevention when possible as well as the timely start of appropriate antibacterial therapy are highly recommended in patients with bronchiectasis.[111]

We observed that almost a third of the patients in the PA group reported having three or more exacerbations in the past two years compared to only 17.1% of those without presence of PA. Similar finding have been previously reported in the European cohort of patients with bronchiectasis by Chalmers et al.[112] In their recently published research, the authors identified that patients with chronic PA infection had over two times the odds for having three or more exacerbations at follow-up even when they had less than three exacerbations at baseline. Rogers et al. in their recent study highlighted that presence of PA in sputum of patients with bronchiectasis was the best predictor of future exacerbations.[113] Chalmers et al. established a "frequent exacerbator phenotype" among patients with NCFB that reflects that prior exacerbations in these patients predict future risk for exacerbations.[112] Considering that exacerbations are frequently associated with bacterial infections, and PA is one of the most prevalent microorganisms in patients with

NCFB, it is critical to recognize the importance of timely identification of PA in sputum which has important management and prognostic implications in this patient population.[24,114]

Our study findings indicate that patients with presence of PA have worse pulmonary function compared to those without. This supports earlier research by Evans et al. that chronic colonization by PA is associated with worse lung function including lower FEV1 and FVC %predicted than in patients without PA.[102] The authors suggest that PA colonization takes place in patients with already rapidly declining lung function and additionally accelerates the decline.[102] This agrees with another study by Davies et al. that PA infection occurs in patients with more severely impaired lung function, however, PA colonization does not influence the rate of decline in pulmonary function over time.[115]

Consistent with previous research, our study results suggest that the presence of PA infection in patients with NCFB is associated with high severity of disease and poor prognosis.[24,102,116] Until recently, there were no bronchiectasis-specific severity assessment instruments that would assist in stratifying the risk for mortality, exacerbations, hospitalizations, and quality of life. Chalmers and colleagues derived and validated the BSI to identify high-risk patients with bronchiectasis and guide appropriate therapy and disease management options.[25] A significantly greater proportion of patients with PA in our study were classified as high severity of disease on m-BSI compared to those without PA. We observed similar results using another bronchiectasis-specific tool, m-FACED, to stratify disease severity by PA presence. Of note, even presence of only one or more positive PA cultures in our study population was significantly associated with disease severity classification that utilizes PA chronic colonization as a predictor.

This suggests that patients with even only presence of PA may have considerably greater risks for poor prognosis.

Our findings of fair agreement (kappa= 0.2632) between the m-BSI and m-FACED in classifying the severity of NCFB support findings by researchers in Portugal. A study by Costa et al. compared the performance of the BSI and FACED and found a similar association between the scores (kappa=0.330, p=0.002).[117]

Rosales-Mayor et al. recently compared the performance of the BSI and FACED within a Spanish cohort of patients with bronchiectasis, and concluded that these prognostic scores classified patients differently.[118] The majority of patients in their study were classified as severe (54.4%) and moderate (25.8%) on BSI, and as mild (59.3%) and moderate (33.5%) on FACED. The authors highlighted that the BSI showed superior ability to predict future exacerbations within their cohort of patients compared to FACED, and suggested modifications to enhance the existing FACED by including an exacerbation severity marker.[118] Similar to the research by Rosales-Mayor et al.[118], our findings indicate that even after modifications made to the original instruments, m-BSI and m-FACED categorize severity of bronchiectasis in patients with NCFB differently, and distribution of severity categories in our study population is similar to the findings by Rosales-Mayor and colleagues. In our study, m-BSI stratified significantly higher number of patients into high severity group compared to m-FACED which suggests worse prognosis and high risk for poor outcomes. This might be related to the fact that FACED does not account for the number of exacerbations, a known important factor in identifying a future risk of the patients with NCFB. FACED has been validated for 5-year all-cause mortality risk and has not been validated for exacerbations.[26]

Wilson et al. showed that health-related quality of life (QoL) of patients with PA colonization was significantly worse compared to those with no PA using several standardized measures.[116] Patients with PA in their study also had worse pulmonary function and greater disease severity on CT scans, although the authors suggest that exacerbation frequency and bacteriology were better correlates to QoL. The authors also highlighted the importance of breaking down the non-PA group into subcategories by the presence of other microorganisms.[116] The QoL measures were not available in our data, although our study assessed and compared shortness of breath between the PA groups. A significantly greater proportion of patients with PA presence reported dyspnea when active and when at rest which may worsen their quality of life.

High severity classification of patients with PA in our study suggest the importance of appropriate management considerations to improve prognosis in this patient population. Wilson and colleagues in their recent work highlighted the challenges associated with the treatment of NCFB patients with presence of PA.[96] The most recent British Thoracic Society (BTS) guidelines for bronchiectasis in adults recommend using the BSI to help guide management of patients.[119] Their updated stepwise management recommendations consider the underlying cause of NCFB and exacerbation frequency in treatment considerations. Wilson et al. underline the opportunities for PA management in patients with NCFB during the three timepoints: at first isolation, during exacerbations, and chronic PA colonization.[96] The authors reflect on the importance of international collaborations in research into management strategies and development of new drugs for patients with this chronic disease, a discussion that took place during an expert forum held at the ERS in 2014.[96] Renewed interest in NCFB, increase in research activity within

international bronchiectasis registries and needs for multidisciplinary approach to management of NCFB to improve patient outcomes were also highlighted at the recent World Bronchiectasis Conferences.[23]

Strengths and Limitations

Among the strengths of the present study, it is important to note the large number of patients with NCFB and NTMLD enrolled in the US BRR, as well as the exceptionally wide range of detailed data collected on clinical characteristics of the BRR cohort and patient outcomes.

As with any registry-based observational study, our study has some limitations. The BRR participants are recruited from the tertiary referral institutions and may not be representative of the general population of patients with NCFB. Additionally, considering the high interest of these institutions in NTMLD, our study cohort may be enriched for patients with NTM. Geographic distribution of the referral medical facilities mainly represents large cities in the Eastern part of the US, which may have introduced a selection bias.

The BRR contains data collected from multiple study sites. Our study did not account for potential differences in patient characteristics, the prevalence of microorganisms or comorbidities, or physician practices and treatment availabilities across the medical institutions. Also, patients within clinical sites might be similar and more correlated in their characteristics.

Clinical data obtained using medical charts abstraction is often subject to recording errors and missing entries which may lead to reporting and non-response

biases. Although, the data management system has incorporated expected range checks to lessen potential data entry errors, and all study coordinators utilized the same standardized data collection forms.

Another potential limitation is that our study modified the bronchiectasis severity scores to adapt to the BRR data collection. Although, the modifications were relatively minor and mainly related to a measure of dyspnea and time period of exacerbations and hospitalization frequencies. In addition, potential selection bias due to missing and incomplete data cannot be excluded.

4.5 Conclusion

PA infection is common in patients with NCFB within the BRR. The severity of bronchiectasis is significantly greater in patients with PA which emphasizes the high burden of the disease. Future longitudinal studies are recommended to assess clinical outcomes and prognosis over time. Further collaborative work in this area are needed including exploration of new management options aimed at the improvement of patient outcomes and prognosis in PA infected NCFB patients.

Funding support: This study was sponsored by the COPD Foundation

Table 4.1 Select baseline characteristics of the study population within the BRR stratified by presence of PA*, n=1,831

	Overall N=1,831	**Presence of PA*** N=465 (25.4%)	**No Presence of PA** N=1,366 (74.6%)
Age, years, mean (SD)	63.7 (14.1)	64.4 (14.8)	63.5 (13.9)
Female, n (%) †	1,443 (78.8)	350 (75.3)	1,093 (80.0)
Race, n (%)			
White	1,676 (91.5)	424 (91.2)	1,252 (91.7)
Black or African-American	46 (2.5)	9 (1.9)	37 (2.7)
Asian	52 (2.8)	13 (2.8)	39 (2.9)
Other**	57 (3.1)	19 (4.1)	38 (2.8)
Hispanic, n (%)	82 (4.5)	27 (5.8)	55 (4.0)
Smoking history, n (%)			
Current	28 (1.5)	2 (0.4)	26 (1.9)
Former	718 (39.5)	184 (39.9)	534 (39.4)
Never	1,072 (59.0)	275 (59.7)	798 (58.7)
NTM-positive*, n (%) ‡	885 (48.3)	179 (38.5)	706 (51.7)
Pre-bronchodilator FEV1 %predicted, mean (SD) ‡	70.9 (22.2)	62.8 (21.3)	73.7 (21.8)
Pre-bronchodilator FVC %predicted, mean (SD) ‡	79.9 (19.7)	74.4 (19.7)	81.8 (19.4)
Three or more exacerbations within the past 2 years, n (%) ‡	377 (20.6)	142 (30.5)	235 (17.2)
History of hospital admissions within the past 2 years, n (%) ‡	384 (21.0)	149 (32.0)	235 (17.1)

BRR- Bronchiectasis Research Registry; PA- *Pseudomonas aeruginosa*; NTM - Nontuberculous mycobacteria; FEV1- Forced Expiratory Volume in the first second; FVC- Forced vital capacity; *≥1cultures positive for PA at baseline, ** includes Native Hawaiian or Other Pacific Islander and American Indian or Alaska Native; ***- history of NTM or ≥1 cultures positive for NTM at baseline; †$p<0.05$, ‡$p<0.0001$

Table 4.2 m-BSI severity markers distribution in the overall study sample and stratified by PA presence, n=1,831

Severity Markers	Score Points	Overall N=1,831	Presence of PA* N=465 (25.4%)	No Presence of PA N=1,366 (74.6%)	p-value
Age					
<50	0	261 (14.25)	75 (16.13)	186 (13.62)	0.0053
50-69	2	862 (47.08)	187 (40.22)	675 (49.41)	
70-79	4	533 (29.11)	148 (31.83)	385 (28.18)	
80+	6	175 (9.56)	55 (11.83)	120 (8.78)	
BMI					
≥ 18.5	0	1,601 (87.44)	409 (87.96)	1,192 (87.26)	0.6961
<18.5	2	230 (12.56)	56 (12.04)	174 (12.74)	
FEV1% Predicted					
>80	0	648 (35.39)	100 (21.51)	548 (40.12)	<.0001
50-80	1	851 (46.48)	225 (48.39)	626 (45.83)	
30-49	2	271 (14.80)	121 (26.02)	150 (10.98)	
<30	3	61 (3.33)	19 (4.09)	42 (3.07)	
Hospital admissions in previous 2 years†*	0	1,447 (79.41)	316 (67.96)	1,131 (82.80)	<.0001
No	5	384 (20.97)	149 (32.04)	235 (17.20)	
Yes					
Number of exacerbations in previous 2 years†*					
<3	0	1,454 (79.41)	323 (69.46)	1,131 (82.80)	<.0001
≥3	2	377 (20.59)	142 (30.54)	235 (17.20)	
Dyspnea†**					
No reported Dyspnea (shortness of breath)	0	748 (40.85)	164 (35.27)	584 (42.75)	0.0119
Dyspnea (shortness of breath) when active	2	759 (41.55)	205 (44.09)	554 (40.56)	
Dyspnea (shortness of breath) when at rest	3	324 (17.70)	96 (20.65)	228 (16.69)	
PA Colonization					
No	0	1,582 (86.40)	216 (46.45)	1,366 (100.00)	<.0001
Yes	3	249 (13.60)	249 (53.55)	--	

Table 4.2 Continued

Severity Markers	Score Points	Overall N=1,831	Presence of PA* N=465 (25.4%)	No Presence of PA N=1,366 (74.6%)	p-value
Colonization with other organisms					
No	0	1,734 (94.70)	440 (94.62)	1,294 (94.73)	0.9301
Yes	1	97 (5.30)	25 (5.38)	72 (5.27)	
Radiological Severity					
<3 lobes involved		1,005 (54.89)	238 (51.18)	767 (56.15)	0.0630
≥3 lobes involved or	0				
cystic bronchiectasis	1	826 (45.11)	227 (48.82)	599 (43.85)	

m-BSI –modified Bronchiectasis Severity Index; BMI- Body Mass Index; FEV1- Forced Expiratory Volume in the first second; PA- *Pseudomonas aeruginosa*; †indicates modified variables. *Original variable in the BSI includes frequency in the previous 1 year.

**Original Dyspnea variable included in the BSI is categorized according to Medical Research Council (MRC) scale: 1-3 (0 points), 4 (2 points), 5 (3 points):

MRC: 1 – Not troubled by breathlessness except on strenuous exercise

2 - Short of breath when hurrying on the level or walking up a slight hill

3 – Walks slower than most people on the level, stops after a mile or so, or stops after 15 minutes walking at own pace

4 – Stops for breath after walking about 100 yards or after a few minutes on level ground

5 - Too breathless to leave the house, or breathless when undressing

Table 4.3 m-FACED severity markers distribution in the overall study sample and stratified by PA presence, n=1,831

Dichotomized Variables	Score Points	Overall N=1,831	Presence of PA* N=465 (25.4%)	No Presence of PA N=1,366 (74.6%)	p-value
F-FEV1% Predicted					
≥50%	0	1,499 (81.87)	325 (69.89)	1,174 (85.94)	<.0001
<50%	2	332 (18.13)	140 (30.11)	192 (14.06)	
A- Age					
<70 years	0	1,123 (61.33)	262 (56.34)	861 (63.03)	0.0105
≥70 years	2	708 (38.67)	203 (43.66)	505 (36.97)	
C- Chronic Colonization by PA					
No	0	1,582 (86.40)	216 (46.45)	1,366 (100.00)	<.0001
Yes	1	249 (13.60)	249 (53.55)	--	
E- Extension					
≤ 2 lobes affected	0	516 (28.18)	129 (27.74)	387 (28.33)	0.8074
> 2 lobes affected	1	1,315 (71.82)	336 (72.26)	979 (71.67)	
D- Dyspnea†*					
No reported Dyspnea (shortness of breath)	0	725 (39.60)	157 (33.76)	568 (41.58)	0.0029
Dyspnea (shortness of breath) when active and/or when at rest	1	1,106 (60.40)	308 (66.24)	798 (58.42)	

m-FACED- modified FACED; PA- *Pseudomonas aeruginosa*; FEV1- Forced Expiratory Volume in the first second; † indicates modified variables. ***** Original **D**yspnea variable included in FACED is dichotomized according to modified Medical Research Council (mMRC) scale: 0-2 (0 points); 3-4 on mMRC scale (1 point):
0-Dyspnea only with strenuous exercise
1 - Dyspnea when hurrying or walking up a slight hill
2 – Walks slower than people of the same age because of dyspnea or has to stop for breath walking at own pace
3 – Stops for breath after walking 100 yards or after a few minutes
4 - Too dyspneic to leave house or breathless when undressing

Table 4.4 Severity of bronchiectasis by m-BSI and m-FACED in the overall study sample and stratified by presence of PA* at baseline including and excluding PA from the severity scores calculation, n=1831

	Overall N=1831	**Presence of PA** N=465 (25.4%)	**No Presence of PA** N=1,366 (74.6%)	**Overall** N=1,831	**Presence of PA** N=465 (25.4%)	**No Presence of PA** N=1,366 (74.6%)
	(PA included in severity scores calculation)			**(PA excluded from severity scores calculation)**		
m-BSI severity categories, n (%)						
Low	426 (23.3)	45 (9.7)	381 (27.9)	460 (25.1)	79 (17.0)	381 (27.9)
Intermediate	755 (41.2)	137 (29.5)	618 (45.2)	791 (43.2)	173 (37.2)	618 (45.2)
High	650 (35.5)	283 (60.9)	367 (26.9)	580 (31.7)	213 (45.8)	367 (26.9)
m-FACED severity categories, n (%)						
Mild	962 (52.5)	157 (33.8)	805 (58.9)	1008 (55.1)	203 (43.7)	805 (58.9)
Moderate	684 (37.4)	188 (40.4)	496 (36.3)	703 (38.4)	207 (44.5)	496 (36.3)
Severe	185 (10.1)	120 (25.8)	65 (4.8)	120 (6.6)	55 (11.8)	65 (4.8)

m-BSI –modified Bronchiectasis Severity Index; m-FACED- modified FACED; PA- *Pseudomonas aeruginosa*; *- ≥1cultures positive for PA at baseline;

Table 4.5 Classification of bronchiectasis severity by m-BSI versus m-FACED, n=1831

m-BSI	**m-FACED**		
	Mild (n=962)	**Moderate** (n=684)	**Severe** (n=185)
Low (n=426)	395	31	0
Intermediate (n=755)	414	332	9
High (n=650)	153	321	176

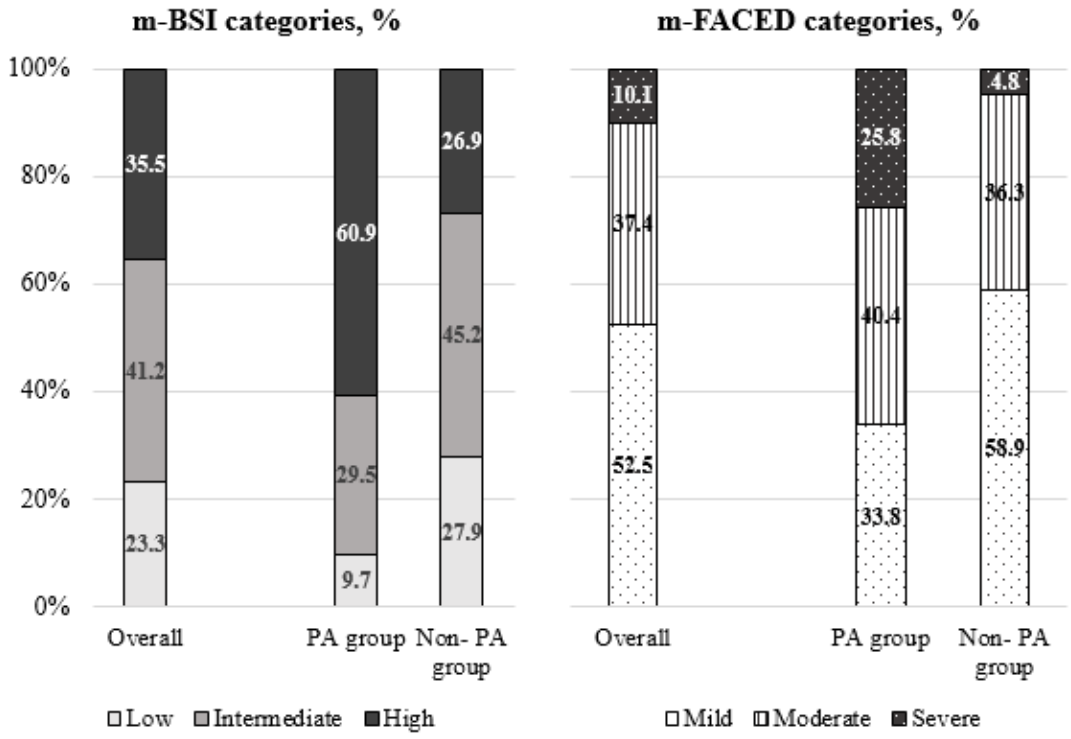
Note: all data are shown as n; Kappa= 0.2632; m-BSI –modified Bronchiectasis Severity Index; m-FACED- modified FACED;

Table 4.6 Results of the unadjusted and adjusted multinomial logistic regressions for outcomes m-BSI and m-FACED including and excluding PA from the severity scores calculation, n=1,831

	OR_{unadj} (95% CI)	OR_{adj} (95% CI)*	OR_{unadj} (95% CI)	OR_{adj} (95% CI)*
	(PA included in severity scores calculation)		**(PA excluded from severity scores calculation)**	
m-BSI				
PA presence				
High severity vs Low	6.53 (4.62-9.23)	6.15 (3.98-9.50)	2.80 (2.08-3.76)	1.56 (1.06-2.29)
Intermediate severity vs Low	1.88 (1.31-2.69)	2.06 (1.37-3.09)	1.35 (1.01-1.81)	1.12 (0.80-1.58)
m-FACED				
PA presence				
Severe vs Mild	9.47 (6.69-13.39)	14.59 (8.53-24.94)	3.36 (2.27-4.96)	1.72 (0.84-3.54)
Moderate vs Mild	1.94 (1.53-2.47)	2.15 (1.59-2.91)	1.66 (1.32-2.07)	1.19 (0.89-1.59)

m-BSI –modified Bronchiectasis Severity Index; m-FACED- modified FACED; PA- *Pseudomonas aeruginosa;* OR- Odds Ratio; CI- Confidence Interval; FEV1- Forced Expiratory Volume in the first second; * Adjusted for age, gender, baseline FEV1% predicted, NTM status and history of exacerbations in the past 2 years;

Figure 4.1 Distribution of m-BSI and m-FACED categories in the overall cohort and stratified by PA presence, n=1,831



m-BSI- modified Bronchiectasis Severity Index; m-FACED- modified FACED; PA- *Pseudomonas aeruginosa;*

CHAPTER 5. CONCLUSION

5.1 Summary

The purpose of this dissertation research was to enhance the body of literature with new findings on symptom burden, disease severity and health-related behaviors in three chronic pulmonary diseases. This research utilized data from three different disease-specific registries to conduct the analyses: 1) patients with Alpha1-Antitrypsin deficiency (AATD) enrolled in AlphaNet's Disease Management And Prevention Program (ADMAPP); 2) COPD Foundation's Patient-Powered Research Network (COPD PPRN) data on patients with a self-reported physician-diagnosed Chronic Pulmonary Obstructive Disease (COPD); and 3) the Bronchiectasis and NTM Research Registry (BRR) data collected from multiple US clinical sites on patients with Non-Cystic Fibrosis Bronchiectasis (NCFB) and Nontuberculous mycobacteria (NTM).

Chapter Two of this research compared health and behavioral characteristics in patients with ZZ and SZ genotypes of AATD within ADMAPP to recognize the differing needs in health education and behavioral intervention between the two AATD genotypes.[27] The findings demonstrated that individuals with SZ genotype had more frequent exacerbations as well as greater number of hospitalizations and physician visits compared to patients with more deficient ZZ genotype. These findings may be related to higher prior exposure of SZs to smoking and lower adherence to the recommendations of ADMAPP. SZs reported longer and heavier prior smoking history, and a greater proportion of them were current smokers. In addition, SZs had worse perception of their health, fitness and other health-related behaviors. Possible explanations may include that the perception of a lower disease risk in SZs may be associated with poor adherence to

healthy lifestyle recommendations of ADMAPP and considerably worse health status compared to more severely deficient ZZs.[27] Of note, SZs in this study sample had significantly more comorbid conditions including hypertension, cerebrovascular disease, and were on average two years older than individuals with ZZ genotype. Also, SZs reported being less comfortable with their knowledge about the disease compared to ZZs. The lower adherence to ADMAPP and lack of knowledge about their condition, as well as poor health-related behavior choices, could be related to the self-perceived low seriousness of the disease in individuals with SZ genotype. Our study suggests that more severely AAT deficient ZZs are more adherent to disease management recommendations and maintain healthier lifestyles even though their condition is considered more severe.

Chapter Three of this research estimated the patient-reported prevalence of moderate to severe cough and phlegm in people with COPD responding to the COPD PPRN survey. This study explored the association between severity of cough and phlegm and patient-reported outcomes including health-related quality of life.

The burden of cough and phlegm among the study population was high with approximately 70% of the respondents reported moderate to high levels of cough and/or phlegm. Considering that cough and sputum production may be underreported in the COPD population[81], symptom burden estimates based on patient-reported data have key importance. Significantly greater proportion of patients with moderate/high cough and phlegm reported being current smokers, had worse self-reported dyspnea and greater numbers of exacerbations in the past year compared to those with no/low cough and phlegm.

Our study findings demonstrated significant association between severity of cough and phlegm and greater levels of fatigue, anxiety, and depression, higher pain interference and sleep disturbance, and lower social abilities and physical function (as measured by the Patient Reported Outcome Measurement Information System (PROMIS) instrument). Other important findings from this chapter concern the longitudinal portion of this study. The patient-reported improvements in cough and phlegm over time were associated with better quality of life measured by PROMIS-29 at the follow-up. The findings of consistent association between high levels of cough and phlegm and worse patient-reported quality of life emphasize the need for new therapies specifically targeting these symptoms.

Chapter Four of this research examined prevalence of *Pseudomonas aeruginosa* (PA) colonization and presence in sputum of NCFB patients within the BRR. This study posited the association between presence of PA and NCFB severity using two modified bronchiectasis severity assessment instruments. Over a quarter of the study population had presence of PA, and 13.6% presented with chronic PA colonization. Patients with PA presence had significantly worse pulmonary function as shown by FEV1 and FVC % predicted, and greater number of exacerbations and hospitalizations due to pulmonary illness, compared to those without PA. An important contribution of this work was to show that while the severity indices require chronic colonization of PA, evidence of a single PA infection was significantly associated with severity on both indices.

The Bronchiectasis Severity Index (BSI), which was designed to identify patients at high risk for mortality, exacerbations, hospitalizations, and worse quality of life,[25] and the FACED,[26] were modified to adapt to the BRR data collection. Our findings supported

earlier reported differences in severity classification between the BSI and FACED.[118] Our study demonstrated that m-BSI and m-FACED show fair agreement (kappa=0.2632) in classifying severity of NCFB. The results of the unadjusted and adjusted multinomial regression analyses demonstrated positive association between presence of PA and severity of bronchiectasis estimated using m-BSI and m-FACED. These findings support previous research and underline the importance of early identification and targeted treatment of PA to reduce disease severity.

5.2 Strengths and Limitations

This dissertation research assessing patient outcomes in people with three chronic pulmonary diseases yielded several important findings. One of the main strengths of this research is the large number of patients included in each study as well as detailed data collected on various demographic and clinical characteristics of the participants. In addition to the baseline, the COPD PPRN study also utilized follow-up data on patient-reported outcomes after one year. Despite the richness of the data, the findings of this research should be interpreted with caution in view of several limitations related to the registry-based observational nature of the studies.

Disease-specific registries and analyses based on patient registry data are gaining popularity.[120] Systematic collection of data on specific diseases allows for follow-up of trends in diagnosis, treatment, and outcomes.[121] The primary purpose of patient registries is mainly to aid in research of natural history of various diseases.[121] In addition, registry data are also used for hypothesis generation, describing patient-reported outcomes, risk factors and exposures.[121,122]

Some of the limitations that are recognized in registry-based studies are selection bias, confounding by disease severity, channeling bias, immortal time bias, as well as several other limitations of the observational studies.[120] In addition, research using only baseline data is not able to provide causal inference due to cross-sectional nature of the studies.

This dissertation research is based on secondary data from several US disease-specific registries. Chapter Two study utilized data collected from participants of AlphaNet, a not-for-profit health management organization that coordinates management and treatment of individuals with AATD and lung disease in the US[27,42]. Only patients with more severe genotypes ZZ and SZ were included in this study. Considering that a greater number ZZs develop lung disease relative to SZs, and only patients with lung disease were invited to enroll in ADMAPP, the potential of ascertainment bias cannot be excluded. In addition, the findings of this study cannot be generalized to patients with ZZ and SZ genotypes without lung disease.

Chapter Three study is based on the COPD PPRN patient-reported data. Only data obtained from patients with self-reported physician-diagnosed COPD were included in this study, which may have introduced potential selection bias. In addition, self-reported data including presence of comorbidities, frequency of physician, ER visits and hospitalizations is subject to a recall bias. Another important to note limitation of this study is use of classification of severity of cough and phlegm based on CAT scores for questions pertaining to these symptoms, which is not a widely used classification and may have introduced a misclassification bias.

Chapter Four of this research utilized data collected from patients with NCFB within the BRR. The BRR is a multi-site registry, and participants are recruited from tertiary referral institutions and may not be representative of the general population of individuals with NCFB. In addition, patients within individual centers might be more correlated in their characteristics and therapy options. Our study analysis did not take into account potential variability in these characteristics across the clinical sites. These tertiary referral institutions have high interest in NTMLD; hence, the BRR population may be enriched for patients with NTM. The BRR data collection takes place using medical chart abstraction, which may have led to recording errors, missing entries and reporting and non-response biases. Another important limitation of this study is use of modified disease severity indices to adapt to the BRR data collection.

Although disease-specific registries intrinsically are subject to potential biases and limitations, they often have the ability to address research questions that could potentially have a long-term influence on disease prevention and development of new therapies.[10] In the case of uncommon and rare diseases such as AATD and bronchiectasis, registry-based studies often represent the only source of data for research.

5.3 Future Research

This dissertation research underlined many important recommendations for future research and considerations for management of chronic pulmonary diseases. Some prevalent chronic lung diseases, like COPD, are well researched, but further studies are needed to fully assess burden of specific symptoms of the disease such as cough and phlegm. The findings in Chapter Three highlight the needs for future research and development of new pharmacotherapies specifically targeting prevalent COPD symptoms

like cough and phlegm. Regrettably, no new and effective cough medication has been developed by the pharmaceutical industry in over a century.[64] Future research is recommended to better understand patient-perceived burden of COPD symptoms, disease outcomes and quality of life including mood and social and physical functioning. Patient-reported data is invaluable in assessing patient-perceived severity of disease, including its burden on daily life and activities.

Less common respiratory diseases such as AATD and Bronchiectasis have started receiving a significant amount of attention from the scientific community leading to increased interest in research and development of new treatments. Disease-specific registries play important roles in continued research of these conditions, as frequently data collected by the registries is the largest source of information on natural history of rare diseases.

The findings of the study in Chapter Two highlight the value of disease management programs in addressing many questions regarding the natural history of rare diseases such as AATD as well as sustained and tailored support provided to the patients with uncommon diseases. Our study findings underline the differences in demographic and clinical characteristics of patients with AATD with ZZ and SZ genotypes. Our results suggest that patients with less severe deficient genotype perceive their disease risk as low and do not fully comply with healthy lifestyle recommendations of the disease management program. Considering the above findings, future research should consider the extent to which genotype-specific health promotion intervention would be useful. Future studies should consider including collection of additional clinical data to enhance future outcome research.

As mentioned in Chapter Four, further research is needed to fully understand the multidimensional nature of NCFB. Pathogenic microorganisms such as *Pseudomonas aeruginosa* (PA) may potentially play a role in the development of bronchiectasis according to the "vicious cycle" hypothesis.[24,79] Hence, early identification of prevalent pathogens such as PA and timely start of appropriate antibacterial therapy remain highly important in patients with NCFB.[111] Future longitudinal studies are recommended to assess clinical outcomes and prognosis over time in this patient population.

This dissertation research has contributed to the characterization of the epidemiology of chronic pulmonary disease burden. These studies expand the amount of knowledge available on disease severity, health behaviors and patient-perceived outcomes in three chronic lung diseases, and emphasize the need for further research and development of new treatment options to improve patients' prognosis.

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VITA

RADMILA CHOATE

EDUCATION

University of Kentucky, Lexington, KY

MPH, Major: Epidemiology — 08/2012 - 05/2014

Graduate Certificate in Global Health

Tbilisi State Medical University, Tbilisi, Georgia — 09/1993 – 06/2000

MD, General Practice

PROFESSIONAL EXPERIENCE

Research Analyst, Department of Preventive Medicine and Environmental Health, University of Kentucky College of Public Health	09/2015 - present
Research Analyst / Epidemiologist, HIV/AIDS Surveillance, Kentucky Department for Public Health/ University of Kentucky	01/2015 - 09/2015
Research Assistant, Department of Epidemiology, University of Kentucky College of Public Health	09/2014 - 12/2014
Research Triangle Institute (RTI) International Intern, RTI International /USAID-funded Georgia HIV Prevention Project, Tbilisi, Georgia	05/2013 - 06/2013
Medical Insurance Manager/Medical Claims Audit, American Hospital, Dubai UAE	09/2002 – 12/2006
Medical Claims Review/Authorization Officer, NEXtCARE, Dubai, UAE	10/2001 – 09/2002

TEACHING EXPERIENCE

Guest lecturer: Fall 2014, Spring 2016 - Public Health Capstone (CPH608)

Guest lecturer: Fall 2018 -Statistical Thinking in Public Health (BST230)

HONORS AND AWARDS

Winner of the 1st place for oral presentation at the Center for Clinical and Translational Science Conference, Lexington, KY	2018
Epidemiology/ Biostatistics PhD program 2018 Award for a High Score in Comprehensive Examination	2018
2017 American Thoracic Society (ATS) Abstract Scholarship	2017
University of Kentucky International Service Award	2014
Winner of the 1st place and "Masters Research Division Outstanding Presentation Award" at the Center for Clinical and Translational Science Conference, Lexington, KY	2014

MEMBERSHIPS – PROFESSIONAL ORGANIZATIONS

American Thoracic Society	2017 - present
Beta Gamma Chapter of the Delta Omega Honorary Society in Public Health	2014 - present
Phi Kappa Phi, University of Kentucky	2013 - 2015

PEER-REVIEWED PUBLICATIONS

Radmila Choate, David Mannino, Kristen Holm, Robert Sandhaus "Comparing Patients with ZZ vs. SZ Alpha-1 Antitrypsin Deficiency: Findings from AlphaNet's Disease Management Program". "Chronic Obstructive Pulmonary Diseases: Journal of the COPD Foundation" http://doi.org/10.15326/jcopdf.6.1.2018.0134 (2019)

Cara Pasquale, Jeffrey Vietri, **Radmila Choate**, Angee McDaniel, Reiko Sato, Kimbal Ford, Elisha Malanga, Barbara Yawn. "Patient reported consequences of community-acquired pneumonia (CAP) in patients with chronic obstructive pulmonary disease". "Chronic Obstructive Pulmonary Diseases: Journal of the COPD Foundation" http://doi.org/10.15326/jcopdf.6.2.2018.0144 (2019)

Edward Eden, **Radmila Choate**, Alan Barker. "The clinical features of Bronchiectasis associated with Alpha-1 antitrypsin deficiency, Common Variable Immunodeficiency, and Primary Ciliary Dyskinesia". "Chronic Obstructive Pulmonary Diseases: Journal of the COPD Foundation" (2019)

Kristen E. Holm, David M. Mannino, **Radmila Choate**, Robert A. Sandhaus. "Genotype is Associated with Smoking and Other Key Health Behaviors among Individuals with Alpha-1 Antitrypsin Deficiency-Associated Lung Disease". "Respiratory Medicine" https://doi.org/10.1016/j.rmed.2018.08.016 (2018)

Omar Ahmad, Alexis E. Shafii, David M. Mannino, **Radmila Choate**, Maher A. Baz. "Impact of Donor Lung Pathogenic Bacteria on Patient Outcomes in the Immediate Post-Transplant Period. "Transplant Infectious Disease" http://dx.doi.org/10.1111/tid.12986 (2018)

Mark L Metersky, Timothy R Aksamit, Alan Barker, **Radmila Choate**, Charles L. Daley, Leigh A Daniels, Angela DiMango, Edward Eden, David Griffith, Margaret Johnson, Michael Knowles, Anne E O'Donnell, Kenneth Olivier, Matthias Salathe, Byron Thomashow, Gregory Tino, Gerard Turino, Kevin L Winthrop, David Mannino "The Prevalence and Significance of Staphylococcus aureus in Patients with non-Cystic Fibrosis Bronchiectasis". "Annals of the American Thoracic Society". https://doi.org/10.1513/AnnalsATS.201706-426OC (2018)

Radmila Choate, and David M. Mannino. "Chronic Obstructive Pulmonary Disease: Epidemiology, Clinical Presentation, and Evaluation." "Journal of Clinical Outcomes Management". http://www.turner-white.com/pdf/jcom_apr17_COPD.pdf (2017)

Melanie A Ruffner, Timothy R Aksamit, Byron Thomashow, **Radmila Choate**, Angela DiMango, Gerard M Turino, Anne E O'Donnell, Margaret M Johnson, Kenneth N Olivier, Kevin Fennelly, Charles L Daley, Kevin L Winthrop, Mark L Metersky, Matthias A Salathe, Michael R Knowles, M Leigh Anne Daniels, Peadar G Noone, Gregory Tino, David E Griffith, Kathleen E Sullivan. "Frequency of untreated hypogammaglobinemia in bronchiectasis". "Annals of Allergy, Asthma & Immunology" https://doi.org/10.1016/j.anai.2017.04.020 (2017)

Perkins J., **Choate R**., Mannino D., Browning S., Sandhaus R. "Benefits among Patients with Alpha-1 Antitrypsin Deficiency Enrolled in a Disease Management and Prevention Program". "Chronic Obstructive Pulmonary Diseases: Journal of the COPD Foundation" http://doi.org/10.15326/jcopdf.4.1.2016.0161 (2016)

Fuller W., Cassity E., Kelly A., **Choate R**., Kalema A., Montgomery A., Wieleczko A., Mannino D., Morris P. "Red Cell Transfusion and Mortality of MICU Patients Receiving Continuous Renal Replacement Therapy". "Chest" https://doi.org/10.1016/j.chest.2016.08.236 (2016)

OTHER PUBLICATIONS

Chesnut LW, **Choate R**, Dunworth CE, Eden AR. Voices from the Front Line: Public Health Leaders speak out for Kentucky Families and Children – June 2015. Qualitative examination of four topics (substance abuse; child abuse & neglect; access to care; resources and services for children with special health care needs) raised as key issues by the 2014 Kentucky Patient Survey. The process included running eleven focus groups across Kentucky, theme coding and analysis, and document development. Created as a supplement to the Kentucky 2015 MCH Needs Assessment process. (2015)

CONTRIBUTIONS

Georgia HIV Prevention Project. Sustainable HIV Prevention in Georgia: Challenges, Opportunities, and Recommended Actions. Policy Paper. Prepared by RTI International for USAID/Georgia (acknowledged as a contributor)
https://pdf.usaid.gov/pdf_docs/PA00K2XB.pdf (2014)

PRESENTATIONS/ SCIENTIFIC CONFERENCES

R. Choate, T. Aksamit, D. Mannino, G. Stone, Bronchiectasis and NTM Research Registry Consortium. "Pseudomonas Aeruginosa Associated with Severity of Non-cystic Fibrosis Bronchiectasis Measured by the Modified Bronchiectasis Severity Score (BSI) and the FACED: the US Bronchiectasis and NTM Research Registry (BRR) Study". American Thoracic Society: ATS International Conference. *May 2019*

R. Choate, C. Pasquale, N. Parada, V. Prieto-Centurion, B. Yawn. "PROMIS-29 Scores Associated with Longitudinal Changes in Cough and Phlegm Severity in Patients with COPD within the Chronic Obstructive Pulmonary Disease Patient-Powered Research Network (COPD PPRN)". American Thoracic Society: ATS International Conference. *May 2019*

A. Basavaraj, **R. Choate**, Bronchiectasis and NTM Research Registry Consortium. "Airway Clearance in Bronchiectasis: Analysis from the United States Bronchiectasis Research Registry". American Thoracic Society: ATS International Conference. *May 2019*

B. Yawn, **R. Choate**, E. Malanga, C. Pasquale, N. Parada, V. Prieto-Centurion, R. Mularski. "COPD Patients' Perspective of the Burden of Cough and Phlegm: A COPD PPRN Study". *PCORI Annual Meeting. Washington D.C. November 2018*

R. Choate, E. Eden, A. Barker. "The clinical features of bronchiectasis associated with Alpha-1 Antitrypsin Deficiency, Common Variable Immunodeficiency, and Primary Ciliary Dyskinesia". *3rd Annual Worldwide Bronchiectasis Conference. Washington, DC. July 2018*

C. Pasquale, J. Vietri, **R. Choate,** E. Malanga, K. Ford, A. McDaniel, R. Sato, B. Yawn. "COPD Assessment Test (CAT) to monitor recovery from Community Acquired Pneumonia in COPD Patients". *COPD11, Birmingham, UK. June 2018*

C. Pasquale, J. Vietri, **R. Choate,** E. Malanga, K. Ford, A. McDaniel, R. Sato, B. Yawn. "Impact of Community-Acquired Pneumonia (CAP) on Patients with Chronic Obstructive Pulmonary Disease (COPD)". *COPD11, Birmingham, UK. June 2018*

B. Yawn, **R. Choate**, C. Pasquale, N. Parada, V. Prieto-Centurion. "The Burden of Cough and Phlegm in People with COPD: A COPD PPRN Study". *COPD11, Birmingham, UK*-Winner of the first place among posters at COPD11. *June 2018*

R. Choate, D. Mannino, K. Holm, R.A. Sandhaus. "Analysis of Factors associated with FEV1 decline in Alpha-1 Antitrypsin Deficient patients: a comparison of statistical approaches". *American Thoracic Society: ATS International Conference 2018. San Diego, CA.* Thematic poster session. *May 2018*

R. Choate, E. Eden, A. Barker. "The clinical features of bronchiectasis associated with Alpha-1 Antitrypsin Deficiency, Common Variable Immunodeficiency, and Primary Ciliary Dyskinesia". *American Thoracic Society: ATS International Conference 2018. San Diego, CA.* RAPiD: Rapid Abstract Poster Discussion. *May 2018*

C. Pasquale, J. Vietri, **R. Choate,** E. Malanga, K. Ford, A. McDaniel, R. Sato. "Consequences of Community Acquired Pneumonia (CAP) in patients with COPD. *American Thoracic Society: ATS International Conference 2018. San Diego, CA.* Thematic poster session. *May 2018*

R. Choate, D. Mannino, T. Aksamit, Bronchiectasis and NTM Research Registry Consortium, G. Stone. "*Pseudomonas Aeruginosa* Impact on Severity of Bronchiectasis". *Center for Clinical and Translational Science conference, College of Public Health Research Day"*, Lexington, KY. Oral presentation. *April 2018*

R. Choate, D. Mannino, R.A. Sandhaus, K. Holm. "Multicomponent Intervention Improves BMI in a Randomized Trial of Alpha-1 Antitrypsin Deficient Patients". *American Thoracic Society: ATS International Conference 2017.* Poster discussion. *May 2017*

R. Choate, D. Mannino, R.A. Sandhaus, K. Holm. "Increase in Exercise Activities in Alpha-1 Antitrypsin Deficient Patients: Results of a Randomized Trial". *American Thoracic Society: ATS International Conference 2017. Washington, DC*. Poster discussion. *May 2017*

R. Choate, D. Mannino, R.A. Sandhaus, K. Holm. "Factors associated with FEV1 decline in Alpha-1 Antitrypsin Deficient Patients". *American Thoracic Society: ATS International Conference 2017. Washington, DC.* Poster discussion. *May 2017*

D.M. Mannino, **R. Choate**, J. Walsh, R.A. Mularski, C. Pasquale, W. Clark, E. Malanga, S. Gillespie, M.A. McBurnie, P. Crawford. "Longitudinal Follow-Up Data from Enrollees in the COPD Foundation Patient-Powered Research Network: Methods and Outcomes". *American Thoracic Society: ATS International Conference 2017. Washington, DC.* Poster discussion. *May 2017*

T.R. Aksamit, **R. Choate**, A.E. O'Donnell, A.F. Barker, C.L. Daley, L.A. Daniels, E. DiMango, E. Eden, K.P. Fennelly, D.E. Griffith, M. Johnson, M. Knowles, P. Noone, K.N. Olivier, M.L. Metersky, M. Salathe, B. Thomashow, G. Tino, G. Turino, K.L. Winthrop, D.M. Mannino. "United States Bronchiectasis Registry Longitudinal Follow Up at Two Years". *American Thoracic Society: ATS International Conference 2017. Washington, DC.* Presenter- T.R. Aksamit. Oral presentation. *May 2017*

A. Otekeiwebia, E. Cassity, A. Kelly, **R. Choate**, D. Mannino, P. Morris, M. Khosravi. "Performance of the Respiratory Shock Index, a New Derived Outcome Prediction Measure for Adults with Sepsis". *American Thoracic Society: ATS International Conference 2017. Washington, DC.* Poster presentation. *May 2017*

R. Choate, D. Mannino, R.A. Sandhaus, K. Holm. "Increase in Exercise Activities in Alpha-1 Antitrypsin Deficient Patients: Results of a Randomized Trial". *Center for Clinical and Translational Science conference, College of Public Health Research Day, Lexington, KY.* Poster presentation. *April 2017*

R. Choate, D. Mannino, R.A. Sandhaus, K. Holm. "Multicomponent Intervention Improves BMI in a Randomized Trial of Alpha-1 Antitrypsin Deficient Patients". *COPD10USA Conference. Chicago, IL.* Poster presentation. *July 2017*

R. Choate, D. Mannino, R.A. Sandhaus, K. Holm. "Increase in Exercise Activities in Alpha-1 Antitrypsin Deficient Patients: Results of a Randomized Trial". *COPD10USA Conference. Chicago, IL.* Poster presentation. *July 2017*

R. Choate, D. Mannino, R.A. Sandhaus, K. Holm. "Factors associated with FEV1 decline in Alpha-1 Antitrypsin Deficient Patients". *COPD10USA Conference. Chicago, IL.* Poster presentation. *July 2017*

D. Mannino, **R. Choate**, J. Walsh, R. Mularski, C. Pasquale, W. Clark, E. Malanga S. Gillespie, P. Crawford, M. McBurnie. "Longitudinal Follow-Up Data from Enrollees in the COPD Foundation Patient-Powered Research Network: Methods and Outcomes". *COPD10USA Conference. Chicago, IL.* Poster presentation. *July 2017*

R. Choate, D. Mannino, T. Aksamit, Bronchiectasis and NTM Research Registry Consortium, G. Stone. "*Pseudomonas Aeruginosa* Impact on Severity of Bronchiectasis". *COPD10USA Conference. Chicago, IL.* Poster presentation. *July 2017*

R. Choate, D. Mannino, D. Barber, R.A. Sandhaus, K. Holm. "Differences between ZZ and SZ patients in the AlphaNet Program". *American Thoracic Society: ATS Conference 2016. San Francisco, CA.* Poster presentation. *May 2016*

R. Choate, D. Mannino, R.A. Sandhaus, D. Barber, K. Holm. "Improving survival among ZZ patients in the AlphaNet Program". *American Thoracic Society: ATS Conference 2016. San Francisco, CA.* Poster presentation. *May 2016*

A. Rajagopal, **R. Choate**, A. Montgomery, D. Mannino. "Central Venous Catheter Patient Safety: A Quality Improvement Initiative". *American Thoracic Society: ATS Conference 2016. San Francisco, CA.* Poster presentation. *May 2016*

W. Fuller, E. Cassity, A. Kelly, **R. Choate**, A. Kalema, A. Montgomery-Yates, A. Wieleczko, D. Mannino, P. Morris. "Red cell transfusion and mortality of MICU patients receiving continuous renal replacement therapy." *CHEST Conference 2016. Los Angeles, California.* Poster presentation. *October 2016*

R. Choate, D. Mannino, D. Barber, R.A. Sandhaus, K. Holm. "Differences between ZZ and SZ patients in the AlphaNet Program". *Center for Clinical and Translational Science conference, College of Public Health Research Day*, *Lexington, KY.* Poster presentation. *April 2016*

R. Choate. "Factors associated with HIV transmission knowledge among youth in Tbilisi, Georgia: Results of the youth behavioral surveillance survey." *Center for Clinical and Translational Science conference, College of Public Health Research Day*", *Lexington, KY.* Oral presentation. *March 2014*