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Risk Factors and Diagnosis of Nontuberculous Mycobacterial Lung Disease in Incident Cohorts of Bronchiectasis and Chronic Obstructive Pulmonary Disease in a National US Managed Care Insurance Plan

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INTRODUCTION

- Nontuberculous mycobacterial lung disease (NTMLD) is often associated with a substantial clinical burden, including structural lung damage, decreased lung function,[1] increased risk of respiratory failure,[2] and increased mortality.[3]
- Structural lung damage caused by bronchiectasis (BE) may render patients more susceptible to NTMLD; similarly, NTMLD may be associated with chronic obstructive pulmonary disease (COPD).
  - These conditions can complicate the evaluation of NTMLD.[4]
- Beyond well-known risk factor, such as cystic fibrosis (CF), HIV infection, and organ transplant, other risk factors for NTMLD are not as well established.

OBJECTIVE

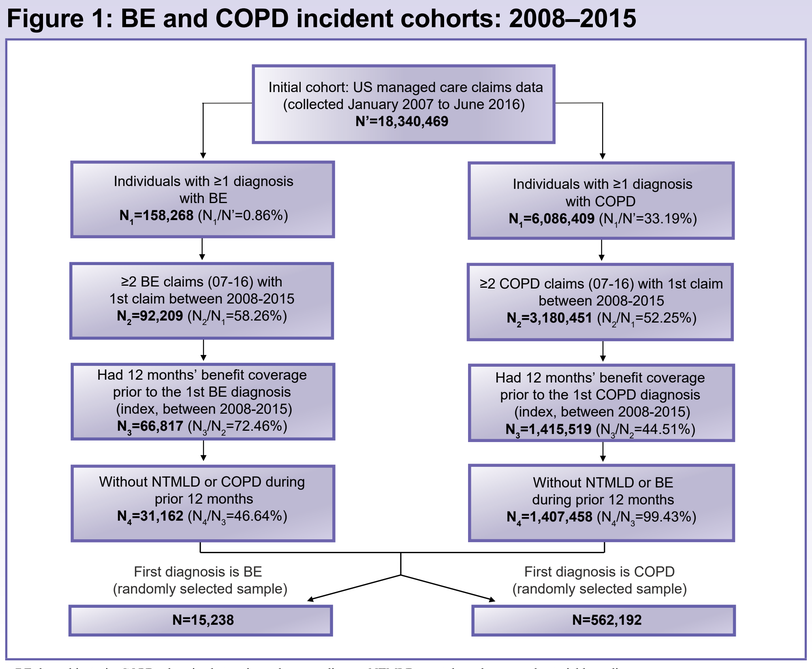
- To evaluate the risk of NTMLD in patients following diagnosis with BE or COPD, and to identify factors that may affect the occurrence of NTMLD in these populations.

METHODS

Study Design

- Individuals with ≥2 medical claims for BE or COPD between 2008 and 2015 were identified from a large, national US managed care claims database (2007-2016; **Figure 1**).
- All patients included in the incident BE or COPD cohort had at least 12 months (baseline) continued healthcare insurance coverage prior to the first available physician claim for BE or COPD.
- Patients who had a physician claim for COPD or NTMLD at baseline were excluded from the incident BE cohort. Likewise, patients who had a physician claim for BE or NTMLD were excluded from the incident COPD cohort.
- NTMLD was defined as having ≥2 medical claims ≥30 days apart.
- Baseline patient characteristics (12 months before the first BE or COPD diagnosis) of each incident cohort were identified.

Figure 1: BE and COPD incident cohorts: 2008–2015



BE=bronchiectasis; COPD=chronic obstructive pulmonary disease; NTMLD=nontuberculous mycobacterial lung disease.

Statistical Analyses

- The observed numbers of patients with NTMLD per 1,000 individuals with incident BE and COPD were calculated using Poisson estimates.
- Cox regression analysis with multivariable adjustment was used to determine hazard ratios (HRs) of NTMLD in BE relative to COPD.
  - Patient demographics (age, gender) and baseline comorbidities were used to adjust the risk of NTMLD (**Table 1**).
  - Insignificant variables were removed, unless clinically meaningful, and only significant predictors were retained as risk factors.

Table 1: Baseline* characteristics of BE and COPD cohorts

Baseline variables %, (n) or mean (SD)	BE n=15,238	COPD n=562,136
Age, mean (SD)	64 (18.5)	58 (21.3)
Female	63 (9,588)	55 (307,124)
Charlson comorbidity index, mean (SD)	1.52 (2.18)	0.89 (1.66)
Aspergillosis	0.8 (119)	0.03 (154)
Asthma	18.4 (2,811)	11.0 (61,860)
Atherosclerosis	5.8 (886)	4.4 (24,512)
Arrhythmia	16.9 (2,575)	11.9 (66,956)
CAD	14.6 (2,227)	12.7 (71,427)
Cancer	17.5 (2,667)	7.7 (43,295)
CHF	8.7 (1,328)	8.2 (46,259)
Colitis	3.8 (579)	2.8 (15,680)
Crohn's disease	0.7 (102)	0.4 (2,265)
CF	2.01 (307)	0.01 (69)
Dementia	1.2 (189)	1.3 (7,450)
Depression	8.1 (1,239)	8.1 (45,476)
Diabetes	20.1 (3,063)	19.7 (110,522)
GERD	21.4 (3,268)	12.9 (72,770)
Heart valve disease	12.2 (1,864)	7.2 (40,673)
HIV	0.3 (45)	0.3 (1,431)
Hyperlipidemia	48.7 (7,424)	38.9 (218,492)
Hypertension	50.7 (7,722)	43.2 (242,994)
Immune system diseases	3.3 (502)	0.9 (4,892)
Immunosuppressant drug use	36.5 (5,556)	24.7 (138,743)
Mental disorder	16.4 (2,502)	16.7 (94,104)
Metastatic carcinoma	4.2 (637)	1.3 (7,228)
Moderate or severe liver disease	0.6 (85)	0.3 (1,842)
Multiple sclerosis	0.4 (60)	0.3 (1,916)
Myocardial infarction	3.6 (542)	3.3 (18,328)
Obesity	6.7 (1,019)	7.9 (44,303)
Organ transplant	0.6 (99)	0.2 (1,060)
Pectus excavatum	0.1 (18)	0.04 (220)
Pneumonia	19.9 (3,035)	6.2 (35,129)
Rheumatoid disease	4.8 (728)	2.2 (12,475)
Tuberculosis	0.4 (56)	0.05 (255)

BE=bronchiectasis; CAD=coronary artery disease; CF=cystic fibrosis; CHF=congestive heart failure; COPD=chronic obstructive pulmonary disease; GERD=gastroesophageal reflux disease; HIV=human immunodeficiency virus.
*Baseline is the 12 months before the first bronchiectasis or COPD diagnosis.

RESULTS

Incident BE and COPD Cohorts

- The incident cohorts of BE and COPD consisted of 15,238 and 562,136 individuals, respectively (**Figure 1**).
- Baseline characteristics of the BE and COPD incident cohorts are shown in **Table 1.**
  - The mean (SD) age was 64 (18.5) years in the BE cohort and 58 (21.3) years in the COPD cohort; 63% and 55% of patients were female in the BE and COPD cohorts, respectively.
  - A greater proportion of patients with BE had asthma (18.4% vs 11.0% of COPD patients) and CF (2.0% vs 0.01% of COPD patients) and were using immunosuppressants (36.5% vs 24.7% of COPD patients).

Risk of NTMLD in Incident BE or COPD Cohort

- The number of patients with NTMLD per 1,000 person-years was 9.13 vs 0.24 in patients with newly dignosed BE and COPD, respectively; thus, the observed relative risk of NTMLD was almost 38 times higher in the BE vs COPD cohort (rate ratio 37.8, 95% CI, 32.7-43.7; *P*<0.001) (**Figure 2**).
- The adjusted risk of NTMLD was 28 times higher in the BE vs COPD cohort (HR=28.04, 95% CI, 24.07–32.67; *P*<0.001) (**Figure 3**).

Figure 2: Number of NTMLD patients per 1,000 person-years in incident BE and COPD cohorts (2013-2015)

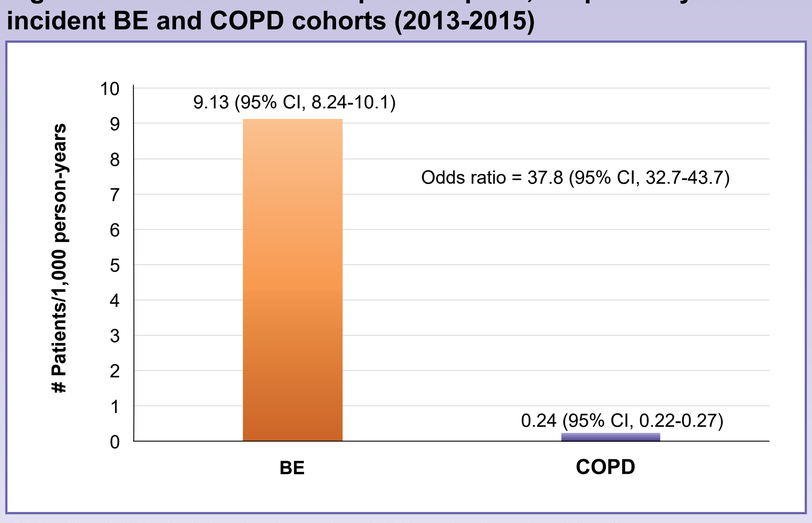


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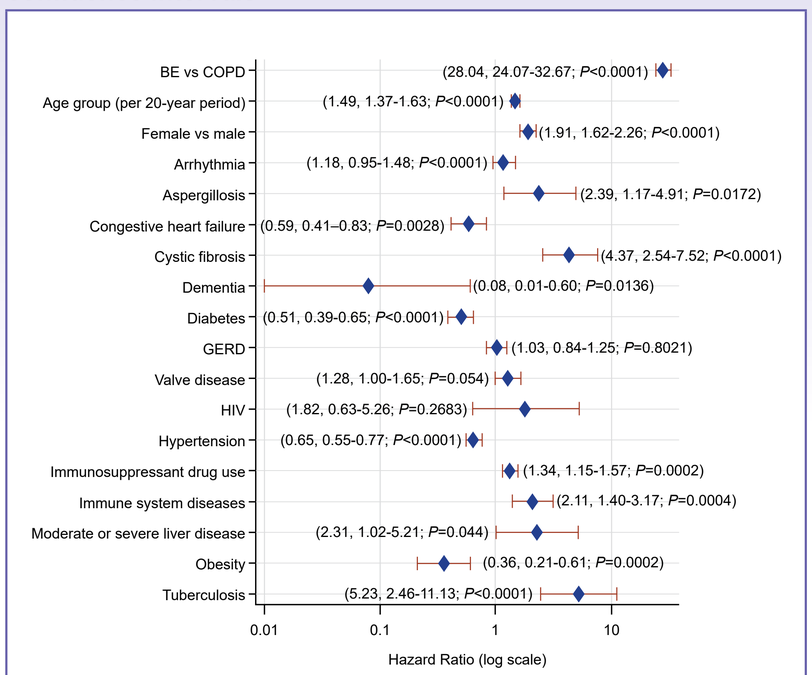
Figure 3: Risk factors for NTMLD: hazard ratios and 95% confidence intervals

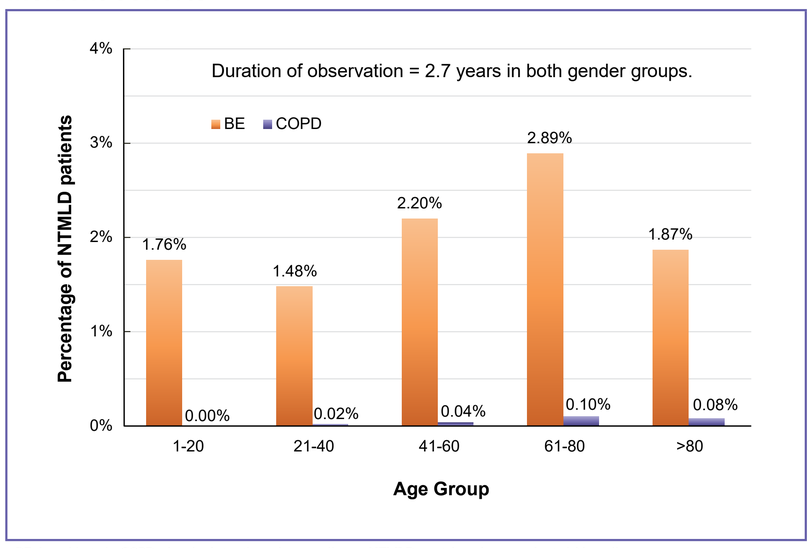


BE=bronchiectasis; COPD=chronic obstructive pulmonary disease; GERD=gastroesophageal reflux disease; HIV=human immunodeficiency virus; NTMLD=nontuberculous mycobacterial lung disease.

Impact of Demographic Factors on NTMLD Risk

- Older age and female gender were associated with increased risk of NTMLD in patients with incident BE or COPD.
  - The percentage of patients with NTMLD increased for every 20 years of age between the ages of 21-80 in BE and COPD cohorts (**Figure 4**).
  - There was a higher percentage of observed NTMLD in female vs male patients in both cohorts (BE cohort: 3.13% vs 1.15%; COPD cohort: 0.08% vs 0.05%).

Figure 4: Age as a risk factor for NTMLD in BE and COPD incident cohorts



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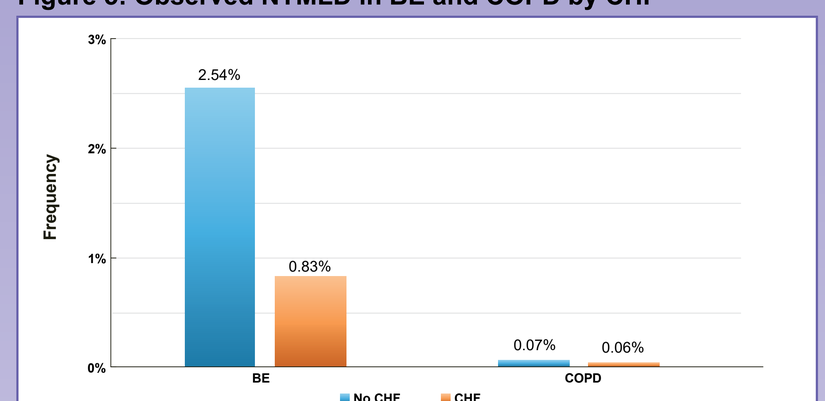
Impact of Comorbidities on NTMLD Risk

- Comorbidities significantly associated with an increased risk of NTMLD in incident BE or COPD cohorts were aspergillosis, CF, immunosuppressant use, immune system diseases, moderate or severe liver disease, and tuberculosis.
- Factors associated with a decreased risk of NTMLD in patients with newly diagnosed BE or COPD were congestive heart failure, dementia, diabetes, hypertension, and obesity.
- Of special interest, a lower risk of NTMLD was observed among individuals with preexisting BE, who had the following comorbid conditions: congestive heart failure (**Figure 5**), heart valve disease (**Figure 6**), and GERD (**Figure 7**).

Figure 5: Observed NTMLD in BE and COPD by CHF



BE=bronchiectasis; CHF=congestive heart failure; COPD=chronic obstructive pulmonary disease; NTMLD=nontuberculous mycobacterial lung disease.

Figure 6: Observed NTMLD in BE and CPOD by valve disorder

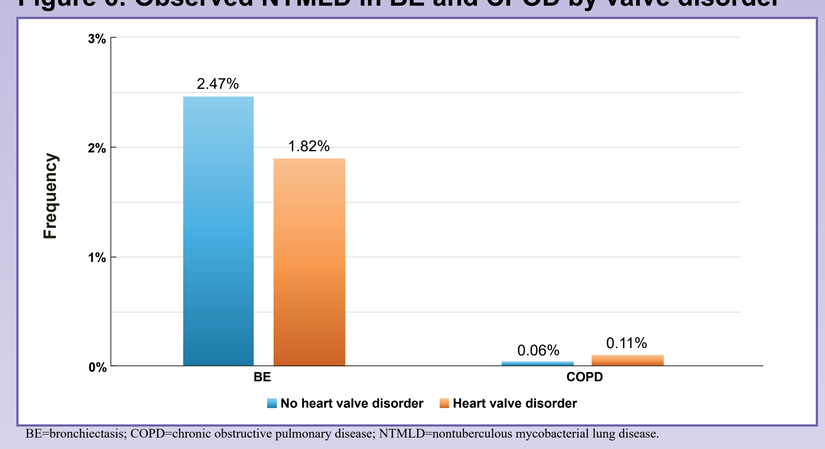


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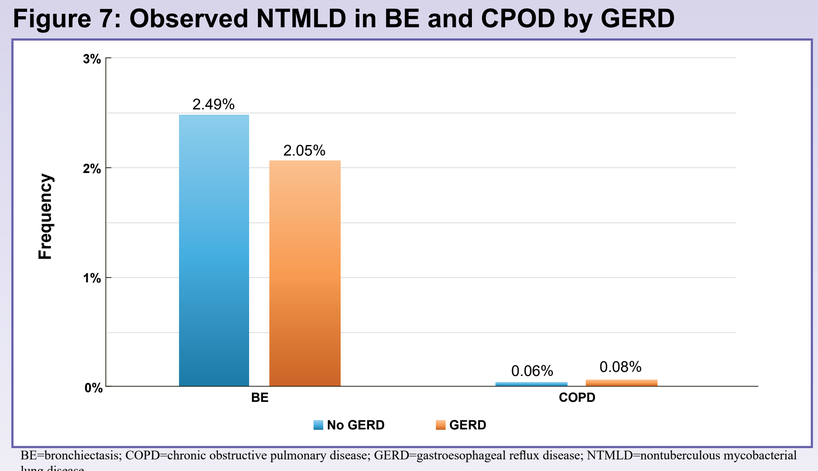
Figure 7: Observed NTMLD in BE and CPOD by GERD



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DISCUSSION

- This is the first reported nationwide (US) population-based study of NTMLD in incident BE and COPD cohorts, and the results add to the limited knowledge about risk factors associated with NTMLD.
  - Identifying the risk factors for NTMLD among patients in incident BE or COPD cohorts may facilitate improved diagnosis of NTMLD.
- Notably, the adjusted risk of NTMLD in the BE cohort was 28 times greater than in the COPD cohort.
- Older age and female gender were associated with increased NTMLD prevalence in both cohorts.
- Additional factors associated with increased NTMLD prevalence in both cohorts included other lung diseases (CF, tuberculosis), factors related to, or indicative of, weakened immune status (eg, aspergillosis, HIV, immunosuppressant drugs, immune system diseases), GERD, arrhythmias, heart valve disease, and moderate to severe liver disease.
- Obesity was associated with a lower risk of NTMLD, consistent with findings in patients with tuberculosis, possibly due to immune-modulating effects of leptin.[5]
  - The finding that patients with diabetes or hypertension had a lower risk of NTMLD may be due to higher rates of obesity in these patients, which may not have been coded in the claims data.
- Reasons for lower risk of NTMLD associated with factors such as dementia were not clear.
- In addition, the subgroup analysis finding that comorbidities such as CHF, GERD, and heart valve disease were associated with a lower risk of NTMLD in patients with BE was unexpected.
  - We speculate that in patients with diseases/conditions that have symptoms in common with NTMLD (eg, shortness of breath, cough, back pain/chest pain), such symptoms may not be actively investigated due to clinical inertia, potentially leading to underdetection/underdiagnosis of NTMLD.

CONCLUSIONS

- The risk of NTMLD is substantially higher in the incident BE cohort compared with the COPD cohort.
- Factors that may contribute to a further increased risk of NTMLD in patients newly diagnosed with BE or COPD include older age, female gender, lung diseases such as CF, factors related to weakened immunity, and GERD.
- Stratified analyses with the incident BE cohort suggest that NTMLD may be underdiagnosed in patients with BE who have additional comorbid conditions with symptoms that overlap with NTMLD symptoms.

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DISCLOSURES

Kenneth Olivier and Jennifer Adjemian are involved in clinical trials sponsored by, have received grant funding from, and are consultants to Insmed Incorporated.

Quanwu Zhang, Gina Eagle, and Engels Chou are employees of Insmed Incorporated.

Raymond Zhang is employed by Orbis Data Solutions, Woburn, MA, which provides consulting services to Insmed Incorporated.

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