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Relative Risk of All-Cause Mortality Associated With Incident Cohorts of Bronchiectasis and Chronic Obstructive Pulmonary Disease in a National US Managed Care Insurance Plan

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INTRODUCTION

- Bronchiectasis (BE) is a chronic, progressive, structural lung condition characterized by abnormal dilatation of bronchial lumen.[1]
- Patients with BE often experience reduced quality of life, progressive decline in lung function, hospitalizations, and increased risk of mortality, posing significant burdens on both patients and healthcare systems.[2,3]
- Few formal studies have been undertaken to explore risk factors associated with mortality in BE.[1]
  - Survival rates with BE have been reported as 91% at 4 years, 83.5% at 8.8 years, and 68.3% at 12.3 years, with respiratory failure as the primary cause of death.[1]
  - Older age, male gender, respiratory infections, and impaired respiratory function have been associated with increased risk of mortality in patients with BE.[1]
- A recent study showed that BE can be an independent risk factor for all-cause mortality in patients with chronic obstructive pulmonary disease (COPD).[4]
- COPD, characterized by chronic airflow obstruction due to inflammation, is expected to be the third leading cause of death worldwide by 2030.[5]
- The objective of the current study was to evaluate risk factors and relative risk of all-cause mortality in patients with incident BE as compared with COPD.

METHODS

Patient Sampling

- Individuals with ≥2 medical claims for BE or COPD between 2008 and 2015 were identified in a large US managed care insurance plan, with cohorts defined as follows:
  - **Incident BE cohort:** Individuals were included with ≥2 medical claims for BE (ICD-9 or ICD-10 codes: 494, J47, 74861, 0115, or Q334) if they had 12 months of continuous medical insurance coverage (baseline) before the first claim of BE and no medical claims for COPD or nontuberculous mycobacterial lung disease (NTMLD; ICD-9 or ICD-10 codes: A310 or 0310) during this baseline period.
  - **Incident COPD cohort:** Individuals were included with ≥2 medical claims for COPD (ICD-9 or ICD-10 codes: 490, 491, 492, 496, J20, J21, J40, J41, J42, J43, or J44) between 2008 and 2015 if they had 12 months (baseline) of continuous medical insurance coverage (baseline) before the first claim of COPD and no medical claims for BE or NTMLD during this baseline period.
- Mortality data originated from the Social Security Death Master File.
  - Note that the numbers of mortality records after 2011 were reduced by about 30% following local court decisions that may have led to changes in reporting practices and/or underreporting in certain states. These decisions were not expected to specifically relate to BE or COPD disease states; therefore, estimations of relative risk of all-cause mortality between BE and COPD are expected to be unbiased.
- This study aimed to estimate relative rather than absolute risk for all-cause mortality between the incident patient cohorts of BE and COPD.

Analyses

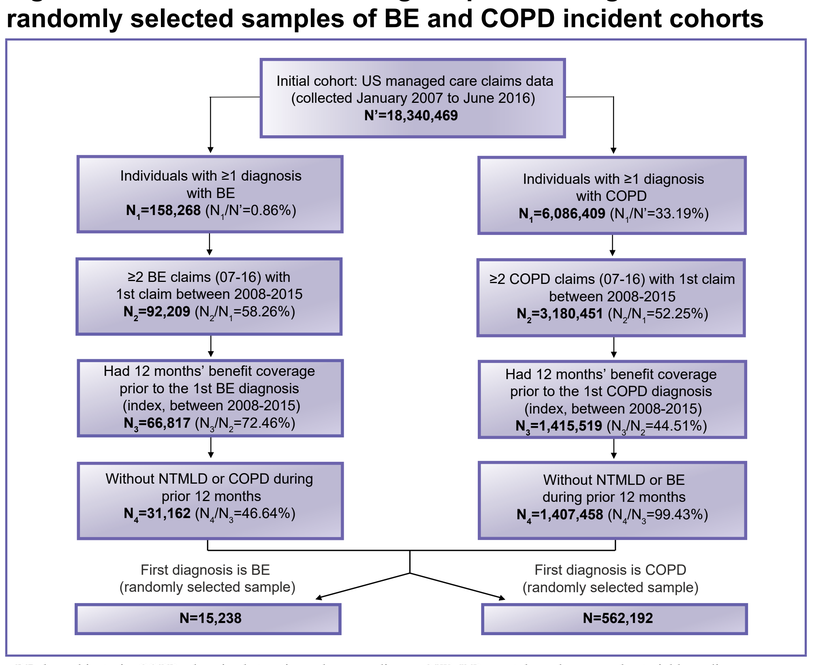
- Characteristics of incident BE and COPD cohort populations were tabulated.
- The all-cause mortality rate ratio was estimated using Poisson regression without adjustment.
- A Cox proportional hazards method was used to compare all-cause mortality between BE and COPD cohorts, with adjustments for demographic factors and baseline morbidities. Statistically significant risk adjusters are reported in the Results section.

RESULTS

Study Sample

- Incident cohorts of BE (n=15,238) and COPD (n=562,136) were extracted from a starting population of 18,340,469 individuals from a US national managed care claims database between January 2007 and June 2016 (**Figure 1**).

Figure 1: Flowchart summarizing the process to generate randomly selected samples of BE and COPD incident cohorts



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

Patient Baseline Characteristics

- In the BE and COPD cohorts, mean patient ages were 64 and 58 years, respectively, and proportions of female patients were 62.9% and 54.6%, respectively (**Table 1**).
- Examination of patient baseline characteristics revealed a greater number, and higher proportions, of morbidities in the BE cohort compared with the COPD cohort (**Table 1**).
  - Mean ± SD Charlson Comorbidity Index (CCI) scores were 1.52 ± 2.18 among patients with BE and 0.89 ± 1.66 among patients with COPD, indicating a greater health burden of preexisting morbidities with BE.
  - Morbidities that showed the greatest disparities in frequency between cohorts were pneumonia (BE vs COPD: 19.9% vs 6.2%), immunosuppressant drug use (36.5% vs 24.7%), hyperlipidemia (48.7% vs 38.9%), cancer (17.5% vs 7.7%), gastroesophageal reflux disease (21.4% vs 12.9%), hypertension (50.7% vs 43.2%), asthma (18.4% vs 11.0%), heart valve disease (12.2% vs 7.2%), and arrhythmia (16.9% vs 11.9%).

Table 1: Baseline* characteristics and morbidities (based on medical claims between 2008 and 2016) for incident BE and COPD cohorts

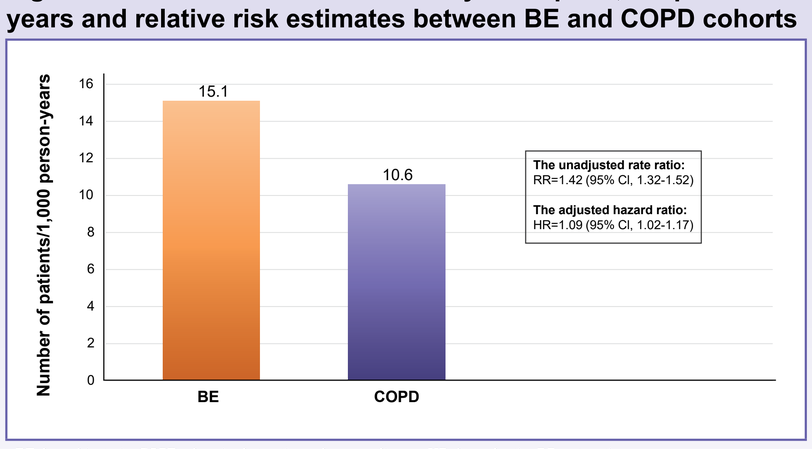
	BE n=15,238		COPD n=562,136		
Baseline variable					
Age, mean (SD)	64 (18.5)		58 (21.3)		
Charlson Comorbidity Index, mean (SD)	1.52 (2.18)		0.89 (1.66)		
Female gender, % (n)	62.9 (9,588)		54.6 (307,124)		
Baseline claims	**%**	**n**	**%**	**n**	**% Δ**
BE ≥ COPD					
Pneumonia	19.9	3,035	6.2	35,129	13.7
Immunosuppressant drug use	36.5	5,556	24.7	138,743	11.8
Hyperlipidemia	48.7	7,424	38.9	218,492	9.8
Cancer	17.5	2,667	7.7	43,295	9.8
Gastroesophageal reflux disease	21.4	3,268	12.9	72,770	8.5
Hypertension	50.7	7,722	43.2	242,994	7.5
Asthma	18.4	2,811	11.0	61,860	7.4
Heart valve disease	12.2	1,864	7.2	40,673	5.0
Arrhythmia	16.9	2,575	11.9	66,956	5.0
Metastatic carcinoma	4.2	637	1.3	7,228	2.9
Rheumatoid disease	4.8	728	2.2	12,475	2.6
Immune system diseases	3.3	502	0.9	4,892	2.4
Cystic fibrosis	2.0	307	0.0	69	2.0
Coronary artery disease	14.6	2,227	12.7	71,427	1.9
Atherosclerosis	5.8	886	4.4	24,512	1.4
Colitis	3.8	579	2.8	15,680	1.0
Aspergillosis	0.8	119	0.0	154	0.8
Congestive heart failure	8.7	1,328	8.2	46,259	0.5
Diabetes	20.1	3,063	19.7	110,522	0.4
Tuberculosis	0.4	56	0.0	255	0.4
Organ transplant	0.6	99	0.2	1,060	0.4
Myocardial infarction	3.6	542	3.3	18,328	0.3
Moderate or severe liver disease	0.6	85	0.3	1,842	0.3
Crohn's disease	0.7	102	0.4	2,265	0.3
Multiple sclerosis	0.4	60	0.3	1,916	0.1
Pectus excavatum	0.1	18	0.0	220	0.1
Depression	8.1	1,239	8.1	45,476	0.0
Human immunodeficiency virus	0.3	45	0.3	1,431	0.0
COPD > BE					
Obesity	6.7	1,019	7.9	44,303	1.2
Mental disorder	16.4	2,502	16.7	94,104	0.3
Dementia	1.2	189	1.3	7,450	0.1

BE=bronchiectasis; COPD=chronic obstructive pulmonary disease.
*Baseline=12 months prior to the first COPD or BE diagnosis.

Unadjusted Relative Risk of All-Cause Mortality

- Unadjusted all-cause mortality rates were 15.1 and 10.6 events per 1,000 person-years in the BE and COPD cohorts, respectively, representing a 40% higher relative risk of mortality in patients with BE compared to those with COPD (rate ratio=1.4; 95% CI, 1.3-1.5; **Figure 2**).

Figure 2: Observed all-cause mortality rates per 1,000 person-years and relative risk estimates between BE and COPD cohorts



BE=bronchiectasis; COPD=chronic obstructive pulmonary disease; HR=hazard ratio; RR=rate ratio.

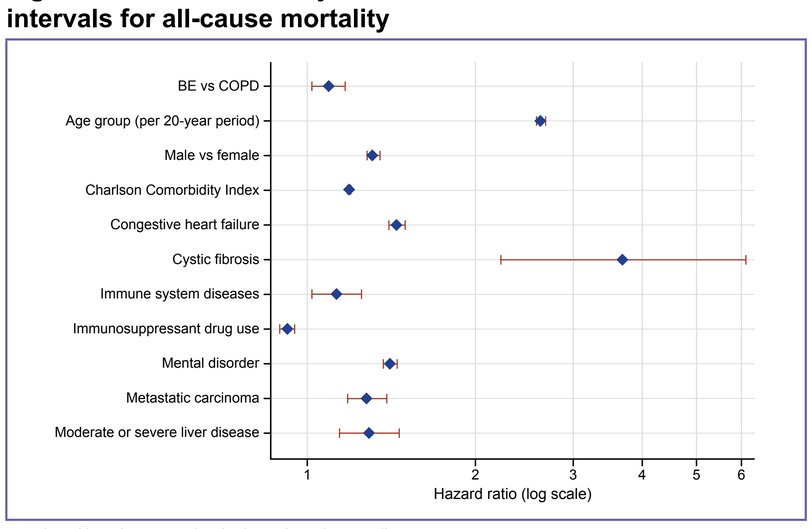
Adjusted Relative Risk of All-Cause Mortality Between BE and COPD

- After adjusting for demographic factors and baseline morbidities, the relative risk of all-cause mortality was attenuated from 1.4 to 1.09 between the BE and COPD cohorts (hazard ratio [HR]=1.09; 95% CI, 1.02-1.17; *P*=0.012; **Figure 3**).

Risk Factors of All-Cause Mortality in the Study Sample

- Overall, the risk estimate of each factor was dependent on the presence of other risk factors, additive or incremental. For example, the risk estimation of metastatic cancer indicated an incremental risk (HR=1.28; 95% CI, 1.18-1.39; *P*<0.001) adding to that of the Charlson Comorbidity Index score, while the latter explained a good portion of mortality risk associated with cancer since cancer diagnosis has a high weight in the Charlson Comorbidity Index score.
- Other significant contributors to increased mortality risk independent of BE and COPD were observed (**Figure 3**).
- Mortality risk in patients with cystic fibrosis was more than 3.5 times that in patients without cystic fibrosis (HR=3.69; 95% CI, 2.22-6.13; *P*<0.0001).
- Mortality risk more than doubled with each additional 20 years of age (HR=2.63; 95% CI, 2.58-2.68; *P*<0.0001).
- Mortality risk increased 19% with each additional point of Charlson Comorbidity Index (HR=1.19; 95% CI, 1.18-1.20; *P*<0.0001).
- Patients with immune system diseases had a 13% increased risk for mortality compared to those without immune system diseases (HR=1.13; 95% CI, 1.02-1.25; *P*=0.023).
- The only factor significantly associated with reduced risk of mortality was the use of immunosuppressant drugs (HR=0.92; 95% CI, 0.89-0.95).

Figure 3: Multivariable adjusted hazard ratios and confidence intervals for all-cause mortality

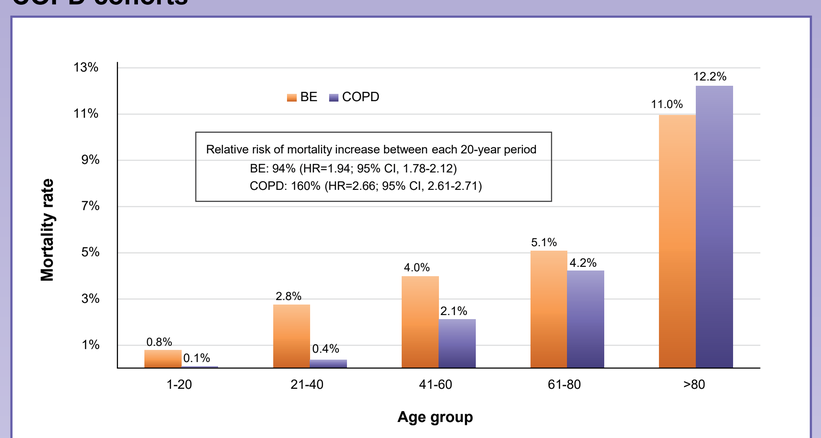


BE=bronchiectasis; COPD=chronic obstructive pulmonary disease.

Interaction Effect of Age Group at Diagnosis and Incident BE vs COPD

- Risk of all-cause mortality increased in different slopes with age at diagnosis within both incident BE and COPD cohorts (**Figure 4**).
  - In the BE cohort, risk of all-cause mortality increased by 94% with every additional 20 years of age (HR=1.94; 95% CI, 1.78-2.12).
  - In the COPD cohort, risk of mortality increased by 160% with every additional 20 years of age (HR=2.66; 95% CI, 2.61-2.71).

Figure 4: Risk of mortality over age group in incident BE and COPD cohorts



BE=bronchiectasis; COPD=chronic obstructive pulmonary disease; HR=hazard ratio.

DISCUSSION

- Our results expand the limited data available concerning risk factors associated with mortality in the patient populations with BE and COPD.
- Morbidities at baseline were more frequently experienced by patients who were subsequently diagnosed with BE compared with COPD.
- The observed unadjusted incident BE cohort was associated with a 40% higher risk for all-cause mortality compared with the COPD cohort; however, the incremental mortality risk was attenuated to 9% after multivariable adjustment for demographic parameters and baseline variables.
  - The statistical significance between BE and COPD after adjustment was likely due to the large sample size, and the relative risk of all-cause mortality between the 2 cohorts does not seem to be clinically meaningful.
- The reduction in relative risk of all-cause mortality after the multivariable adjustment may suggest:
  - Risks of all-cause mortality in BE and COPD appeared medically comparable.
  - The observed incremental mortality risk associated with BE was explained, in part, by baseline morbidities, implying the need for the effective management of comorbid conditions with BE.
- Prior data show that, despite several clinical similarities between BE and COPD,[6] there are notable differences.
  - Major risk factors for COPD are known to be primarily behavioral and environmental (eg, smoking or pollutants), whereas, BE has more complex pathophysiological etiologies (eg, genetics, infection, idiopathy).[7]
  - In our study, specific patient characteristics such as CHF, immune system disease, and metastatic carcinoma increased the risk of mortality independent of BE and COPD.
- Limitations
  - The mortality data may have been affected by changes in reporting practices and/or underreporting; however, as these decisions were not expected to specifically relate to BE or COPD, our estimations of relative risk for all-cause mortality are expected to be unbiased.
  - Healthcare claims data-based studies may be affected by accuracy of medical coding.

CONCLUSIONS

- Patients with BE, compared with COPD, have a broader range of morbid conditions.
  - Common preexisting morbidities in BE include pneumonia, need for immunosuppressant drug use, hyperlipidemia, cancer, gastroesophageal reflux disease, hypertension, asthma, heart valve disease, and arrhythmia.
- After multivariable adjustment, the risk of all-cause mortality with BE was likely not clinically significantly different from that with COPD.
- Effective interventions for preexisting morbidities in patients with BE may help reduce mortality risk in this patient population.

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DISCLOSURES

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

Quanwu Zhang, Engels Chou, and Carlos Fernandez 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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