

# The Incremental Burden of Nontuberculous Mycobacterial Lung Disease (NTMLD) in Patients With Chronic Obstructive Pulmonary Disease (COPD): Hospitalizations and ER Visits Among US Medicare Beneficiaries

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## BACKGROUND

- NTMLD, an uncommon mycobacterial infection with increasing global prevalence, is characterized by worsening lung function and increased healthcare resource burden<sup>1,2</sup>
- A large proportion of patients with NTMLD have respiratory comorbidities such as COPD<sup>3,4</sup>
- Diagnosis of NTMLD may be delayed in patients with preexisting lung disease<sup>5</sup> such as COPD
- Management of NTMLD in patients with COPD may not get adequate attention, as clinical management of COPD is sometimes prioritized to help improve the symptoms of NTM infections such as cough and shortness of breath<sup>6</sup>
- There is a lack of data quantifying the incremental burden of NTMLD in patients with COPD

## OBJECTIVE

- To assess the incremental burden of NTMLD in patients with underlying COPD by comparing HCRU in terms of hospitalizations and ER visits to that of age- and sex-matched patients with COPD without NTMLD

## METHODS

### Data Source

- This retrospective cohort study was conducted using the US Medicare claims database (2010-2017; 100% beneficiary sample)

### Study Population

- Medicare beneficiaries with NTMLD and preexisting comorbid COPD were identified as meeting the following requirements:
  - First diagnosis of NTMLD was dated between 2011 and 2016
  - Had prior COPD
  - Eligible for Medicare due to age (≥ 65 years)
- All eligible patients with COPD and NTMLD (cases) were matched 1:3 to patients with COPD without NTMLD (controls) by age and sex
- The index date (defined as the date of the first diagnosis of NTMLD; see definition of NTMLD) of a given case was assigned to the matched controls; therefore, HCRU was compared over the same period for cases and controls
- All cases and matched controls had continuous coverage of Medicare Parts A and B 12-month pre- and 12-month post-index date

### Study Outcomes

Over the 12-month post-index period, the following HCRU outcomes were compared between patients with COPD with NTMLD and matched controls of patients with COPD without NTMLD:

- Hospitalizations
  - All-cause hospitalization
  - Respiratory-associated hospitalization: respiratory condition (ICD-9-CM 460-519 or ICD-10-CM J00-J99) assigned as a primary or secondary diagnosis
  - COPD-associated hospitalization: COPD assigned as a primary or secondary diagnosis
- ER visits
  - Inpatient ER visit: an ER visit followed by a hospital admission
  - Outpatient ER visit: an ER visit without subsequent hospital admission

### Analysis Plan

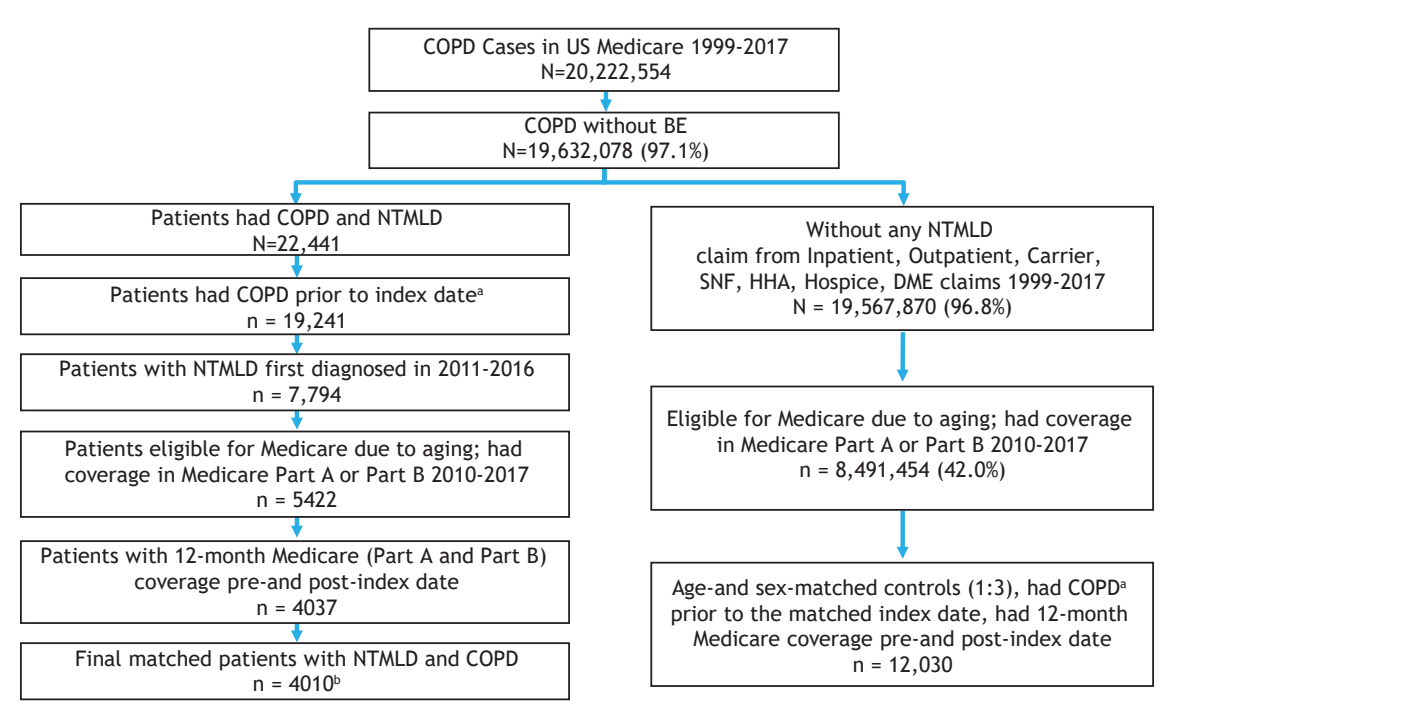
- Incremental burden associated with NTMLD in patients with preexisting COPD was analyzed with both univariate and multivariate analyses on patient HCRU outcomes (hospitalizations and ER visits) accrued over the 12-month post-index period
- Univariate analyses by 3 metrics: the proportion of patients with an outcome, the number of outcome events per patient, and the Kaplan-Meier failure curves on time to outcomes after the index date (a patient without an outcome by the end of the 12-month post-index period was censored)
- Multivariate analyses included logistic regression (OR), Poisson regression (IRR), and Cox proportional hazards model (HR) to adjust for confounding comorbidities during the 12-month pre-index period
- Statistical tests comparing the case and control groups included McNemar test for categorical variables, Wilcoxon signed-rank test for continuous variables (Wilcoxon rank-sum test for continuous variables in the subgroup analysis), and log-rank test for time to event variables; an  $\alpha$  of 0.05 was defined as statistically significant

## RESULTS

### Study Population

- A total of 4010 patients with COPD with NTMLD met the study case definitions and were matched to 12,030 control patients with COPD without NTMLD (Figure 1)

Figure 1. Patient Identification From the US Medicare Database



\* Index date: the date that the first claim with NTMLD diagnosis (ICD-9 031.0 or ICD-10 A31.0) was received.  
 \*\* 99.3% of all eligible patients with COPD with NTMLD (N = 4037) were successfully matched to patients with COPD without NTMLD (controls).

### Patient Demographics and Clinical Characteristics

- A significantly higher percent of patients with COPD with NTMLD had non-pulmonary comorbidities of RA and GERD; a significantly lower percent had diabetes and overweight/obesity (Table 1)
- A significantly higher percent of patients with COPD with NTMLD had almost all the pulmonary conditions except cystic fibrosis (Table 1)

## ABBREVIATIONS

BE, bronchiectasis; CI, Charlson Comorbidity Index; COPD, chronic obstructive pulmonary disease; CPT, Current Procedural Terminology; CI, confidence interval; GERD, gastroesophageal reflux disease; ICD-9-CM, *International Classification of Diseases, Ninth Revision, Clinical Modification*; DME, durable medical equipment; ER, emergency room; HCRU, healthcare resource utilization; HHA, home health aide; ICD-10-CM, *International Classification of Diseases, Tenth Revision, Clinical Modification*; HR, hazard ratio; IRR, incidence rate ratio; LOS, length of stay; NTMLD, nontuberculous lung disease; OR, odds ratio; Q, quartile; RA, rheumatoid arthritis; SNF, skilled nursing facility.

Table 1. Patient Demographics and Clinical Characteristics During the 12-Month Pre-Index Period

	COPD With NTMLD N = 4010	COPD Without NTMLD N = 12,030	P Value <sup>a</sup>
Age at index date, mean (SD), years	76.6 (6.6)	76.6 (6.6)	
Female, n (%)	2283 (56.9)	6849 (56.9)	
Race/ethnicity, n (%)			
White	3661 (91.3)	10,756 (89.4)	
Black	139 (3.5)	715 (5.9)	
Asian	85 (2.1)	204 (1.7)	
Hispanic	36 (0.9)	152 (1.3)	
North American Native	17 (0.4)	45 (0.4)	
Other	58 (1.5)	105 (0.9)	
Unknown	14 (0.4)	53 (0.4)	
Charlson Comorbidity Index, mean (SD)	2.65 (1.53)	2.08 (1.57)	< 0.0001
Nonpulmonary comorbid conditions, n (%)			
Diabetes mellitus <sup>a</sup>	1005 (25.1)	4261 (35.4)	< 0.0001
High blood pressure <sup>a</sup>	3177 (79.2)	9779 (81.3)	< 0.0001
Overweight and obesity <sup>a</sup>	330 (8.2)	1506 (12.5)	< 0.0001
Chronic kidney disease <sup>a</sup>	678 (16.9)	1973 (16.4)	< 0.0001
All cardiovascular diseases <sup>a</sup>	3697 (92.2)	10,794 (89.7)	< 0.0001
Acute myocardial infarction	151 (3.8)	377 (3.1)	< 0.0001
Stroke	857 (21.4)	2601 (21.6)	< 0.0001
All cancers <sup>a</sup>	1319 (32.9)	2104 (17.5)	< 0.0001
Crohn's disease	35 (0.9)	66 (0.6)	0.002
Ulcerative colitis	36 (0.9)	106 (0.9)	< 0.0001
Chronic viral hepatitis	30 (0.8)	47 (0.4)	0.0527
Dementia <sup>a</sup>	400 (10.0)	1472 (12.2)	< 0.0001
RA <sup>a</sup>	266 (6.6)	519 (4.3)	< 0.0001
Osteoarthritis	1283 (32.0)	3951 (32.8)	< 0.0001
Multiple sclerosis	9 (0.2)	14 (0.1)	0.2971
Systemic lupus erythematosus	37 (0.9)	61 (0.5)	0.0153
Human immunodeficiency virus	17 (0.4)	11 (0.1)	0.2568
Transplant of kidney, heart, lung, or liver <sup>a</sup>	43 (1.1)	29 (0.2)	0.099
GERD <sup>a</sup>	1655 (41.3)	3521 (29.3)	< 0.0001
Pulmonary comorbid conditions, n (%)			
Hemoptysis	485 (12.1)	115 (1.0)	< 0.0001
Cough	2525 (63.0)	2790 (23.2)	< 0.0001
Dyspnea	2827 (70.5)	4416 (36.7)	< 0.0001
Asthma <sup>a</sup>	1104 (27.5)	2147 (17.8)	< 0.0001
Idiopathic pulmonary fibrosis <sup>a</sup>	89 (2.2)	46 (0.4)	0.0002
Cystic fibrosis with pulmonary manifestations	2 (0.0)	1 (0.0)	0.5637
Simple and mucopolysaccharide chronic bronchitis <sup>a</sup>	1578 (39.4)	1965 (16.3)	< 0.0001
Emphysema	1481 (36.9)	1263 (10.5)	< 0.0001
Pulmonary tuberculosis <sup>a</sup>	381 (9.5)	6 (0.1)	< 0.0001
Malignant neoplasm of bronchus and lung	591 (14.7)	346 (2.9)	< 0.0001
Lung transplant	29 (0.7)	8 (0.1)	0.0006
Smoking history	1503 (37.5)	2092 (17.4)	< 0.0001
Idiopathic interstitial lung disease <sup>a</sup>	1021 (25.5)	490 (4.1)	< 0.0001

<sup>a</sup> Comorbidities included in all 3 multivariate regression analyses.  
<sup>b</sup> P values were based on a McNemar test for categorical variables and Wilcoxon signed-rank test for continuous variables.

### Proportion of Patients With HCRU Events and ORs Associated With NTMLD

- A significantly higher percent of patients with COPD with NTMLD had HCRU events than matched controls with COPD without NTMLD by univariate analysis (Figure 2A)
- A significantly higher likelihood for HCRU events was associated with NTMLD, adjusted for confounding pre-index comorbidities by multivariate logistic regression analysis (Figure 2B); compared with patients with COPD only, patients with COPD with NTMLD were:
  - 1.9 times more likely to experience all-cause hospitalization (OR [95% CI], 1.9 [1.8-2.1]; P < 0.0001)
  - 2.4 times more likely to experience respiratory-associated hospitalization (OR [95% CI], 2.4 [2.2-2.7]; P < 0.0001)
  - 1.8 times more likely to experience COPD-associated hospitalization (OR [95% CI], 1.8 [1.5-2.0]; P < 0.0001)
  - 1.2 times more likely to experience outpatient ER visit (OR [95% CI], 1.2 [1.1-1.3]; P = 0.0003)
  - 1.8 times more likely to experience inpatient ER visit (OR [95% CI], 1.8 [1.7-2.0]; P < 0.0001)

### Rates of HCRU Events per Patient and IRRs Associated With NTMLD

- A significantly higher per-patient HCRU event rate was observed among patients with COPD with NTMLD than among controls with COPD without NTMLD by univariate analysis (Figure 3A)
- A significantly higher IRR of HCRU events was associated with NTMLD, adjusted for confounding pre-index comorbidities by multivariate Poisson regression analysis (Figure 3B); compared with patients with COPD only, patients with COPD with NTMLD had:
  - 1.7 times the rate of all-cause hospitalization (IRR [95% CI], 1.7 [1.6-1.8]; P < 0.0001)
  - 2.2 times the rate of respiratory-associated hospitalization (IRR [95% CI], 2.2 [2.1-2.4]; P < 0.0001)
  - 1.8 times the rate of COPD-associated hospitalization (IRR [95% CI], 1.8 [1.6-2.0]; P < 0.0001)
  - 1.1 times the rate of outpatient ER visit (IRR [95% CI], 1.1 [1.0-1.1]; P = 0.0013)
  - 1.7 times the rate of inpatient ER visit (IRR [95% CI], 1.7 [1.6-1.8]; P < 0.0001)

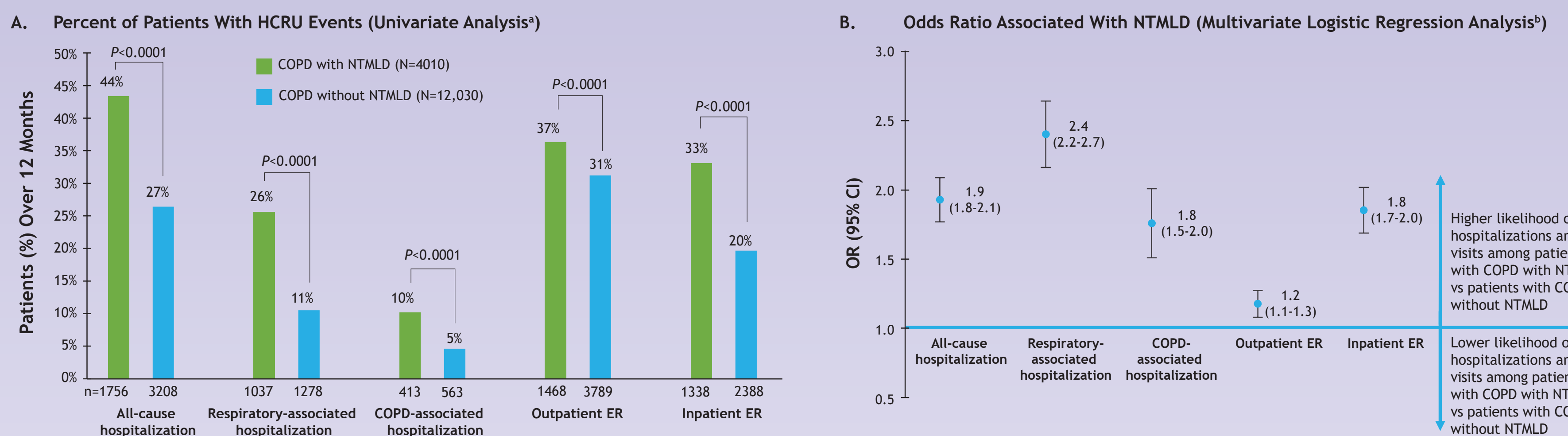
### Time to HCRU Events and HRs Associated With NTMLD

- A significantly shorter time to HCRU events was observed among patients with COPD with NTMLD than among controls with COPD without NTMLD by univariate analysis (Figure 4A)
- A significantly higher HR of HCRU events was associated with NTMLD, adjusted for confounding pre-index comorbidities by multivariate Cox proportional hazards regression analysis (Figure 4B); patients with COPD with NTMLD had:
  - 81% increased hazard of all-cause hospitalization (HR [95% CI], 1.81 [1.7-1.9]; P < 0.0001)
  - Over twice the hazard of respiratory-related hospitalization (HR [95% CI], 2.27 [2.1-2.5]; P < 0.0001)
  - 72% increased hazard of COPD-related hospitalization (HR [95% CI], 1.72 [1.5-2.0]; P < 0.0001)
  - 15% increased hazard of outpatient ER visit (HR [95% CI], 1.15 [1.1-1.2]; P < 0.0001)
  - 75% increased hazard of inpatient ER visit (HR [95% CI], 1.75 [1.6-1.9]; P < 0.0001)

### Subgroup Analysis in Patients Who Had HCRU Event(s) During the 12-Month Post-Index Period Follow-Up

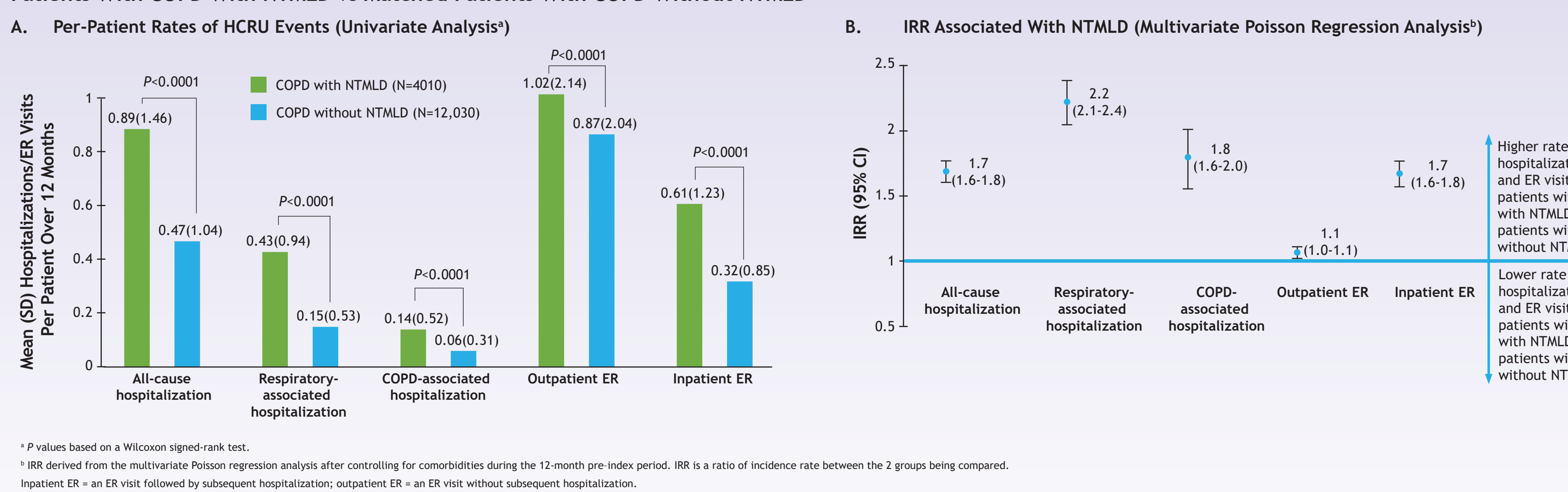
- Mean number of hospitalizations (all cause, respiratory-associated, and COPD-associated) and inpatient ER visits per patient were significantly higher among patients with COPD with NTMLD than among controls with COPD without NTMLD (Figure 5)
- Days to HCRU events (mean and median) were significantly shorter among patients with COPD with NTMLD than among controls with COPD without NTMLD (Table 2)
- Length of stay (days) of hospitalizations (all-cause, respiratory-associated, and COPD-associated) was significantly longer among patients with COPD with NTMLD than controls with COPD without NTMLD (Table 2)

Figure 2. Proportion of Patients With HCRU Events (A) and ORs Associated With NTMLD After Multivariate Analysis Adjustment (B) Over a 12-Month Follow-Up Period in Patients With COPD With NTMLD vs Matched Patients With COPD Without NTMLD



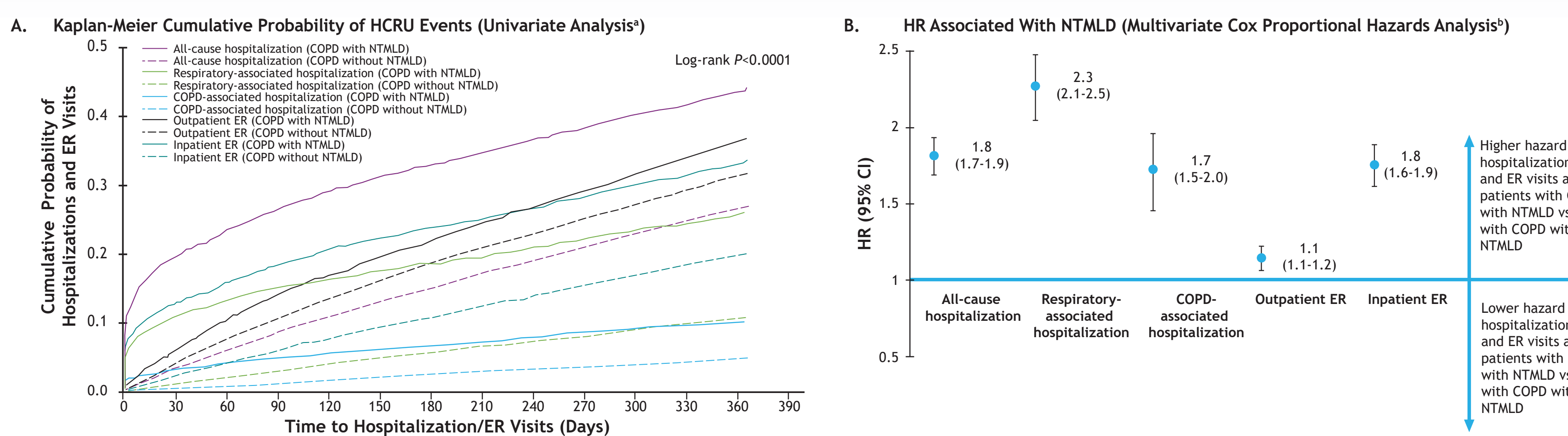
\* P values based on a McNemar test. Respiratory-associated hospitalization = disease of respiratory system as the primary or secondary diagnosis of the inpatient claim. COPD-associated hospitalization = COPD as the primary or secondary diagnosis of the inpatient claim.  
<sup>a</sup> OR derived from the logistic regression analysis controlling for comorbidities during the 12-month pre-index period. Comorbidities controlled for in the multivariate regression analysis were diabetes mellitus; high blood pressure; overweight and obesity; chronic kidney disease; total cardiovascular diseases; cancer; dementia; rheumatoid arthritis; transplant of kidney, heart, lung, or liver; GERD; pulmonary tuberculosis; asthma; simple and mucopolysaccharide chronic bronchitis; idiopathic pulmonary fibrosis; and idiopathic interstitial lung disease.  
 Inpatient ER = an ER visit followed by subsequent hospitalization; outpatient ER = an ER visit without subsequent hospitalization.

Figure 3. Per-Patient Rates of HCRU Events (A) and IRRs Associated With NTMLD After Multivariate Analysis Adjustment (B) Over a 12-Month Follow-Up Period in Patients With COPD With NTMLD vs Matched Patients With COPD Without NTMLD



\* P values based on a Wilcoxon signed-rank test.  
<sup>a</sup> IRR derived from the multivariate Poisson regression analysis after controlling for comorbidities during the 12-month pre-index period. IRR is a ratio of incidence rate between the 2 groups being compared.  
 Inpatient ER = an ER visit followed by subsequent hospitalization; outpatient ER = an ER visit without subsequent hospitalization.

Figure 4. Time to HCRU Events (A) and HRs Associated With NTMLD After Multivariate Analysis Adjustment (B) Over a 12-Month Follow-Up Period in Patients With COPD With NTMLD vs Matched Patients With COPD Without NTMLD



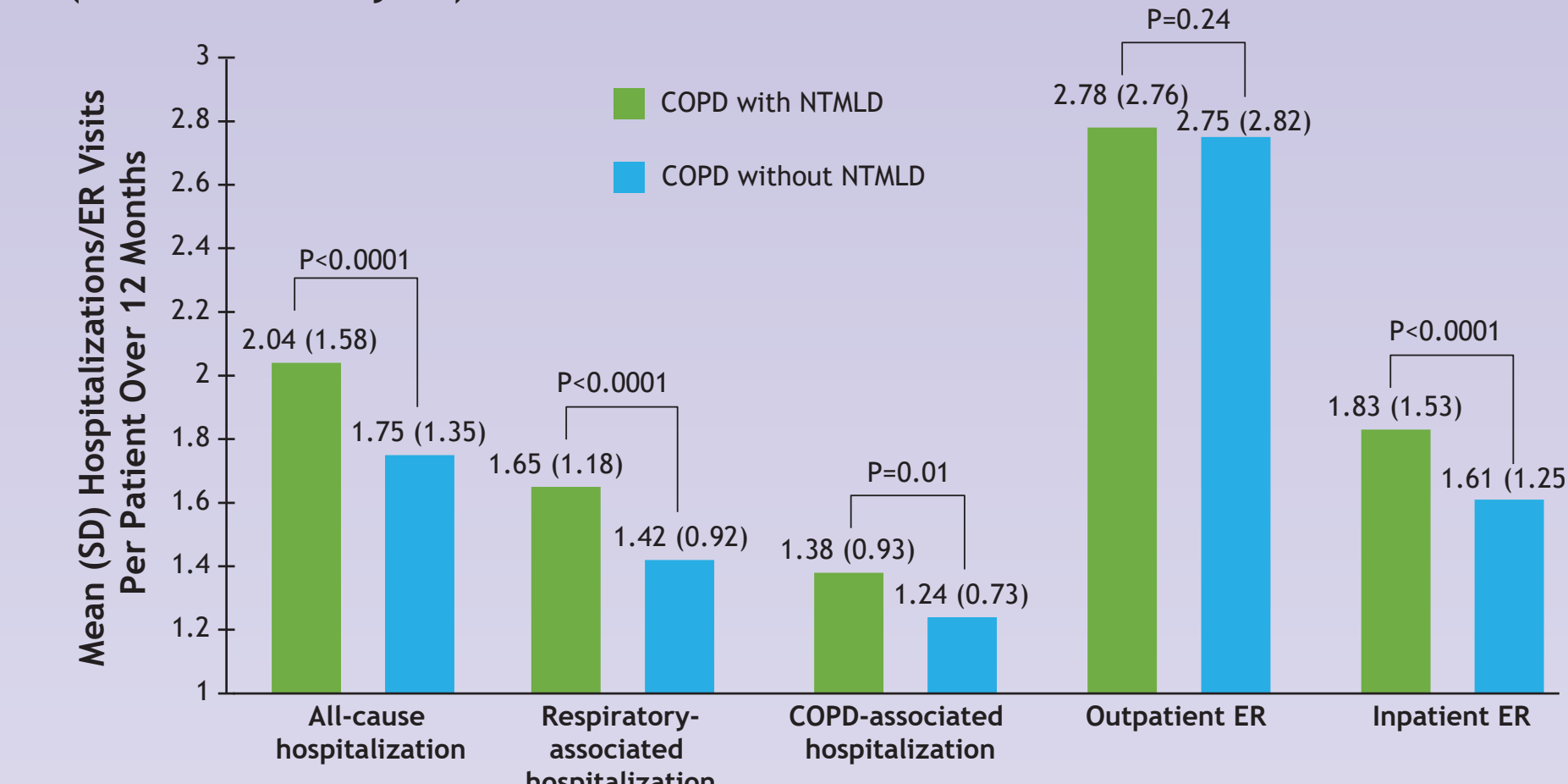
\* P values based on a log-rank test between cases and controls for each outcome.  
<sup>a</sup> HR derived from the multivariate Cox proportional hazards regression analysis after controlling for comorbidities during the 12-month pre-index period.  
 Inpatient ER = an ER visit followed by subsequent hospitalization; outpatient ER = an ER visit without subsequent hospitalization.

### Definitions of NTMLD, COPD, and BE<sup>a</sup>

- A case of NTMLD was defined as a beneficiary who had ≥ 2 medical encounters with a diagnostic code for NTMLD (ICD-9-CM 031.0 or ICD-10-CM A31.0) from a physician's office visit (diagnostic code must be assigned by a physician), or a hospital inpatient stay or a hospital outpatient visit that were dated at least 30 days apart but within 365 days
- A case of BE was defined as a beneficiary who had either ≥ 2 ambulatory encounters with a diagnostic code for BE (ICD-9-CM 494.0, 494.1 or ICD-10-CM J47.0, J47.1) that were dated ≥ 30 days apart, or ≥ 1 ambulatory encounter with a BE diagnosis and a computed tomography scan of the thorax (CPT-4 71250, 71260, 71270) within 60 days prior to the encounter, or ≥ 1 hospitalization with a principal or secondary diagnosis for BE
- A case of COPD<sup>b</sup> was defined as a beneficiary who had either ≥ 2 ambulatory encounters with a diagnostic code for COPD (ICD-9-CM 491.0, 491.1, 491.8, 491.9, 491.20, 491.21, 491.22, 492.0, 492.8, 496 or ICD-10-CM J41.0, J41.1, J41.8, J42, J43.0, J43.1, J43.2, J43.8, J43.9, J44.0, J44.1, J44.9) that were dated ≥ 30 days apart or ≥ 1 hospitalization with a principal or secondary diagnosis for COPD

<sup>a</sup> Patients with COPD and BE were excluded

Figure 5. Subgroup Analysis in Patients With an HCRU Event: Number of Hospitalizations and ER Visits Per Patient Over a 12-Month Follow-Up Period (Univariate Analysis<sup>a</sup>)



Note: For each of the 5 HCRU outcomes, patient counts in the subgroups varied; subgroup patient counts are indicated above the bars.  
<sup>a</sup> P value based on a Wilcoxon rank-sum test.  
 Inpatient ER = an ER visit followed by subsequent hospitalization; outpatient ER = an ER visit without subsequent hospitalization.

Table 2. Days to HCRU Events and LOS Among Patients With an HCRU Event

	COPD With NTMLD	COPD Without NTMLD	P value <sup>a</sup>
<b>Days to HCRU Events Among Patients With HCRU Events</b>			
All-cause hospitalization, N	1756	3208	
Mean (SD)	99 (113)	164 (107)	< 0.0001
Median (Q1, Q3)	50 (2, 181)	154 (70, 255)	< 0.0001
Respiratory-associated hospitalization, N	1037	1278	
Mean (SD)	108 (117)	173 (106)	< 0.0001
Median (Q1, Q3)	57 (3, 206)	166 (83, 268)	< 0.0001
COPD-associated hospitalization, N	413	563	
Mean (SD)	131 (118)	177 (103)	< 0.0001
Median (Q1, Q3)	103 (18, 235)	175 (92, 271)	< 0.0001
Outpatient ER, N	1468	3789	
Mean (SD)	153 (111)	160 (107)	< 0.0001
Median (Q1, Q3)	138 (51, 250)	147 (64, 251)	< 0.0001
Inpatient ER, N	1338	2388	
Mean (SD)	113 (117)	169 (107)	< 0.0001
Median (Q1, Q3)	70 (5, 211)	163 (74, 260)	< 0.0001
<b>LOS (in Days) Among Patients With Hospitalizations</b>			
All-cause hospitalization, N	1756	3208	
Mean (SD)	6 (7)	5 (14)	< 0.0001
Median (Q1, Q3)	5 (3, 8)	4 (2, 6)	< 0.0001
Respiratory-associated hospitalization, N	1037	1278	
Mean (SD)	7 (9)	5 (5)	< 0.0001
Median (Q1, Q3)	5 (3, 9)	4 (3, 6)	< 0.0001
COPD-associated hospitalization, N	413	563	
Mean (SD)	5 (4)	4 (3)	0.0002
Median (Q1, Q3)	4 (2, 6)	3 (2, 5)	0.0002

<sup>a</sup> P values based on log-rank test.  
<sup>b</sup> P values based on Wilcoxon rank-sum test.

## CONCLUSIONS

- In the US Medicare claims database, patients with NTMLD and preexisting COPD had a significantly higher disease burden due to hospitalizations and ER visits than patients with COPD without NTMLD</