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Real-world disease burden, mortality, and healthcare resource utilization associated with bronchiectasis

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Abstract

Objectives: To assess real-world survival and healthcare resource utilization (HCRU) in US patients with non-cystic fibrosis bronchiectasis (NCFBE). **Methods:** This retrospective analysis, using data from the STATinMED RWD Insights database from Jan 2015–Oct 2022, included adults with NCFBE (from Jan 2015–Oct 2021) and non-NCFBE comparators (from Jan 2015–Aug 2020); baseline characteristics were balanced by inverse probability treatment weighting. Outcomes included survival through end of study. HCRU was assessed over 12 months. **Results:** 117,718 patients with NCFBE and 306,678 comparators were included. Patients with NCFBE had a 77% higher risk of death than comparators (hazard ratio [HR] 1.77 [95% CI 1.74-1.80]). Risk of death was higher among patients aged ≥65 years (vs 18–34 years; HR 11.03 [95% CI 10.36-11.74]), among Black patients (vs White; HR 1.53 [95% CI 1.50-1.55]), and among patients with comorbid COPD (HR 1.42 [95% CI 1.40-1.44]). Patients with NCFBE incurred higher all-cause and respiratory-related HCRU than comparators for outpatient office, outpatient hospital, emergency department (ED), inpatient and respiratory-related pulmonologist visits (all $p < .0001$); HCRU increased with exacerbations. **Conclusions:** Patients with NCFBE have high mortality burden and incur high HCRU, both of which are further increased with exacerbations. Prevention and delay of exacerbations are key areas for improvement of disease management.

Keywords

Bronchiectasis, exacerbation, survival, healthcare resource utilization

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Introduction

Non-cystic fibrosis bronchiectasis (NCFBE) is a heterogeneous chronic respiratory disease characterized by irreversible dilation of the bronchi, recurrent infection, and chronic airway inflammation, which causes a progressive worsening of disease and substantial impact on patient health-related quality of life.[1,2] The estimated prevalence of NCFBE in the US ranges from 139 to 213 per 100,000 adults, and prevalence rates per 100,000 adults have risen by approximately 8% per year since 2001.[3–5]

Patients with NCFBE are at risk of recurrent exacerbations, which are associated with progressive lung damage and significant morbidity and mortality.[6,7] Bronchiectasis exacerbations are commonly defined as a deterioration in ≥3 specified symptoms for ≥48 hours causing a change in treatment.[8] Patients with a history of multiple exacerbations

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are at higher risk for future exacerbations and likely to have lower quality of life, more hospital admissions, and poorer prognosis than those with fewer exacerbations.[7,9,10]

NCFBE treatment goals are to reduce symptoms, improve quality of life, prevent exacerbations and hospital admissions, preserve lung function, and reduce mortality.[3,11,12] Current guidelines recommend management strategies that are focused on alleviating disease symptoms and treatment of infections[13]; however, these recommendations may not all be supported by strong evidence.[11,12] Current management approaches focus on three main components: treatment of underlying conditions, airway clearance, and short- or long-term antimicrobial treatment.[13]

There are limited real-world data on mortality in patients with NCFBE, particularly in the US. The available studies were performed in small populations outside of the US and report varying survival rates but generally suggest poor prognosis.[14] Reported 4-year survival ranges from 58% to 91% and declines considerably over time, with factors including advanced age, *Pseudomonas aeruginosa* infection, comorbidities, lung function, body mass index, hospitalizations, and exacerbations impacting survival.[14–16] Additionally, despite NCFBE's significant economic burden,[12,17,18] which is largely driven by hospitalization costs related to exacerbations,[19] there is a paucity of real-world studies evaluating disease-related healthcare resource utilization (HCRU). Understanding the disease burden and HCRU associated with NCFBE would contribute toward improving disease management and optimizing healthcare resource allocation.

This real-world study aimed to assess survival, disease burden, and HCRU in patients with NCFBE, compared with patients without NCFBE, from a large US claims database.

Methods

Study design and data source

This was a retrospective, longitudinal, observational study using deidentified data from the STATinMED Real-World Data Insights database from January 1, 2014, to October 31, 2022 (Figure 1). The STATinMED Real-World Data Insights database is an all-payer medical and pharmacy claims source with commercial, Medicaid, and Medicare health plan data that covers nearly 80% of the US healthcare system (300 million unique patients) and includes mortality data from the Death Master Index that has records for approximately 90% of all US deaths.[20] Data were deidentified, and data use complied with the Health Insurance Portability and Accountability Act for the privacy and security of protected health information.[21]

Study population

Included in this study were adult patients (≥18 years) with a NCFBE diagnosis defined as ≥2 outpatient claims with a diagnosis code for NCFBE dated ≥30 days apart, or ≥1 inpatient claim with NCFBE as the primary diagnosis, or ≥1 high-resolution chest computerized tomography scan followed by ≥1 inpatient or ≥2 outpatient claims for NCFBE.[22] Patients were required to have ≥12 months of continuous data capture prior to the index date (baseline period) and after the index date (follow-up period); data capture included both medical and pharmacy benefits. Excluded were patients with ≥1 inpatient or ≥2 outpatient claims ≥30 days apart with a diagnosis code for cystic fibrosis, interstitial fibrosis, pulmonary fibrosis, or sarcoidosis during the baseline period. Patients without a NCFBE diagnosis who met all other inclusion and exclusion criteria (apart from the NCFBE diagnosis criteria) were included as comparators. The index date was the earliest claim used to identify each patient with NCFBE during the case-identification period (January 1, 2015, to October 31, 2021) or a randomly assigned date for non-NCFBE comparators during the comparator-identification period (January 1, 2015, to August 30, 2020).

Inverse probability treatment weighting

Patients with NCFBE were compared with non-NCFBE comparators using IPTW to balance patient characteristics. The propensity score was calculated using a logistic model with patients with NCFBE and comparators included in the model, using the comparator patients as the reference. The baseline characteristics controlled for in the IPTW model were based on clinical rationale and standardized differences (Supplement Table S1). The propensity score acts as a balancing score between patients with NCFBE and comparators. After calculating the propensity score, the distribution of the propensity scores was reviewed. Patients with NCFBE were assigned a weight of 1/(propensity score) and comparators were assigned a weight of 1/(1-propensity score). A ratio of 1:2.5 patients with NCFBE to comparators was used for the IPTW weighting analysis. For patients with a very low propensity score, a very large weight was generated, which can increase the variability of the estimated effect. To address this issue, the weights were stabilized by multiplying the weights for both patients with NCFBE and comparators by a constant, equal to the mean of propensity score for each group (expected value of being in the NCFBE or comparator groups, respectively). This reduced both the variability of the weights and the variance of the effect estimates.

Study endpoints

Demographic characteristics were assessed at index, and clinical characteristics were assessed during the baseline period. Prespecified comorbidities were identified using *ICD-9/10-CM* codes and selected based on clinician input.

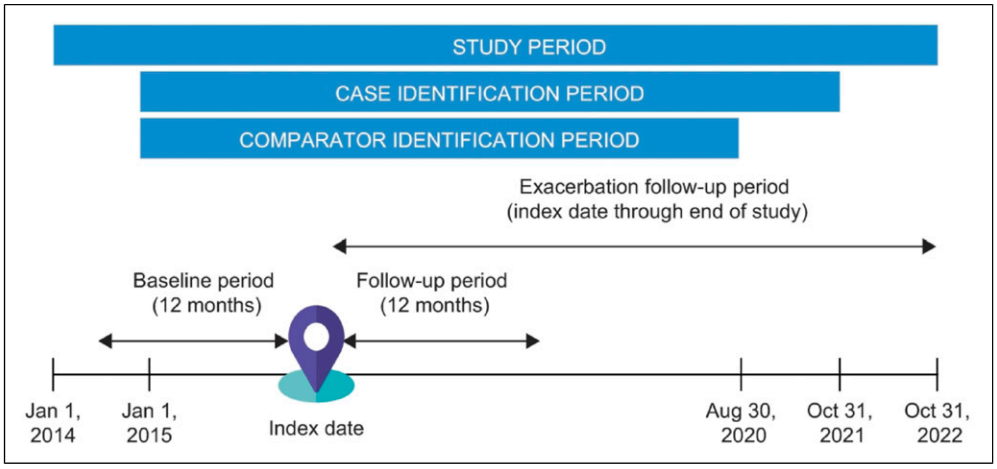

Figure 1. Study design. The identification periods differed between cases and comparators as the comparator cohort was previously established while the case cohort was able to utilize more recent data. The case and comparator cohorts were matched using IPTW, with a ratio of 1:2.5 patients with NCFBE to comparators, to account for potential bias. The index date was the earliest claim used to identify each patient with NCFBE during the case-identification period or a randomly assigned date for comparator patients during the comparator-identification period. IPTW, inverse probability treatment weighting; NCFBE, non-cystic fibrosis bronchiectasis.

Risk of death in patients with NCFBE was compared with non-NCFBE comparators through end of the study period to minimize immortal time bias. The probability of survival in patients who were alive at the end of the 12-month follow-up period was assessed at 1, 3, and 5 years post follow-up.

Bronchiectasis exacerbations were assessed over the baseline, 12-month, and 24-month follow-up periods. Bronchiectasis exacerbations were those that led to either (1) an inpatient claim with a primary/admitting diagnosis of NCFBE or an outpatient claim with any intravenous (IV) antibiotic procedure code or (2) any pharmacy claim for an oral antibiotic filled for up to a 14-day supply. Oral antibiotics included quinolone (ciprofloxacin), amoxicillin, amoxicillin and clavulanate, sulfamethoxazole and trimethoprim, cephalosporins (including ceftriaxone), tetracycline (doxycycline), and clarithromycin. Azithromycin was not included to minimize bias from capturing its use as long-term anti-inflammatory therapy. Risk factors for exacerbations, by severity and frequency of exacerbations, were reported.

All-cause, respiratory-related, and exacerbation-related HCRU (hospital and ED. visits and length of stay) in the follow-up period were assessed for patients with NCFBE and comparators, patients with NCFBE with or without exacerbations, and patients with NCFBE with exacerbations, by frequency of exacerbations. Disease-specific HCRU was based on the existence of NCFBE - or exacerbation-specific codes available in the claims.

Statistical analyses

Between-group differences were evaluated using *t* tests for continuous variables, chi-square tests for categorical variables, and Wilcoxon tests as appropriate. Time-to-death and mortality risk were examined using Cox proportional hazards regression models weighted with the propensity scores to adjust for confounders. The proportional hazards assumption was evaluated by visually inspecting the Kaplan-Meier curves by month among the NCFBE cases and comparators. A landmark analysis was conducted for patients surviving within the study (alive at 12 months postindex) to predict the probability of survival at 1, 3, and 5 years beyond the end of the follow-up period.

A logistic regression with a backward stepwise selection at a 0.05 significance level was used to analyze the relationship between NCFBE cases and exacerbations, controlling for all variables in the IPTW. Ordinal logistic regression was used to examine the odds of a NCFBE case having ≥1 exacerbation event.

Generalized linear models (GLMs) were used to examine all-cause, respiratory-related, and exacerbation-related HCRU. For length of stay for inpatient hospitalizations, a GLM with negative binomial distribution was used and log link function was applied. For a number of visits, a GLM with Poisson distribution with a log link was used. The least square means were reported for NCFBE cases and comparators.

Results

Patient population

A total of 117,718 patients with NCFBE and 306,678 non-NCFBE comparators were included in the study (Supplement Figure S1). Sample sizes were 355,353 in the NCFBE cohort and 833,167 in the comparator cohort after IPTW weighting to balance patient characteristics. Patients

with NCFBE were older than comparators (68.9 vs 57.8 years) and more likely to have disease-associated comorbidities or symptoms (Quan-CCI [Charlson Comorbidity Index] score 3.3 vs 1.1) (Table 1; Supplement Table S2 for standardized differences). The most common baseline comorbidities or symptoms in the NCFBE group were hypertension (55.0%), cough (44.4%), cardiovascular disease (40.9%), COPD (34.5%) and gastroesophageal reflux disease (30.1%). More patients with NCFBE had anxiety (15.8% vs 9.9%) and depression (8.9% vs 4.3%). After IPTW weighting, mean age of patients with NCFBE was 63.1 years vs 65.2 years for comparators, while Quan-CCI score was 2.3 for patients with NCFBE vs 4.7 for comparators.

Mortality risk

Patients with NCFBE had a 77% higher risk of death than non-NCFBE comparators through end of study (HR 1.77 [95% CI 1.74-1.80]; $p < .0001$; Table 2 and Supplement Figure S2). Risk of death increased with age and was highest among patients aged ≥65 years (HR 11.03 [95% CI 10.36-11.74]; $p < .0001$). Black patients had a 53% higher risk of death than White patients (HR 1.53 [95% CI 1.50-1.55]; $p < .0001$). Patients with NCFBE and comorbid COPD had a 42% higher risk of death than patients without NCFBE (HR 1.42 [95% CI 1.40-1.44]; $p < .0001$).

Survival post follow-up period

Among patients who survived longer than the 12-month follow-up period, those with NCFBE had a lower probability of survival than non-NCFBE comparators at 1, 3, and 5 years post follow-up (Table 3). The probability of survival at 1 year post follow-up was 92.1% among patients with NCFBE (vs 97.7% in comparators, $p < .0001$) and decreased to 75.2% at 5 years post follow-up (vs 93.9% in comparators, $p < .0001$). The probability of survival in patients with NCFBE decreased by 10.1% (vs 2.4% in comparators) from 1 to 3 years post follow-up and 9.2% from 3 to 5 years post follow-up (vs 1.5% in comparators).

Exacerbation-specific outcomes among patients with NCFBE

In the 12-month follow-up period, 63.6% of patients with NCFBE had ≥1 exacerbation, including 42.8% who experienced ≥2 exacerbations and 30.2% ≥ 3 exacerbations (Figure 2). After IPTW weighting, 61.0% of patients with NCFBE had ≥1 exacerbation, including 38.3% who had ≥1 exacerbation requiring hospitalization or IV antibiotic use.

After controlling for baseline variables, patients with any exacerbations were more likely to have comorbidities or symptoms, including COPD, alpha-1 antitrypsin (AAT) deficiency, cough, graft-vs-host disease (GVHD), and pulmonary tuberculosis than patients without exacerbations (all $p < .0001$; Supplement Figures S3–S5). Certain comorbidities were associated with >3.0 times higher odds of exacerbations requiring hospitalization or IV antibiotic use, particularly AAT deficiency, GVHD, and pulmonary tuberculosis (all $p < .0001$). Factors associated with reduced odds of having any exacerbations included Black race, evidence of chronic kidney disease, hypertension, obesity, or pregnancy. Congestive heart failure and peptic ulcer disease were associated with reduced odds of having exacerbations requiring oral antibiotic use.

After controlling for baseline variables, odds of increased exacerbation frequency were 2.0 to 3.5 times higher in patients with cough, primary ciliary dyskinesia (PCD), GVHD, history of immune deficiency (AAT deficiency or common variable immunodeficiency), COPD, or pulmonary tuberculosis compared with patients without the respective symptom or comorbidity (all $p < .0001$; Supplement Figures S6–S8). Odds of increased exacerbation frequency were 1.8 times higher in patients with *P aeruginosa* ($p < .0001$) and were 2.9 times higher among patients aged 55 to 64 years than patients aged 18 to 34 years. Patients on Medicaid had >2 times the risk of increased exacerbation frequency than commercial payers.

HCRU among patients with NCFBE

In the 12-month follow-up period and after adjustment for baseline variables, patients with NCFBE incurred higher all-cause and respiratory-related HCRU than non-NCFBE comparators in terms of outpatient office, outpatient hospital, ED., and inpatient visits (all $p < .0001$), as well as for respiratory-related pulmonologist visits ($p < .0001$) (Table 4; unadjusted HCRU is in Supplement Table S3). However, inpatient length of stay was shorter among patients with NCFBE, both for all-cause ($p < .0001$) and respiratory-related visits ($p = .0085$).

HCRU among patients with exacerbations

Exacerbation-related HCRU for patients with exacerbations was generally higher than respiratory-related HCRU for patients without exacerbations, in terms of outpatient office, ED, pulmonologist, and inpatient visits, as well as exacerbation-related length of stay (all $p < .0001$) (Supplement Table S4; unadjusted HCRU is in Supplement Table S5). However, there were fewer exacerbation-related outpatient visits among patients with exacerbations than respiratory-related outpatient visits among patients without exacerbations ($p < .0001$).

Table 1. Patient sociodemographic and clinical characteristics at baseline, unadjusted and after IPTW weighting.

		Unadjusted		After IPTW weighting[a]	
Baseline		NCFBE cohort (*N* = 117,718)	Non-NCFBE comparator cohort (*N* = 306,678)	NCFBE cohort (*N* = 355,353)	Non-NCFBE comparator cohort (*N* = 833,167)
Age, mean (SD)		68.9 (11.5)	57.8 (17.5)	63.1 (27.9)	65.2 (24.7)
Age, *n* (%)	18–34 years	2312 (2.0)	43,139 (14.1)	31,506 (8.9)	53,478 (6.4)
	35–54 years	9790 (8.3)	73,676 (24.0)	61,105 (17.2)	105,631 (12.7)
	55–64 years	20,776 (17.6)	60,185 (19.6)	66,982 (18.8)	177,198 (21.3)
	≤64 years	32,878 (27.9)	177,000 (57.7)	159,592 (44.9)	336,307 (40.4)
	≥65 years	84,840 (72.1)	129,678 (42.3)	195,761 (55.1)	496,860 (59.6)
Female sex, *n* (%)		71,856 (61.0)	180,395 (58.8)	201,570 (56.7)	417,834 (50.2)
Race, *n* (%)	White	67,850 (57.6)	170,263 (55.5)	193,099 (54.3)	437,058 (52.5)
	Black	7598 (6.5)	21,965 (7.2)	26,369 (7.4)	68,422 (8.2)
	Asian	2532 (2.2)	5749 (1.9)	6812 (1.9)	14,188 (1.7)
	Other	409 (0.3)	1042 (0.3)	1379 (0.4)	1795 (0.2)
	Unknown	39,329 (33.4)	107,659 (35.1)	127,694 (35.9)	311,705 (37.4)
Health insurance, *n* (%)	Commercial	22,241 (18.9)	160,947 (52.5)	132,902 (37.4)	226,482 (27.2)
	Medicare	78,377 (66.6)	98,351 (32.1)	163,594 (46.0)	442,209 (53.1)
	Medicaid	16,504 (14.0)	38,299 (12.5)	52,496 (14.8)	154,443 (18.5)
	Other/unknown	596 (0.5)	9081 (3.0)	6362 (1.8)	10,034 (1.2)
Geographic region, *n* (%)	Northeast	22,171 (18.8)	63,156 (20.6)	73,132 (20.6)	174,848 (21.0)
	North central	30,666 (26.1)	67,755 (22.1)	81,964 (23.1)	172,811 (20.7)
	South	42,712 (36.3)	108,654 (35.4)	129,096 (36.3)	346,692 (41.6)
	West	22,137 (18.8)	66,683 (21.7)	70,608 (19.9)	138,357 (16.6)
	Other	32 (0.0)	430 (0.1)	553 (0.2)	459 (0.1)
Quan-CCI score, mean (SD)		3.3 (2.9)	1.1 (1.8)	2.3 (3.9)	4.7 (8.0)
Quan-CCI comorbidities, *n* (%)	AIDS	1038 (0.9)	1387 (0.5)	1685 (0.5)	18,835 (2.3)
	Cancer	26,355 (22.4)	22,509 (7.3)	53,416 (15.0)	183,453 (22.0)
	Cerebrovascular disease	10,354 (8.8)	10,945 (3.6)	19,180 (5.4)	156,564 (18.8)
	COPD	40,557 (34.5)	7522 (2.5)	49,656 (14.0)	391,582 (47.0)
	CHF	17,210 (14.6)	11,875 (3.9)	34,272 (9.6)	186,471 (22.4)
	Dementia	2539 (2.2)	4331 (1.4)	5148 (1.4)	45,784 (5.5)
	Diabetes	31,211 (26.5)	68,896 (22.5)	63,689 (17.9)	321,112 (38.5)
	Hemiplegia or paraplegia	1184 (1.0)	1868 (0.6)	2591 (0.7)	20,819 (2.5)
	Liver disease	10,527 (8.9)	8585 (2.8)	22,744 (6.4)	124,168 (14.9)
	Metastatic carcinoma	5271 (4.5)	1754 (0.6)	6606 (1.9)	73,869 (8.9)
	Myocardial infarction	581 (0.5)	498 (0.2)	801 (0.2)	9648 (1.2)
	Peptic ulcer disease	1988 (1.7)	1796 (0.6)	3643 (1.0)	41,820 (5.0)
	PVD	19,472 (16.5)	13,188 (4.3)	38,131 (10.7)	164,847 (19.8)
	Renal disease	3492 (3.0)	4025 (1.3)	8876 (2.5)	36,657 (4.4)
	RD	9622 (8.2)	3742 (1.2)	13,695 (3.9)	129,374 (15.5)
Comorbidities or symptoms with NCFBE claim, *n* (%)[b]	Abnormal sputum	687 (0.6)	65 (0.0)	1276 (0.4)	18,838 (2.3)
	Acute lower respiratory tract infections	681 (0.6)	160 (0.1)	1314 (0.4)	1041 (0.1)
	Acute upper respiratory tract infections	7052 (6.0)	8086 (2.6)	15,647 (4.4)	36,653 (4.4)
	Alpha-1 antitrypsin deficiency	447 (0.4)	33 (0.0)	1460 (0.4)	339 (0.0)
	Aspergillus	1547 (1.3)	22 (0.0)	1685 (0.5)	10,680 (1.3)
	Aspiration	2576 (2.2)	442 (0.1)	5814 (1.6)	102,201 (12.3)
	Asthma	27,048 (23.0)	9950 (3.2)	40,151 (11.3)	202,716 (24.3)
	CRS	9452 (8.0)	4419 (1.4)	22,010 (6.2)	23,117 (2.8)
	CVID	5932 (5.0)	1666 (0.5)	8297 (2.3)	38,930 (4.7)
	CTD	8690 (7.4)	3226 (1.1)	12,590 (3.5)	115,067 (13.8)
	Cough	52,226 (44.4)	15,784 (5.1)	68,200 (19.2)	425,437 (51.1)
	Dyspnea	21,779 (18.5)	5365 (1.7)	27,990 (7.9)	215,094 (25.8)
	Fatigue or malaise	26,663 (22.6)	26,964 (8.8)	57,265 (16.1)	321,647 (38.6)
	GERD	35,399 (30.1)	29,738 (9.7)	65,873 (18.5)	358,001 (43.0)
	GVHD	368 (0.3)	17 (0.0)	909 (0.3)	78 (0.0)
	IBD	1535 (1.3)	1380 (0.4)	4038 (1.1)	17,566 (2.1)
	Influenza	239 (0.2)	80 (0.0)	607 (0.2)	510 (0.1)
	NTM	438 (0.4)	2 (0.0)	471 (0.1)	48 (0.0)
	Otitis	2003 (1.7)	3224 (1.1)	5563 (1.6)	9849 (1.2)
	Pathogens of interest[c]	4083 (3.5)	256 (0.1)	4602 (1.3)	16,207 (1.9)
	Pneumonia	1803 (1.5)	306 (0.1)	1899 (0.5)	125,004 (15.0)
	PCD	18,697 (15.9)	1278 (0.4)	46,218 (13.0)	87,706 (10.5)
	Pseudomonas aeruginosa	930 (0.8)	157 (0.1)	1022 (0.3)	42,510 (5.1)
	Pulmonary tuberculosis	939 (0.8)	26 (0.0)	969 (0.3)	5477 (0.7)

(continued)

Table 1. (continued)

Baseline		Unadjusted		After IPTW weighting[a]	
		NCFBE cohort (*N* = 117,718)	Non-NCFBE comparator cohort (*N* = 306,678)	NCFBE cohort (*N* = 355,353)	Non-NCFBE comparator cohort (*N* = 833,167)
Comorbidities or symptoms separate from NCFBE claim, *n* (%)[d]	Allergic rhinitis	15,751 (13.4)	13,150 (4.3)	33,698 (9.5)	151,968 (18.2)
	Anxiety	18,606 (15.8)	30,303 (9.9)	43,265 (12.2)	148,119 (17.8)
	Atrial fibrillation	15,206 (12.9)	14,300 (4.7)	32,416 (9.1)	116,837 (14.0)
	Bronchitis	1545 (1.3)	623 (0.2)	2811 (0.8)	4494 (0.5)
	CVD	48,135 (40.9)	43,084 (14.0)	107,974 (30.4)	439,015 (52.7)
	CKD	16,357 (13.9)	18,591 (6.1)	39,777 (11.2)	151,372 (18.2)
	CHF	17,210 (14.6)	11,875 (3.9)	34,272 (9.6)	186,471 (22.4)
	Depression	10,443 (8.9)	13,241 (4.3)	22,831 (6.4)	99,823 (12.0)
	Emphysema	329 (0.3)	54 (0.0)	766 (0.2)	251 (0.0)
	Hemoptysis	5083 (4.3)	321 (0.1)	15,675 (4.4)	99,872 (12.0)
	Hypertension	64,745 (55.0)	107,949 (35.2)	166,197 (46.8)	458,629 (55.0)
	Interstitial lung disease	7630 (6.5)	231 (0.1)	7883 (2.2)	144,244 (17.3)
	Intraoperative and postprocedural complications/disorders of respiratory system, not elsewhere classified	342 (0.3)	131 (0.0)	633 (0.2)	1664 (0.2)
	Lung diseases due to external agents	79 (0.1)	13 (0.0)	197 (0.1)	81 (0.0)
	MRSA	688 (0.6)	419 (0.1)	1615 (0.5)	3710 (0.4)
	Obesity	13,700 (11.6)	29,223 (9.5)	31,043 (8.7)	182,065 (21.9)
	Osteoarthritis	23,755 (20.2)	29,889 (9.7)	51,118 (14.4)	191,521 (23.0)
	Osteoporosis	14,065 (11.9)	9382 (3.1)	29,738 (8.4)	69,899 (8.4)
	Other diseases of the pleura	2317 (2.0)	267 (0.1)	5758 (1.6)	22,709 (2.7)
	Other diseases of the respiratory system	8090 (6.9)	974 (0.3)	12,956 (3.6)	55,823 (6.7)
	Other diseases of upper respiratory tract	741 (0.6)	85 (0.0)	1500 (0.4)	412 (0.0)
	Peptic ulcer disease	1988 (1.7)	1796 (0.6)	3643 (1.0)	41,820 (5.0)
	Pregnancy	286 (0.2)	9023 (2.9)	1597 (0.4)	10,258 (1.2)
	Tobacco dependence	15,605 (13.3)	19,116 (6.2)	40,470 (11.4)	110,247 (13.2)

[a]The IPTW model controlled for the following baseline characteristics: age group; sex, race, payer type, region, CCI score, anxiety/depression, asthma, COPD, cough, CHF, CKD, CVD, dyspnea, GERD, hypertension, interstitial lung disease, primary tuberculosis, prior infections (including pneumonia, *P aeruginosa*, aspergillus, NTM, and pathogens of interest [*Haemophilus influenzae* and *Mycobacterium avium*]), and RD/CTD.
[b]Comorbidities that were included on the same claim as that for NCFBE were identified in the NCFBE cohort. Patients in the comparator group with the identified comorbidities are also shown.
[c]*Haemophilus influenzae* and *Mycobacterium avium*.
[d]Comorbidities that were claimed on a separate claim as that for NCFBE were identified in the NCFBE cohort. Patients in the comparator group with the identified comorbidities are also shown.
CCI, Charlson Comorbidity Index; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRS, chronic rhinosinusitis; CTD, connective tissue disease; CVD, cardiovascular disease; CVID, common variable immunodeficiency; GERD, gastroesophageal reflux disease; GVHD, graft-vs-host disease; IBD, inflammatory bowel disease; IPTW, inverse probability treatment weighting; MRSA, methicillin-resistant *Staphylococcus aureus*; NCFBE, non-cystic fibrosis bronchiectasis; NTM, nontuberculous mycobacteria; PCD, primary ciliary dyskinesia; PVD, peripheral vascular disease; RD, rheumatologic disease.

HCRU increased with exacerbation frequency (Supplement Table S6). Patients with 1 exacerbation incurred higher all-cause HCRU than patients without exacerbations. Patients with ≥2 or ≥3 exacerbations also had generally higher HCRU compared with patients without exacerbations, except for length of inpatient stay, which was similar.

Discussion

In this real-world claims-based study, which aimed to assess patient survival, disease burden, and HCRU associated with NCFBE, risk of death was 77% higher in patients with NCFBE than in non-NCFBE comparators, and the probability of survival over time was significantly lower (75.2% vs 93.9% at 5 years). The difference in survival was observed despite a higher proportion of patients having severe comorbidities, such as metastatic carcinoma, in the comparator group. Prior studies on survival in patients with NCFBE were conducted in single centers with small patient groups and reported varying survival estimates. In an outpatient study of sequential patients with NCFBE in the UK ($N = 91$), 4-year survival was 91%, decreasing to 68.3% by 12 years.[16] In newly diagnosed patients with NCFBE in Belgium ($N = 245$), overall mortality after 5.2 years was estimated at 20.4%.[23] In a retrospective cohort study of patients with NCFBE in Turkey ($N = 56$), mortality was 35.7% at 5.4 years.[24] A prospective study of consecutive outpatients with NCFBE in Turkey ($N = 98$) reported 1-year survival rates of 97%, which was reduced to 58% by 4 years.[15]

Table 2. Mortality risk among patients with NCFBE vs comparators through end of study.

		NCFBE cohort vs non-NCFBE comparator cohort		
Mortality		Hazard ratio	95% CI	*p* Value
Overall		1.77	1.74, 1.80	<0.0001
Age group (ref: 18-34 years)	35–54 years	5.53	5.19, 5.88	<0.0001
	55–64 years	5.79	5.46, 6.15	<0.0001
	≥65 years	11.03	10.36, 11.74	<0.0001
Sex (ref: Male)	Female	0.99	0.98, 1.00	0.1751
Race (ref: White)	Black	1.53	1.50, 1.55	<0.0001
	Asian	0.26	0.24, 0.29	<0.0001
	Other	0.59	0.48, 0.73	<0.0001
	Unknown	1.32	1.30, 1.34	<0.0001
Payer channel (ref: Commercial)	Medicare	1.44	1.41, 1.47	<0.0001
	Medicaid	1.28	1.25, 1.31	<0.0001
	Unknown/other	0.45	0.42, 0.48	<0.0001
Region (ref: Northeast)	North central	0.79	0.78, 0.81	<0.0001
	South	0.65	0.64, 0.66	<0.0001
	West	0.81	0.79, 0.82	<0.0001
	Other	0.53	0.34, 0.82	0.0047
Comorbidities	COPD	1.42	1.40, 1.44	<0.0001

COPD, chronic obstructive pulmonary disease; NCFBE, non-cystic fibrosis bronchiectasis; ref, reference.

Table 3. Probability of survival during the follow-up period and at 1, 3, and 5 years post follow-up among patients with NCFBE vs comparators.

	NCFBE cohort		Non-NCFBE comparator cohort		
	N	% (95% CI)	*N*	% (95% CI)	*p* Value
Follow-up period (index to 12 months)	117,178	94.5 (94.3–94.6)	306,678	98.5 (98.4–98.5)	<0.0001
1 year follow-up survival (12-24 months postindex)	112,548	92.1 (92.0–92.3)	305,633	97.7 (97.6–97.7)	<0.0001
3-year follow-up survival (12-36 months postindex)	89,049	82.8 (82.5–83.0)	236,898	95.3 (95.2–95.4)	<0.0001
% Change: Follow-up years 1 to 3		10.1		2.4	-
5-year follow-up survival (12-60 months postindex)	61,149	75.2 (74.9–75.5)	134,156	93.9 (93.8–94.0)	<0.0001
% Change: Follow-up years 3 to 5		9.2		1.5	-

NCFBE, non-cystic fibrosis bronchiectasis.

In this study, key factors increasing the risk of death were advanced age, Black race, and having comorbid COPD. The survival rates were based on an employed, insured population, with approximately 28% of patients ≤64 years of age (mean, 69 years). In comparison, survival rates reported in an older population (mean age, 77 years) of Medicare patients with NCFBE were lower (63% at 5 years) than this study.[9] Other studies have also noted the association of advanced age with increased mortality.[15,16,23–25] Studies that assessed patient age among survivors and nonsurvivors with NCFBE found that surviving patients were younger (mean age 59.0–59.7 years) than nonsurvivors (mean age 71.0–72.1 years).[15,26] The presence of comorbidities has been associated with increased mortality in other reports.[24] A prospective observational cohort study of patients with NCFBE in Europe reported that an increase of one comorbidity equated to a 17% increase in mortality.[27] The presence of COPD has been noted as an important factor for increased risk of death in other reports.[23,26,28] This study found that Black patients with NCFBE had increased risk of death compared with White patients despite having fewer exacerbations reported. This discrepancy may reflect a higher risk of death from other causes or underreporting of exacerbations in Black patients because of socioeconomic factors, decreased access to care, and social drivers of health inequalities.[29]

All-cause and respiratory-related HCRU were generally higher in patients with NCFBE than comparators. Other real-world studies have found that patients with NCFBE used more healthcare resources than matched controls.[18,30]

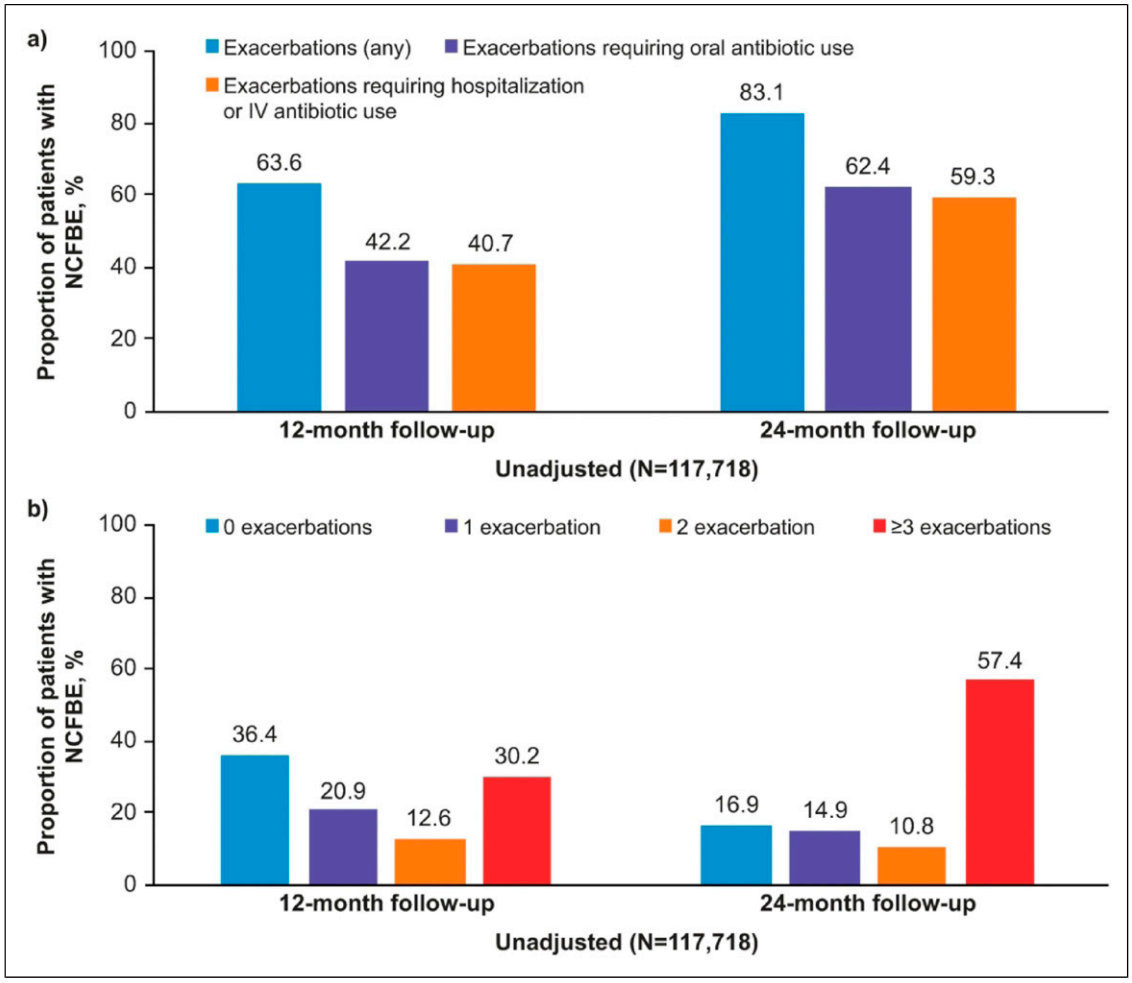

Figure 2. Exacerbations during 12 and 24 months of follow-up among patients with NCFBE, based on (a) exacerbations requiring oral antibiotic use or exacerbations requiring hospitalization or IV antibiotic use and (b) frequency of exacerbations.
Note. groups in panel A are not mutually exclusive. IV, intravenous; NCFBE, non-cystic fibrosis bronchiectasis.

The higher HCRU in patients with NCFBE may be attributed to increased medical appointments, hospital days, and use of antibiotics.[30] By contrast, the current analysis noted that length of inpatient stay, both all-cause and respiratory-related visits, was shorter in patients with NCFBE than in comparators. Other reports have noted a recent trend toward shorter length of stay for patients hospitalized with COPD or NCFBE and suggested the decline may be related to improved quality of care and focus on stabilization and early discharge.[31]

Among patients with NCFBE, HCRU was considerably higher in those with exacerbations than without. Notably, HCRU increased as number of exacerbations increased. These findings support other reports that identified exacerbations as a main driver of HCRU associated with NCFBE,[12,17] with hospitalizations related to exacerbations constituting a major component of the resource burden of NCFBE.[19] Notably, length of inpatient stay was similar between patients with 2 or 3 exacerbations, suggesting a consistent standard of care after ≥2 exacerbations, although future claims-based studies of patients with multiple exacerbations would be needed to confirm this.

Limitations

The use of IPTW to balance patient characteristics among cohorts is increasing rapidly in literature,[32] although it is associated with limitations. For example, results may be affected by residual systematic differences in baseline characteristics between case and comparator patients, even if predictors of artificial censoring and the outcome are accounted for by the correction.[32] There may also be issues with extreme weights[33]; however, this can be addressed by weight stabilization (applied in this study) and/or truncation.[34] IPTW is also sensitive to misspecifications of the propensity-score model biasing the effect estimate.[34] HRs

Table 4. HCRU in patients with NCFBE vs comparators during 12-month follow-up.

HCRU[a]		NCFBE cohort (*N* = 117,718)		Non-NCFBE comparator cohort (*N* = 306,678)		*p* Value (cases vs comparators)
		LS means	95% CI	LS means	95% CI	
All-cause healthcare utilization	Outpatient office visits	9.63	9.17–10.12	5.17	4.93–5.43	<.0001
	Outpatient hospital visits	1.96	1.74–2.22	0.67	0.6–0.76	<.0001
	ED visits	1.71	1.57–1.86	0.93	0.85–1.01	<.0001
	Inpatient visits	4.32	3.71–5.03	1.37	1.18–1.6	<.0001
	Length of inpatient stay, days	8.36	6.01–11.62	9.96	7.52–13.21	<.0001
Respiratory-related healthcare utilization	Outpatient office visits	2.72	2.47–3.00	0.81	0.73–0.89	<.0001
	Outpatient hospital visits	2.72	2.34–3.15	0.45	0.39–0.52	<.0001
	ED visits	1.09	0.90–1.31	0.47	0.39–0.56	<.0001
	Pulmonologist visits	0.02	0.01–0.04	0.004	0.00–0.01	<.0001
	Inpatient visits	1.97	1.56–2.49	0.37	0.29–0.46	<.0001
	Length of inpatient stay, days	5.16	2.67–9.98	6.95	3.74–12.92	0.0085

[a]Patients without HCRU for a service were included. Zero-inflated negative binomial models were used for length of stay; Poisson distribution was used for visits.

ED, emergency department; HCRU, healthcare resource utilization; LS means, least square means; NCFBE, non-cystic fibrosis bronchiectasis.

can be estimated using IPTW with less bias compared with propensity-score stratification or adjustment using the propensity score.[34] Despite these limitations, IPTW allows all eligible patients to be retained, thus increasing the effective sample size, whereas unmatched individuals are often discarded during propensity-score analysis.[33,34] Consistent with other propensity score-based analysis methods, IPTW can be used to summarize all patient characteristics to a single covariate (the propensity score). These methods are warranted in analyses with either a large number of confounders or a small number of events.[34]

Additionally, this study was subject to inherent limitations of a claims database, including data entry and coding errors that may result in misclassification of patients. The presence of a diagnosis code on a claim cannot be considered confirmatory of disease, and the presence of a claim for a filled prescription does not indicate the medication was consumed or taken as prescribed. Medications filled over the counter or provided as samples by the physician are not observed in claims data, and patients paying out of pocket may not be represented. Specific to this study, patients with PCD, which can be a cause of NCFBE,[1] were captured in both the NCFBE and non-NCFBE comparator groups; in the comparator group, this likely represents individuals who had a diagnosis claim for PCD without a separate diagnosis claim for NCFBE. The advantage of using a comprehensive claims database is that it incorporates all medical and pharmacy claims and allows for longitudinal analysis of a large sample, thus providing unique information across the continuum of care. Despite being of interest, the impact of *P aeruginosa* infection could not be assessed when comparing patients with NCFBE with non-NCFBE comparators because of the small number of patients recorded as having the infection. The impact of COVID-19 was not controlled for in this study, which may have disproportionally impacted the NCFBE group that used more recent data.

Conclusions

NCFBE was associated with a significant mortality burden, particularly among older patients, Black patients, and those with comorbid COPD, and the risk of death increased over time. HCRU for NCFBE was high and increased with exacerbation frequency. These results highlight the need for more effective treatments to manage NCFBE and reduce the frequency of exacerbations. Current management of NCFBE focuses on preventing infections, optimizing mucus clearance, and addressing underlying comorbidities. Opportunities to potentially improve patient care include readdressing adherence to individuals' current management of NCFBE, a better understanding of socioeconomic factors to address lifestyle concerns in risk management and disparities in geographic access to specialty care, and an increased awareness of neutrophil-mediated inflammation and the patient burden associated with NCFBE.

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Declaration of conflicting interests

S.S., J.M., L.B., and A.J.F., are employees of STATinMED, a paid consultant for Insmed Incorporated. J.F., M.M., and M.L. are employees and shareholders of Insmed Incorporated. E.C.D.

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Ethical Statement

This study was performed in accordance with relevant guidelines and regulations. Since this study did not involve the collection, use, or transmittal of individually identifiable data, institutional review board approval was not required. Only analyzed deidentified data were used in the study, which are a priori exempt from the Federal Policy for the Protection of Human Subjects (1991) and does not meet the identification criteria necessary to be privileged under the Health Insurance Portability and Accountability Act (HIPAA) of 1996. Nonetheless, both the dataset and the security of the offices where the dataset was kept met HIPAA requirements, and by default, this study was in accord with the same.

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Supplemental Material

Supplemental material for this article is available online.

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