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Original Research

Disease Onset and Burden in Patients With Chronic Bronchitis and COPD: A Real-World Evidence Study

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Abstract

Background: Chronic bronchitis (CB), classically defined as having cough and sputum production for at least 3 months per year for 2 consecutive years, is frequently associated with chronic obstructive pulmonary disease (COPD).

Methods: This retrospective cohort study using the Optum® de-identified electronic health record data set (Optum® EHR) aimed to identify patients with CB, COPD, and both CB and COPD through the application of the classical definition of CB, and to compare the characteristics of these populations, and the timing of diagnosis as well as their health care resource utilization (HCRU). Scanning of the EHRs was performed electronically using a specially developed algorithm.

Results: Of 104,633,876 patients in the study period between January 2007 and September 2020, 628,545 patients had CB only (i.e., nonobstructive disease), 129,084 had COPD only (COPD cohort), and 77,749 had both COPD and CB (COPD-CB cohort). A total of 75.9% of patients (59,009 of 77,749) fulfilled the criteria for a CB diagnosis before their first diagnosis with COPD, compared with 24.1% who had COPD before being diagnosed with CB. HCRU over 5 years was highest in the COPD-CB cohort, whereas the COPD cohort and CB cohorts had similar HCRU over 5 years. The COPD-CB cohort had a greater percentage of common COPD comorbidities and exposure to more drug classes than the other cohorts.

Conclusion: These results highlight the importance of increased attention to CB. CB often precedes the diagnosis of COPD and subsequently leads to high HCRU. Interventions to better manage CB and prevent the progression of CB to COPD could improve morbidity in this population.

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Abbreviations:

% pred=percentage predicted; **BMI**=body mass index; **CB**=chronic bronchitis; **CFTR**=cystic fibrosis transmembrane conductance regulator; **COPD**=chronic obstructive pulmonary disease; **EHR**=electronic health record; **FEV$_1$**=forced expiratory volume in 1 second; **FVC**=forced vital capacity; **HCRU**=health care resource utilization; **HIPAA**=Health Insurance Portability and Accountability Act; **ICD-10-CM**=International Classification of Diseases, Tenth Revision, Clinical Modification; **NHLBI**=National Heart, Lung, and Blood Institute; **SPIROMICS**=SubPopulations and InteRmediate Outcome Measures in COPD

This article has an online supplement.

Introduction

Chronic bronchitis (CB) is classically defined as having cough and sputum production for at least 3 months per year for 2 consecutive years and is commonly associated with a history of smoking.[1,2] CB occurs in up to three-quarters of patients with chronic obstructive pulmonary disease (COPD)[3] and also in individuals with normal lung function (nonobstructive CB, hereafter termed CB), with prevalence estimates varying widely among both categories.[4] CB has a higher prevalence generally among those with smoking exposure.[3] Due to variability in CB definitions, estimation of the true burden of CB remains challenging. Compared to patients who do not have CB, those with CB have a higher risk of developing incident COPD, respiratory mortality, and all-cause mortality.[4] The COPD Genetic Epidemiology observational study revealed that among patients with COPD, those with CB have worse respiratory symptoms, worse quality of life, and a higher exacerbation risk than those without CB.[5]

Despite the existing literature describing the impact of CB on prognosis, the prevalence of patients with CB or COPD alone, compared to those who have both conditions and their respective health care resource utilization (HCRU) has not been estimated before in a real-world population. In this analysis, our primary aim was to identify patients with CB, COPD, and both CB and COPD through the application of the classical definition of CB to real-world clinical notes in electronic health records (EHRs) and to compare the characteristics of these populations as well as their HCRU. We also examined medication use patterns in these populations and the distribution of the timing of CB versus COPD onset for patients who eventually have both. Additionally, patients who develop COPD are at risk for several other comorbidities due to complex genetic and environmental exposure interactions. These comorbidities have been shown to cluster, potentially due to common underlying mechanisms.[6] One potential underlying mechanism that may contribute to comorbidity clustering is smoking-related acquired cystic fibrosis transmembrane conductance regulator (CFTR).[7,8] Acquired systemic CFTR dysfunction is associated with CB, gastroesophageal reflux disease, and osteoporosis.[6,9,10] Therefore, the final aim of this analysis was to determine if comorbidities that are associated with CFTR dysfunction are more prevalent in patients with both COPD and CB using real-world data.

Methods

Study Design

This was a retrospective cohort study based on the secondary use of data from the Optum® de-identified EHR data set. Optum® EHR is a longitudinal EHR repository derived from dozens of health care provider organizations in the United States. Administrative medical data is obtained from both inpatient and ambulatory EHRs, practice management systems, and other internal systems and is processed, normalized, and standardized across the continuum of care from both acute inpatient stays and outpatient visits. The Optum data has been de-identified pursuant to the Health Insurance Portability and Accountability Act (HIPAA) and Optum, using the expert determination method, and has documented the methods and results of the analysis that justify such determination as set forth in 45 C.F.R. 164.514 and the "Guidance Regarding Methods for De-identification of Protected Health Information in Accordance with the HIPAA Privacy Rule."[11,12] As this study is a secondary analysis of fully anonymized data, an institutional review board or additional informed consent was not required.[13]

The study period was from January 1, 2007, to September 30, 2020. Patients were studied from 2 years prior to first diagnosis with a post-diagnosis follow-up period for each patient of 5 years.

Electronic Health Record Review Process

Patients' EHRs were electronically reviewed using an algorithm that "read" each record, searching for particular terms used to define CB. The rules for searching within the EHRs are outlined in more detail in the online data supplement. Manual chart reviews were not performed.

Definitions of Chronic Bronchitis and COPD

Cohorts were defined based on the contents of Optum® EHR using 2 sources: clinical notes for CB, and the International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) codes for COPD. Both sources were then combined to derive a definition of the COPD and CB (COPD-CB) cohort (Figure 1).

Definition of Patients With Chronic Bronchitis Cohort Using Optum® Electronic Health Record Clinical Notes (CB+)

CB is defined clinically as a cough with sputum production for at least 3 months a year during a period of 2 consecutive years.[1,2] To apply this definition, records in Optum® EHR were scanned for documentation of both sputum and cough in the medical encounter notes, within 2 consecutive 3-month periods, 2 years in a row. For these analyses, "symptoms for 2 consecutive 3-month periods" was interpreted as the equivalent of symptoms reported

in the clinical notes during 2 quarters in a row, i.e., at least 90 days apart and no more than 180 days apart. These 3-month periods had to be identified in each of 2 consecutive years to meet the definition of CB. See the online data supplement for further details on symptom scanning in clinical notes.

Definition of Patients With COPD Cohort Using International Classification of Diseases, Tenth Revision, Clinical Modification Codes (COPD+)

The ICD-10-CM codes J43 (emphysema) and J44 (other chronic obstructive pulmonary disease) were used to identify patients with COPD. Patients had to have at least 2 diagnoses of COPD with these codes in their EHRs, at least 30 days apart. Patients with ICD-10-CM codes J41 (simple and mucopurulent CB) and J42 (unspecified CB), which are frequently included for COPD, in their EHR were not used to identify patients in this cohort as these codes are used for CB.

Definition of Chronic Bronchitis, COPD, and COPD-Chronic Bronchitis Cohorts

The CB cohort was defined as patients who had CB (as per the above definition) only without COPD. Index day for this cohort was defined as the date of their first record of "cough and sputum" symptoms. Patients were included in the cohort if they had 2 years of Optum® EHR data prior to the index day and 5 years of follow-up Optum® EHR data after the index day, all within the study period defined above. The COPD cohort was defined as patients who had COPD only without CB. Index day for this cohort was defined as the date of their first record of COPD diagnosis. Patients were included in the cohort if they had 2 years of Optum® EHR data prior to index day and 5 years of follow-up Optum® EHR data after the index day, all included within the study period. The COPD-CB cohort was identified as patients with both CB and COPD as defined above at any time during the study period. For the COPD-CB cohort, the index day was the later of the index days for CB and COPD, i.e., the first time a patient qualified for inclusion in both cohorts. Note that due to the large sample size, all results with numerical differences between different cohorts had p-values < 0.05.

Definition of Smoking Status

Clinical notes on smoking status recorded in Optum® EHR were reviewed to determine smoking status as outlined in the online data supplement.

Spirometry

Forced expiratory volume in 1 second (FEV$_1$) and forced vital capacity (FVC) percentage predicted were computed from the FEV$_1$ and FVC measurements recorded in the Optum® EHR, and where available, in the follow-up window as per previously published calculations.[14] Averages over the 5-year period were calculated for patients who had more than one measurement in their EHR.

Time to Diagnosis Within the COPD-Chronic Bronchitis Cohort

For patients in the COPD-CB cohort, the time between their first CB diagnosis and their first diagnosis with COPD was assessed. Patients diagnosed with COPD first followed by CB had a negative value.

Health Care Resource Utilization

Data were used to assess the clinical characteristics of the cohorts and their HCRU. For the purpose of the study, HCRU encompasses the following data: the number of medical encounters, the number of pulmonologist visits, the number of imaging referrals, the number of hospitalizations, and the number of days in the hospital. Medical encounters are defined by the following activities recorded in the EHRs: visits to the hospital and specialists, and in-person, written, or telephone contact with a doctor. The mean number of medical encounters in each cohort was calculated for each year. All medical encounters are counted individually regardless of whether they relate to the same issue on the same day. Encounters are not restricted to those related to COPD or CB only.
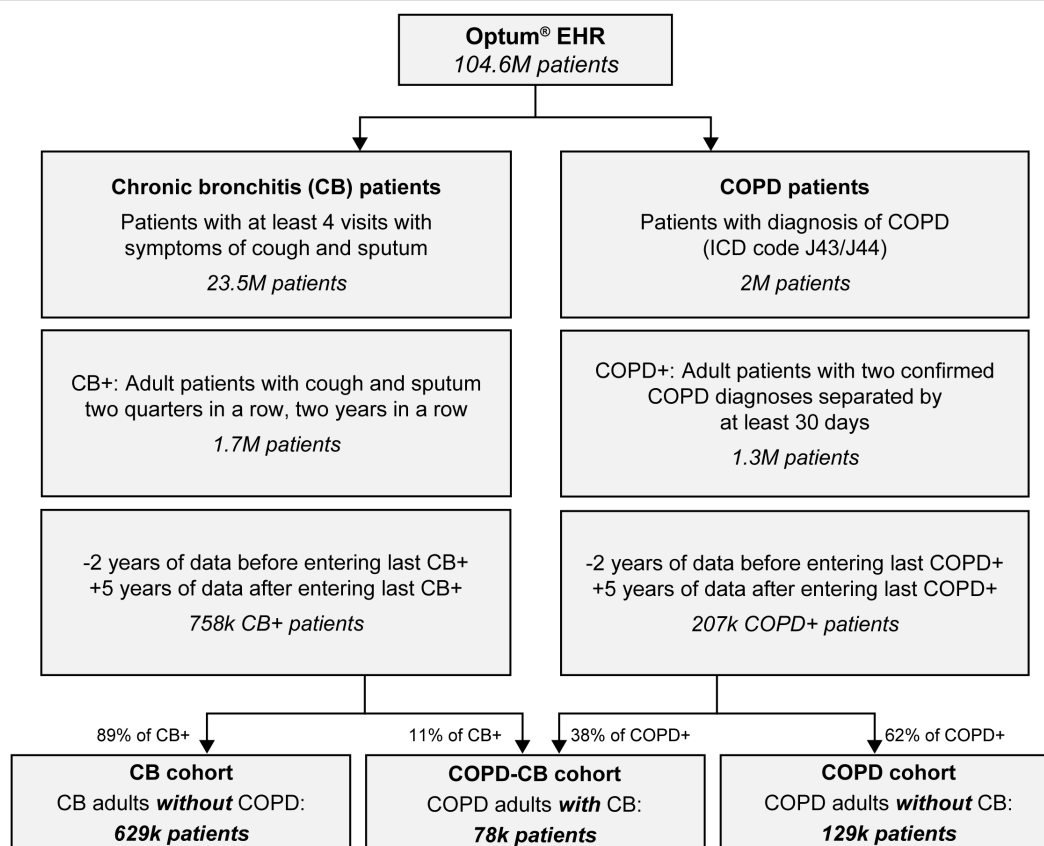
For each patient, lists of admission dates of distinct hospital visits in the follow-up period were extracted and grouped by the year of the follow-up window. The frequency for each patient was calculated by dividing the total number of hospital visits in the follow-up window by the number of years of the follow-up window. The number of days spent in the hospital was computed using the visit start and end dates from the EHRs. Specialist visits and oxygen therapy were computed using the definitions in the online data supplement.

Medication Use

The number of drug prescriptions for the following medications in the follow-up period was extracted from the EHR: mucolytics and phosphodiesterase type 4 inhibitors, macrolides, long-acting muscarinic antagonists, long-acting beta2-agonists, and inhaled corticosteroids. See the online data supplement for further details.

Analysis of Common COPD Comorbidities

The prevalence of gastroesophageal reflux disease, diabetes, osteoporosis, bronchiectasis, lung cancer, and chronic rhinosinusitis, which are potentially associated with CFTR dysfunction,[10,15-17] was evaluated in all 3 cohorts. These comorbidities were identified using ICD-10-CM codes, which is further described in the online data supplement.

Figure 1. Patient Selection Flow Chart

Optum® EHR
104.6M patients

Chronic bronchitis (CB) patients
Patients with at least 4 visits with symptoms of cough and sputum
23.5M patients

COPD patients
Patients with diagnosis of COPD (ICD code J43/J44)
2M patients

CB+: Adult patients with cough and sputum two quarters in a row, two years in a row
1.7M patients

COPD+: Adult patients with two confirmed COPD diagnoses separated by at least 30 days
1.3M patients

-2 years of data before entering last CB+
+5 years of data after entering last CB+
758k CB+ patients

-2 years of data before entering last COPD+
+5 years of data after entering last COPD+
207k COPD+ patients

89% of CB+   11% of CB+   38% of COPD+   62% of COPD+

CB cohort
CB adults *without* COPD:
629k patients

COPD-CB cohort
COPD adults *with* CB:
78k patients

COPD cohort
COPD adults *without* CB:
129k patients

COPD+ indicates patients fulfilling the definition criteria for COPD; CB+ indicates patients fulfilling the definition criteria for chronic bronchitis.

EHR=electronic health record; CB=chronic bronchitis; COPD=chronic obstructive pulmonary disease

Results

The total population of the Optum® EHR for the study period was 104,633,876 individual patients. The analysis revealed 628,545 patients in the CB cohort, 129,084 in the COPD cohort, and 77,749 in the COPD-CB cohort (Figure 1). Of the 3 cohorts, the COPD-CB cohort had the lowest proportion of patients who had never smoked, as expected since both COPD and CB are associated with smoking (Table 1). Where spirometry data were available, the CB cohort patients had a higher mean FEV1 and mean FEV1/FVC ratio compared with the COPD and COPD-CB cohorts, with the latter 2 having broadly similar spirometry results to each other (Table 1). A greater proportion of patients with CB only or with both CB and COPD were women, whereas the numbers of men and women were almost balanced across patients with COPD only (Table 1).

Time to Diagnosis Within the COPD-Chronic Bronchitis Cohort

More patients fulfilled the criteria for CB diagnosis before their first diagnosis with COPD (59,009 patients [75.9%]), than had COPD before being diagnosed with CB (18,740 patients [24.1%], Figure 2).

Health Care Resource Utilization

The COPD-CB cohort had the greatest number of interactions with health care (Table 1). Further, the COPD-CB cohort had the greatest HCRU in terms of the 5 metrics analyzed (medical encounters, interaction with a pulmonologist, referral to imaging, all-cause hospitalizations, and days in hospital, Table 2, Figure 3) and received the highest number of drug classes (Table S1 in the online supplement) among the 3 cohorts. Among patients with COPD or CB only, HCRU (represented by the 5 metrics described above) was similar over 5 years.

Medication Use

Macrolide prescriptions were more common in patients in the CB and COPD-CB cohorts than in the COPD cohort (Table S1 in the online supplement). In particular, individuals in the COPD-CB cohort experienced more frequent changes in classes of inhaled therapy, compared to patients with COPD alone, who did not have CB symptoms. This is illustrated in the more complex flow pattern observed for the COPD-CB cohort compared to the COPD-only cohort in Figure S2 in the online supplement.

Table 1. Demographic Characteristics of Cohorts Up to 5 Years Post-Index Date

	CB Cohort	COPD Cohort	COPD-CB Cohort
Number of Patients, N	628,545	129,084	77,749
Female (n, %)	413,583 (65.8%)	68,931 (53.4%)	46,727 (60.1%)
Never Smoked[a] (n, %)	25,142 (4%)	1549 (1.2%)	233 (0.3%)
Age in Years at Index Date, mean (SD)	59.5 (18.4)	72.0 (10.7)	71.7 (10.9)
BMI,[b] mean (SD)	31.0 (7.7)	29.9 (7.9)	30.9 (8.2)
Emphysema Diagnosis, n (%)[a,c]	0.0 (0%)	29,689 (23%)	26,435 (34%)
Pneumonia, n (%)[a]	31,427 (5%)	14,199 (11%)	19,437 (25%)
Lung Function (where available, over the 5-year follow-up)			
FEV$_1$ Available, n (%)	16,352 (2.60%)	7827 (6.06%)	8213 (10.56%)
FEV$_1$ (L), mean (SD)	2.02 (1.05)	1.69 (0.75)	1.55 (0.71)
Available FEV$_1$ (%-pred), n (%)	14,678 (2.34%)	5188 (4.02%)	8035 (10.33%)
FEV$_1$ (%-pred), mean (SD)	77.6 (0.4)	65.5 (0.6)	61.7 (0.5)
Data Available for FVC, in Liters, n (%)	16,967 (2.70%)	8274 (6.41%)	9172 (11.80%)
FVC (L), mean (SD)	2.58 (1.28)	2.73 (0.98)	2.44 (0.92)
Data Available for FVC Percentage Predicted, n (%)	15,307 (2.44%)	5749 (4.45%)	8993 (11.57%)
FVC (%-pred), mean (SD)	80.1 (0.4)	83.5 (0.6)	77.7 (0.4)
FEV$_1$/FVC Available, n (%)	13452 (2.14%)	6946 (5.38%)	6926 (8.91%)
FEV$_1$/FVC, mean (SD)	0.77 (0.11)	0.61 (0.22)	0.63 (0.15)

[a]Measured at any time in the 2 years prior to and 5 years after index date
[b]Average in follow-up period per patient
[c]Emphysema diagnosis based on 2 occurrences of ICD-10-CM code J43

CB=chronic bronchitis; COPD=chronic obstructive pulmonary disease; SD=standard deviation; BMI=body mass index; FEV$_1$=forced expiratory volume in 1 second; %-pred=percentage predicted; FVC=forced vital capacity; ICD=10-CM=International Classification of Diseases, Tenth Revision, Clinical Modification

Figure 2. Number of Years Between Diagnoses of Chronic Bronchitis and COPD in the Chronic Bronchitis-COPD Cohort
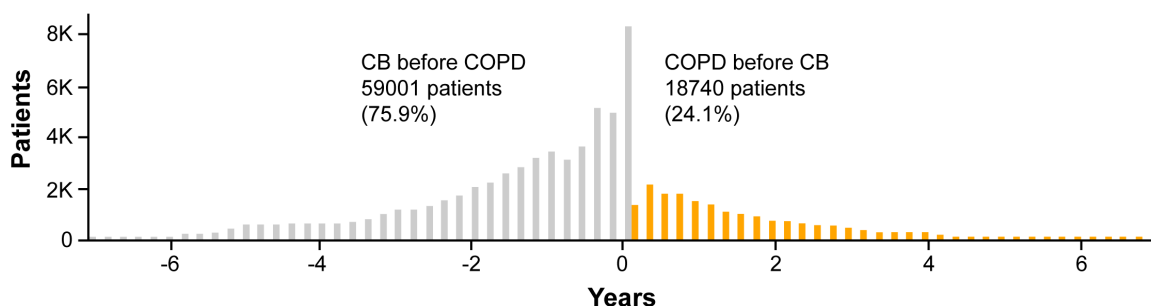
Grey=CB diagnosed before COPD
Orange=COPD diagnosed before CB

CB=chronic bronchitis; COPD=chronic obstructive pulmonary disease

Analysis of Common COPD Comorbidities

The COPD-CB cohort had a greater percentage of common COPD comorbidities than the COPD cohort and the CB cohort (Table S2 in the online supplement).

Discussion

Real-world data on the prevalence of the CB phenotype in patients with COPD are scarce.[18] Similarly, clinical trials frequently focus on COPD as a whole rather than different clinical phenotypes.[19] Additionally, the definition of CB varies significantly in epidemiologic studies.[3] While the use of algorithms to interrogate EHRs is becoming more common,[20,21] this study used a novel method of applying the classical definition of CB directly to physician notes in EHRs to determine the proportions of patients with COPD-CB or CB alone within the Optum® EHR. In clinical practice, physicians are unlikely to separate COPD and CB, therefore, the application of the CB definition to patient EHRs is a valuable tool to differentiate patients.

The proportion of patients with CB in our analysis is aligned with previously reported studies[19,22] and the spirometry results for the patients at baseline also reflect previously reported distributions of phenotypes based on pulmonary function.[23] A greater proportion of patients with

Table 2. Health Care Resource Use Over 5-Year Follow-Up Period

	CB Cohort	COPD Cohort	COPD-CB Cohort
Number of Patients, N	628,545	129,084	77,749
All Medical Encounters[a] Per Year, mean (SD) per patient	53.6 (47.4)	44.8 (58.4)	85.3 (78.1)
Hospital Visits Per Year, mean (SD)	0.9 (1.9)	0.6 (1.1)	1.5 (2.6)
Hospital Visits With COPD as Primary Diagnosis, Per Year, mean (SD)[b]	0.0 (0.0)	0.32 (0.2)	0.77 (0.63)
Hospital Days per Year, mean (SD)	1.8 (5.0)	1.6 (4.7)	3.7 (7.8)
Number of Medical Encounters[a] Per Year, n (%)			
0 to 10	25,142 (4%)	18,072 (14%)	1555 (2%)
10 to 30	188,564 (30%)	46,470 (36%)	11,662 (15%)
> 30	414,840 (66%)	64,542 (50%)	64,532 (83%)
Appointment With a Pulmonologist, n (%)	219,991 (35%)	72,287 (56%)	57,534 (74%)
Pulmonologist Referral to Imaging, n (%)[c]	18856 (3%)	7745 (6%)	8552 (11%)
All-Cause Hospitalizations Per Year, n (%)			
0	238,,847 (38%)	52,924 (41%)	23,325 (30%)
>0 and ≤1	232,562 (37%)	49,052 (38%)	21,770 (28%)
>1 and ≤2	75,425 (12%)	18,072 (14%)	13,217 (17%)
> 2	81,711 (13%)	10,327 (8%)	18,660 (24%)
Days in Hospital Per Year, n (%)			
0	238,847 (38%)	52,924 (41%)	23,325 (30%)
> 0 to 3	295,416 (47%)	56,797 (44%)	28,767 (37%)
> 3	94,282 (15%)	20,653 (16%)	24,880 (32%)
Patients on Oxygen Therapy, n (%)	1571 (0.25%)	1936 (1.5%)	5131 (6.6%)

[a]Medical encounters: all activities recorded in the database undertaken by patients regarding their health (this includes visits to the hospital, specialists, and written or telephone contact with a doctor). All medical encounters are counted individually regardless of whether they relate to the same issue on the same day. Encounters are not restricted to those related to COPD or CB only.
[b]Defined as hospital visits with primary diagnosis of ICD-10-CM code J43 or J44.
[c]Encounters of type "imaging" where the provider was a pulmonologist.

CB=chronic bronchitis; COPD=chronic obstructive pulmonary disease; SD=standard deviation

Figure 3. Five-Year Health Care Resource Use Among Cohorts
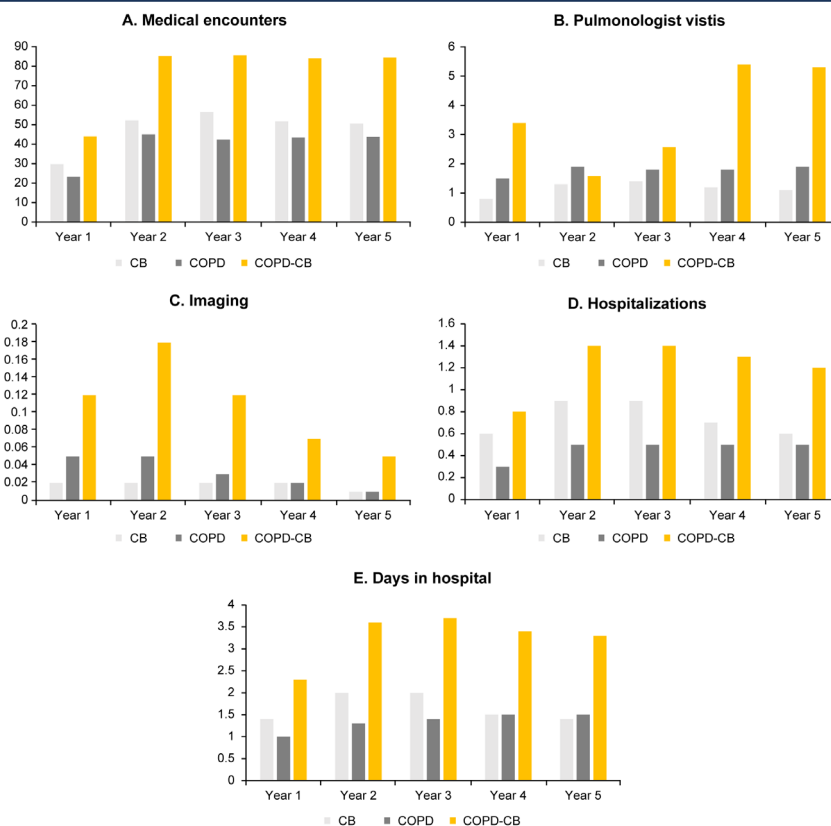
Number of (a) medical encounters; (b) pulmonologist visits; (c) imaging (referral by pulmonologist); (d) hospitalizations; and (e) days in hospital over 5-year follow-up shown.

CB=chronic bronchitis; COPD=chronic obstructive pulmonary disease

CB only or with both CB and COPD were women, whereas, men and women were of almost equal proportion in patients with COPD only. Although it is frequently reported that CB is more common in men than women,[24] some studies have shown that CB predominantly affects women, in line with our results.[25,26]

Treatment and HCRU burden are important in COPD, particularly as disease severity increases.[27-32] Patients with COPD often have multiple comorbidities, which can also affect the HCRU burden.[15] Compared to both the COPD cohort and the CB cohort, the COPD-CB cohort exhibited greater HCRU, including specialist visits. In addition, the COPD-CB cohort was exposed to a greater number of drug classes than the other cohorts (Table S2 and Figure S2 in the online supplement), suggesting that multiple medications were tried to improve control of burdensome patient symptoms. The frequent medication class changes in the COPD-CB cohort suggest that a clear treatment pathway was not available. Most patients in the COPD-CB cohort fulfilled the criteria for CB diagnosis before COPD diagnosis, and while persistent cough and sputum symptoms may have driven health care contact and diagnosis more rapidly than other COPD symptoms, it also suggests that halting the progression of CB to COPD-CB could reduce future HCRU burden. This reflects what has been previously described in other studies on a smaller scale[33,34] and in a recent systematic review,[35] where CB increased all-cause and respiratory disease-related mortality; and was associated with additional decline in FEV_1.

Our results demonstrate the large HCRU burden for COPD-CB patients and confirm that most patients in this cohort initially had CB only, experiencing symptoms of cough and sputum which were reported in health care encounters, highlighting the importance of finding efficacious early interventions. This may also reflect the presence of cough and sputum symptoms driving patients to seek medical attention which then leads to the diagnosis of COPD. Interestingly, the HCRU of patients with CB alone was comparable or higher than in patients with COPD alone. Currently, there is uncertainty for clinicians and investigators about how to manage patients who present with CB and/or COPD-like symptoms and normal spirometric measurements.[36] There have been suggestions to reintroduce the term "pre-COPD" to identify patients in whom spirometry is unable to detect airflow obstruction but who are at risk of subsequently developing COPD with a reduced FEV_1/FVC ratio.[37] Our study demonstrates that this severe progression path can be identified in the real world by asking patients whether they persistently experience symptoms of cough and sputum.

The longitudinal data presented here show that this patient population, across all cohorts, experiences a constant HCRU burden without clear improvement over time, and finding a treatment tailored to CB and/or COPD-CB would

be instrumental to reducing this burden. There remains a need to improve treatment available, both to improve symptom control and to address underlying causes. New targets investigated for CB and COPD include the CFTR,[7] interleukins (IL; IL-5, IL-4, IL-13, IL-33) or their receptors, and antithymic stromal lymphopoietin.[38,39]

A major strength of this study is that it is the first to report on CB and COPD in a broad, real-world U.S. population. The Optum® EHR database captures data from mostly commercially insured patients (44%), but also Medicaid, Medicare, and uninsured patients (12%, 12%, and 14%, respectively) at over 700 hospitals and 140,000 health care providers and contains data from over 113 million patients. These patients are distributed across the Midwest, Northeast, South, and West U.S. census regions, with the Midwest region over-represented as compared to U.S. census numbers. There are also some limitations in that patients >65 years of age are overrepresented compared to their proportion of the population. African American, Hispanic, and Asian patients are underrepresented when compared to their proportion of the U.S. population according to U.S. census data.[40]

The study has several limitations: HCRU and prescription data can be undercounted in Optum® EHR. However, as these data are likely missing at random, this limitation in the EHRs will affect all cohorts equally. The novel method of applying the classical definition of CB to EHRs to diagnose CB presents some limitations: first, the definition of CB was applied retrospectively, and second, because the CB cohort definition is a translation of the World Health Organization's definition adapted to the EHR format (i.e., clinical notes), there is the possibility of false positive diagnoses, e.g., some of patients diagnosed with CB may have had bronchiectasis instead, which is common in patients with COPD and CB and is also associated with high HCRU.[41,42] A review of symptoms in the Optum® EHR did not exclude negative descriptions (e.g., not detected, not confirmed, etc.). For a CB diagnosis, it was assumed that "symptoms for 2 consecutive 3-month periods" from a patient's perspective were the equivalent of symptoms reported at least 90 days apart and no more than 180 days apart, but they could possibly constitute 2 episodes of acute bronchitis over a 3-month period. However, this spacing was necessary to minimize the risk of solely capturing one acute episode that was managed with 2 encounters. Data on smoking status were often missing, so only those patients where there was clear evidence of never smoking were categorized as "never smokers." This group may, therefore, be underestimated, but this should affect all cohorts equally. Furthermore, the cause of CB remains unknown in those without a history of smoking or a diagnosis of COPD. Oxygen use was determined by a one-time listing of a Healthcare Common Procedure Coding System code and these data were limited in the dataset. Potential limitations also arise

from the real-world nature of the clinical notes of the EHRs. For example, imaging may have been ordered but may not have been documented in the medical note as being ordered by a pulmonologist. Furthermore, any medical encounter on the same day is labeled as an individual medical encounter, i.e., there is no grouping in relation to a particular event or query, therefore, medical encounter data may appear higher than expected. More complete spirometric data could have provided more context for diagnosis within the COPD cohort and reduced the likelihood of misclassification. Furthermore, spirometry data would have enabled more detailed characterization of the CB cohort and especially the COPD-CB cohort which has the highest HCRU.

Notwithstanding the limitations of this study, these results demonstrate the prevalence of CB, both on its own and in patients with COPD. Furthermore, our study highlights the importance of a CB diagnosis, not only for patients with COPD where the disease may be more severe with worse clinical outcomes, but also for those patients with CB only, who experience a high burden of disease and have few treatment options. Patients with COPD, with or without CB, have many unmet needs. Besides the need to improve therapies available to patients, it is important to note that CB is not just a subtype of COPD but rather CB and COPD are 2 separate conditions that can overlap. There is a pressing requirement to detect CB at an earlier stage, before the onset of airway obstruction, to potentially alter the course of disease progression.

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Author contributions:

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Declaration of Interests

References

1. 1. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease, 2022 report. GOLD website. Published 2022. Accessed September 2024. https://goldcopd.org/wp-content/uploads/2021/12/GOLD-REPORT-2022-v1.1-22Nov2021_WMV.pdf

2. Kim V, Criner GJ. The chronic bronchitis phenotype in chronic obstructive pulmonary disease: features and implications. *Curr Opin Pulm Med.* 2015;21(2):133-141. https://doi.org/10.1097/MCP.0000000000000145

3. Fortis S, Shannon ZK, Garcia CJ, et al. Association of nonobstructive chronic bronchitis with all-cause mortality: a systematic literature review and meta-analysis. *Chest.* 2022;162(1):92-100. https://doi.org/10.1016/j.chest.2022.02.003

4. Wu F, Fan H, Liu J, et al. Association between non-obstructive chronic bronchitis and incident chronic obstructive pulmonary disease and all-cause mortality: a systematic review and meta-analysis. *Front Med.* 2022;8:805192. https://doi.org/10.3389/fmed.2021.805192

5. Kim V, Han MK, Vance GB, et al. The chronic bronchitic phenotype of COPD: an analysis of the COPDGene study. *Chest.* 2011;140(3):626-633. https://doi.org/10.1378/chest.10-2948

6. Fabbri LM, Celli BR, Agustí A, et al. COPD and multimorbidity: recognising and addressing a syndemic occurrence. *Lancet Respir Med.* 2023;11(1):1020-1034. https://doi.org/10.1016/S2213-2600(23)00261-8

7. Martinez FJ, Criner GJ, Gessner C, et al. Icenticaftor, a CFTR potentiator, in COPD: a multicenter, parallel-group, double-blind clinical trial. *Am J Respir Crit Care Med.* 2023;208(4):417-427. https://doi.org/10.1164/rccm.202303-0458OC

8. Dransfield MT, Wilhelm AM, Flanagan B, et al. Acquired cystic fibrosis transmembrane conductance regulator dysfunction in the lower airways in COPD. *Chest.* 2013;144(2):498-506. https://doi.org/10.1378/chest.13-0274

9. Burke H, Wilkinson TMA. Unravelling the mechanisms driving multimorbidity in COPD to develop holistic approaches to patient-centred care. *Eur Respir Rev.* 2021;30(160):210041. https://doi.org/10.1183/16000617.0041-2021

10. Miravitlles M, Criner GJ, Mall MA, et al. Potential systemic effects of acquired CFTR dysfunction in COPD. *Respir Med.* 2024;221:107499. https://doi.org/10.1016/j.rmed.2023.107499

11. National Archives, Code of Federal Regulations (CFR). 45 CFR 164.514(b)(1)-Security and privacy. Electronic CFR website. Published December 2020. Updated February 2025. Accessed September 2024. https://www.ecfr.gov/current/title-45/subtitle-A/subchapter-C/part-164

12. U.S. Department of Health and Human Services. Guidance regarding methods for de-identification of protected health information in accordance with the health insurance portability and accountability act (HIPAA) privacy rule. Published November 26, 2012. Accessed September 2024. https://www.hhs.gov/sites/default/files/ocr/privacy/hipaa/understanding/coveredentities/De-identification/hhs_deid_guidance.pdf

13. U.S. Department of Health and Human Services (HHS). 45 CFR 46. HHS website. Published 2018. Accessed September 2024. https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/index.html

14. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault J-C. Lung volumes and forced ventilatory flows. *Eur Respir J.* 1993;6(Suppl 16):5-40. https://doi.org/10.1183/09041950.005s1693

15. Krishnan JK, Martinez FJ, Altman P, et al. Multimorbidities in COPD are associated with increased exacerbations and health care resource utilization in real-world patients from a U.S. database. *Chronic Obstr Pulm Dis.* 2024;11(5):472-481. https://doi.org/10.15326/jcopdf.2024.0515

16. Raju SV, Solomon GM, Dransfield MT, Rowe SM. Acquired cystic fibrosis transmembrane conductance regulator dysfunction in chronic bronchitis and other diseases of mucus clearance. *Clin Chest Med.* 2016;37(1):147-158. https://doi.org/10.1016/j.ccm.2015.11.003

17. Zhang J, Wang Y, Jiang X, Chan HC. Cystic fibrosis transmembrane conductance regulator-emerging regulator of cancer. *Cell Mol Life Sci.* 2018;75(10):1737-1756. https://doi.org/10.1007/s00018-018-2755-6

18. de Oca MM, Halbert RJ, Lopez MV, et al. The chronic bronchitis phenotype in subjects with and without COPD: the PLATINO study. *Eur Respir J.* 2012;40(1):28-36. https://doi.org/10.1183/09031936.00141611

19. Kim V, Crapo J, Zhao H, et al. Comparison between an alternative and the classic definition of chronic bronchitis in COPDGene. *Ann Am Thorac Soc.* 2015;12(3):332-339. https://doi.org/10.1513/AnnalsATS.201411-518OC

20. Bali V, Turzhitsky V, Schelfhout J, et al. Machine learning to identify chronic cough from administrative claims data. *Sci Rep.* 2024;14:2449. https://doi.org/10.1038/s41598-024-51522-9

21. Chu SH, Wan ES, Cho MH, et al. An independently validated, portable algorithm for the rapid identification of COPD patients using electronic health records. *Sci Rep.* 2021;11:19959. https://doi.org/10.1038/s41598-021-98719-w

22. Choi JY, Yoon HK, Shin KC, et al. CAT score and SGRQ definitions of chronic bronchitis as an alternative to the classical definition. *Int J Chron Obstruct Pulmon Dis.* 2019;14:3043-3052. https://doi.org/10.2147/COPD.S228307

23. Young KA, Strand M, Ragland MF, et al. Pulmonary subtypes exhibit differential global initiative for chronic obstructive lung disease spirometry stage progression: the COPDGene® Study. *Chronic Obstr Pulm Dis.* 2019;6(5):414-429. https://doi.org/10.15326/jcopdf.6.5.2019.0155

24. Lu M, Yao W, Zhong N, et al. Chronic obstructive pulmonary disease in the absence of chronic bronchitis in China. *Respirology.* 2010;15(7):1072-1078. https://doi.org/10.1111/j.1440-1843.2010.01817.x

25. Ehrlich RI, White N, Norman R, et al. Predictors of chronic bronchitis in South African adults. *Int J Tuberc Lung Dis.* 2004;8(3):369-376.

26. Han MK, Postma D, Mannino DM, et al. Gender and chronic obstructive pulmonary disease: why it matters. *Am J Respir Crit Care Med.* 2007;176(12):1179-1184. https://doi.org/10.1164/rccm.200704-553CC

27. Sav A, Thomas ST, Cardona M, Michaleff ZA, Dobler CC. Treatment burden discussion in clinical encounters: priorities of COPD patients, carers and physicians. *Int J Chron Obstruct Pulmon Dis.* 2022;17:1929-1942. https://doi.org/10.2147/COPD.S366412

28. Negewo NA, Gibson PG, Wark PA, Simpson JL, McDonald VM. Treatment burden, clinical outcomes, and comorbidities in COPD: an examination of the utility of medication regimen complexity index in COPD. *Int J Chron Obstruct Pulmon Dis.* 2017;12:2929-2942. https://doi.org/10.2147/COPD.S136256

29. de Nigris E, Haughney J, Lee AJ, et al. Short- and long-term impact of prior chronic obstructive pulmonary disease exacerbations on healthcare resource utilization and related costs: an observational study (SHERLOCK). *COPD.* 2023;20(1):92-100. https://doi.org/10.1080/15412555.2022.2136065

30. Iheanacho I, Zhang S, King D, Rizzo M, Ismaila AS. Economic burden of chronic obstructive pulmonary disease (COPD): a systematic literature review. *Int J Chron Obstruct Pulmon Dis.* 2020;15:439-460. https://doi.org/10.2147/COPD.S234942

31. Løkke A, Lange P, Lykkegaard J, et al. Economic burden of COPD by disease severity – a nationwide cohort study in Denmark. *Int J Chron Obstruct Pulmon Dis.* 2021;16:603-613. https://doi.org/10.2147/COPD.S295388

32. Wallace AE, Kaila S, Bayer V, et al. Health care resource utilization and exacerbation rates in patients with COPD stratified by disease severity in a commercially insured population. *J Manag Care Spec Pharm.* 2019;25(2):205-217. https://doi.org/10.18553/jmcp.2019.25.2.205

33. de Marco R, Accordini S, Cerveri I, et al. Incidence of chronic obstructive pulmonary disease in a cohort of young adults according to the presence of chronic cough and phlegm. *Am J Respir Crit Care Med.* 2007;175(1):32-39. https://doi.org/10.1164/rccm.200603-381OC

34. Guerra S, Sherrill DL, Venker C, Ceccato CM, Halonen M, Martinez FD. Chronic bronchitis before age 50 years predicts incident airflow limitation and mortality risk. *Thorax.* 2009;64(10):894-900. https://doi.org/10.1136/thx.2008.110619

35. Wu F, Fan H, Liu J, et al. Association between non-obstructive chronic bronchitis and incident chronic obstructive pulmonary disease and all-cause mortality: a systematic review and meta-analysis. *Front Med (Lausanne).* 2021;8:805192. https://doi.org/10.3389/fmed.2021.805192

36. Woodruff PG, Lazarus SC. Long-term sequelae of nonobstructive chronic bronchitis-is airflow obstruction important? *JAMA Intern Med.* 2020;180(5):686-687. https://doi.org/10.1001/jamainternmed.2019.7280

37. Han MK, Agusti A, Celli BR, et al. From GOLD 0 to pre-COPD. *Am J Respir Crit Care Med.* 2021;203(4):414-423. https://doi.org/10.1164/rccm.202008-3328PP

38. Rabe KF, Celli BR, Wechsler ME, et al. Safety and efficacy of itepekimab in patients with moderate-to-severe COPD: a genetic association study and randomised, double-blind, phase 2a trial. *Lancet Respir Med.* 2021;9(11):1288-1298. https://doi.org/10.1016/S2213-2600(21)00167-3

39. Fieldes M, Bourguignon C, Assou S, et al. Targeted therapy in eosinophilic chronic obstructive pulmonary disease. *ERJ Open Res.* 2021;7(2):00437-2020. https://doi.org/10.1183/23120541.00437-2020

40. Optum. Data on file. Published 2023. Accessed 2024. Url not available.

41. Martinez-Garcia MA, Miravitlles M. Bronchiectasis in COPD patients: more than a comorbidity? *Int J Chron Obstruct Pulmon Dis.* 2017;12:1401-1411. https://doi.org/10.2147/COPD.S132961

42. Feliciano J, Tkacz J, Lewing B, et al. Incremental health care utilization and costs associated with bronchiectasis in a Medicare population. *Chest.* 2023;164(4):A4933-A4934. https://doi.org/10.1016/j.chest.2023.07.3198