ORIGINAL ARTICLE

Multicenter Study Comparing Case Definitions Used to Identify Patients with Chronic Obstructive Pulmonary Disease

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Abstract

Rationale: Clinical trials in chronic obstructive pulmonary disease (COPD) usually require evidence of airflow obstruction and clinical risk factors. International Classification of Diseases, Ninth Revision (ICD-9) diagnosis codes or patient-reported physician diagnoses are often used for epidemiologic studies and performance improvement programs.

Objectives: To evaluate agreement between these case definitions for COPD and to assess the comparability of study populations identified as having COPD not using the clinical trial reference standard.

Methods: We recruited patients from the COPD Outcomes-based Network for Clinical Effectiveness and Research Translation multicenter clinical registry in a cross-sectional study. Demographics, clinical, and post-bronchodilator spirometry data were collected at an in-person study visit. The kappa statistic (κ) was used to evaluate agreement. A multivariable logistic regression model was used to identify patient characteristics associated with meeting the trial reference standard.

Measurements and Main Results: A total of 998 (82.8%) of 1,206 study participants met at least one case definition for COPD (of the 998: 91% using ICD-9 codes, 73% using patient-reported physician diagnosis, 56% using trial reference standard); agreement between case definitions was poor (κ = 0.20–0.26). Lack of airflow obstruction was the principal (89%) reason patients identified as having COPD did not meet the trial reference standard. Patients who were black (vs. white), obese (vs. normal weight), or had depression (vs. not) were less likely to meet the trial reference standard (odds ratio [95% CI], 0.37 [0.26–0.53], 0.51 [0.34–0.75], 0.53 [0.40–0.71], respectively).

Conclusions: Findings highlight concerns about the applicability of findings in clinical trials to patients meeting other case definitions for COPD.

Keywords: COPD; spirometry; ICD-9-CM; comparative effectiveness; case definitions

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At a Glance Commentary

Scientific Knowledge on the Subject: Airflow obstruction plus clinical risk factors for chronic obstructive pulmonary disease (COPD) are used as eligibility criteria for most clinical trials in COPD. By contrast, International Classification of Diseases, Ninth Revision diagnosis codes and patient-reported physician diagnoses are used to identify patients for performance improvement programs and epidemiologic studies.

What This Study Adds to the Field: This multicenter study found poor agreement among the three different methods of identifying patients with COPD. The findings raise concerns about the comparability of studies using different COPD case definitions and the applicability of findings in COPD clinical trials to patients identified using International Classification of Diseases, Ninth Revision diagnosis codes and patient-reported physician diagnoses.

Chronic obstructive pulmonary disease (COPD), the third leading cause of death in the United States, is estimated to affect between 12 and 24 million individuals, resulting in nearly $50 billion in healthcare expenditures (1). Worldwide, COPD represents the fourth leading cause of death with an estimated prevalence of 64 million and the 13th highest burden when based on disability-adjusted life-years (2). According to the Global Initiative for Chronic Obstructive Lung Disease guidelines, the diagnosis of COPD requires the presence of post-bronchodilator airflow limitation plus clinical risk factors (e.g., smoking) (2). This guideline definition is the cornerstone of eligibility criteria for most clinical trials in COPD (3). However, epidemiologists, health services researchers, clinicians, and payers often rely on COPD-related International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9) diagnosis codes, or on patient-reported physician diagnosis to identify patients with COPD (4).

Surprisingly, there is a paucity of data about the level of agreement between these three case definitions for COPD, the characteristics of patients included in each case definition, and their implications for research and policy. Such data are needed to interpret studies using different COPD case definitions and to assess the applicability of findings in clinical trials to populations identified using other COPD case definitions. To address this gap in knowledge, we conducted a cross-sectional study using data from the multicenter National Heart, Lung, and Blood Institute–sponsored COPD Outcomes-based Network for Clinical Effectiveness and Research Translation (CONCERT) DataHub. Preliminary results of this study have been previously reported as an abstract (5).

Methods

Study Design and Subject Recruitment

This cross-sectional study was one of the primary goals of the CONCERT–Comparative Effectiveness Research (CONCERT-CER) program funded by the National Heart, Lung and Blood Institute (RC2 HL101618) (6). Clinical data from healthcare encounters between 2006 and 2010 at eight US clinical centers (four academic medical centers, two community medical centers, and two integrated health systems) contributed to the DataHub. The CONCERT DataHub includes more than 220,000 patients age 40 years or older who have clinical data suggesting COPD based on ICD-9 diagnosis codes, pulmonary function data, or medication lists. See the online supplement for more information about the DataHub.

A probability sample of patients in the CONCERT DataHub was contacted to complete a single in-person study visit. Written informed consent was obtained from all patients for the study visit. We sought to enroll 1,200 participants to complete in-person study visits. Patients were excluded from the current study if they were unable to complete the data collection procedures described below.

Data Collection and Definitions

An interviewer-administered questionnaire was used to collect demographics, self-reported comorbid conditions, and other clinical information. Measures of height, weight, and modified Borg dyspnea score (7) were obtained. Post-bronchodilator spirometry and 6-minute-walk distance (6MWD) were performed and interpreted per the American Thoracic Society standards (8, 9). The proportion of patients with a 6MWD less than 350 m was calculated, because a walk distance below this threshold is associated with increased mortality (10). We examined three COPD case definitions:

1. ICD-9 diagnosis codes: patients with any of the ICD-9 codes commonly used to identify patients with COPD (11, 12), in a primary or secondary position in inpatient or outpatient encounters.
2. Patient-reported physician diagnosis: patients were asked questions used in the National Health and Nutrition Examination Survey (13): "Has a physician ever said that you have or had COPD?", "Has a physician ever said that you have or had emphysema?" and "Has a physician ever said that you have or had chronic bronchitis?" A positive answer to any of these questions defined patient-reported physician diagnosis of COPD.
3. Clinical trial reference standard: post-bronchodilator FEV_1/FVC ratio less than 70% plus history of smoking or α_1-antitrypsin deficiency (2). We used a fixed FEV_1/FVC ratio less than 70% because it is most often used in clinical trials (14, 15).

Statistical Analysis

The kappa statistic (κ) was used to determine the level of agreement between the different case definitions (16). Bivariate analyses used chi-square or Fisher exact tests, where appropriate. A multivariate logistic regression model was used to identify characteristics of patients associated with meeting the clinical trial reference standard. The Hosmer-Lemeshow test was used to assess the fit of the logistic regression model. A two-sided α less than 0.05 was considered statistically significant. Statistical analysis was performed using SAS/STAT v9.3 software (SAS Institute Inc., Cary, NC).

Results

Demographics and Clinical Characteristics

A total of 1,206 patients completed in-person visits (36% of patients in the DataHub who we attempted to contact); of these, 208 were ineligible (87 were unable to perform spirometry meeting the American Thoracic Society quality criteria; 121 patients did not meet any of the three COPD case definitions). Of the 998 eligible participants, most were male, white, and overweight or obese (Table 1). The most prevalent

Table 1. Demographic Characteristics of Patients Who Met and Did Not Meet the Clinical Trial Reference Standard

Patient Demographics	Total Sample (*n = 998*)	Meets Clinical Trial Reference Standard		*P* Value
		Yes* (*n = 560*)	No† (*n = 438*)	
Age, mean (SD)	67 (11)	68 (10)	66 (11)	0.0003
Female, %	43	40	48	0.01
Race, %				
White	73	79	66	<0.0001
Black	22	17	27	
Other	5	4	7	
Hispanic, %	2	1	3	0.01
Education, %				
High school/GED or less	37	41	33	0.003
Some college	40	40	40	
College degree+	23	19	27	
Income, %				
<30,000	46	45	48	0.26
30,000–50,000	27	30	24	
50,001–75,000	15	13	16	
>75,000	12	11	12	
Body mass index, kg/m^2, %				
<18.5 (underweight)	3	5	0.9	<0.0001
18.5–24.9 (normal)	22	25	17	
25–29.9 (overweight)	30	33	26	
⩾30 (obese)	45	37	56	
Smoking status, %				
Current	31	33	30	<0.0001
Former	57	67	43	
Never	12	0	27	

Younger, nonwhite, obese, women, those with higher education, and never smokers were less likely to meet the trial reference standard. Income was missing in 12% (11% and 13%) and body mass index was missing in 0.6% (0.5% and 0.7%) of those who met and did not meet the trial reference standard, respectively.
*(*A* + *D* + *E* + *G*) and †(*B* + *C* + *F*) in Figure 2.

comorbidities were hypertension (66%), depression (42%), and arthritis (36%) (Table 2). About half reported dyspnea at rest and had a 6MWD less than 350 m.

Agreement among Case Definitions

Most patients (84%) had multiple encounters; over half (54%) of patients were identified by more than one ICD-9 code and 17% by three or more ICD-9 codes at different encounters (Figure 1). The most common ICD-9 codes that identified patients as having COPD were 496.x (Chronic airway obstruction NOS, 82%), 491.x (Chronic bronchitis, 31%), and 492.x (Emphysema, 23%).

Nearly all participants (91%) had a diagnosis of COPD based on ICD-9 codes, three-quarters (73%) had a patient-reported physician diagnosis of COPD, and just over half (56%) met the clinical trial reference standard (Figure 2). Only 57% (520 of 909) and 61% (442 of 726) of patients who met the ICD-9 and patient-reported physician diagnosis case definitions, respectively, met the clinical trial reference standard. The level of agreement, κ, between all three COPD case definitions was poor (κ = 0.20–0.25). Only 42% of patients met all three case definitions (Figure 2). We did not observe differences in the distribution of ICD-9 codes between patients who met and did not meet the clinical trial reference standard, but were identified as having COPD using the other two case definitions (*see* Figure E2 and Table E1 in the online supplement).

Characteristics Associated with Meeting versus Not Meeting Clinical Trial Reference Standard

Patients who met the clinical trial reference standard (n = 438; 44%), were slightly older, more likely male, white, non-Hispanic, and had a normal weight or were underweight (Table 1). They were also more likely to have a formal education level of high school or less, and to be a current or former smoker compared with those who did not meet the clinical trial reference standard. Lack of airflow obstruction (FEV_1/FVC <70%, rather than an absence of a history of smoking or α_1-antitrypsin deficiency) was the most common reason (89%) that patients did not meet the trial reference standard. Several comorbid conditions were less common in patients who met the trial reference standard: hypertension, heart failure, depression, arthritis, and diabetes (Table 2). Cancer was more common in patients who met the reference standard. 6MWD (% who walked <350 m) was similar between groups.

In multivariable analyses, patients who were black (vs. white), had a college or more formal education (vs. high school or less), were obese (vs. normal weight), and had depression or diabetes were significantly less likely to meet the clinical trial reference standard (Table 3). In contrast, patients who were underweight (vs. normal weight) or had cancer were more likely to meet the clinical trial reference standard.

Discussion

In this multicenter study of nearly 1,000 individuals in the United States, we found poor agreement between three case definitions commonly used to identify patients with COPD: ICD-9 diagnosis codes,

Table 2. Clinical Characteristics of Patients Who Met and Did Not Meet the Clinical Trial Reference Standard

Characteristic	Total Sample (*n* = 998)	Clinical Trial Reference Standard		*P* Value
		Yes* (*n* = 560)	No† (*n* = 438)	
Comorbid conditions, %				
Cardiovascular disease	76	74	78	0.15
Hypertension	66	63	69	0.03
Heart failure	18	16	22	0.01
Coronary artery disease	23	22	24	0.66
Myocardial infarction	19	18	20	0.43
Stroke	15	14	15	0.95
Depression	42	36	50	<0.0001
Arthritis	36	33	41	0.006
Diabetes	28	22	34	<0.0001
Cancer history	23	26	19	0.02
Anemia	28	26	30	0.17
Kidney disease	20	18	21	0.30
Dementia	2	2	3	0.15
Dyspnea at rest (Borg), %				
0, no dyspnea	52	54	50	0.02
0.5–2, slight	38	38	37	
⩾3, moderate to very severe	10	7	13	
Spirometry, post-bronchodilator, %				
FEV_1/FVC <70%	61	100	11	<0.0001
FEV_1 <80% predicted	72	86	55	<0.0001
6-minute-walk distance, %				
Distance walked <350 m	53	52	54	0.67

Patients who met the trial reference standard are more likely to have airflow obstruction by spirometry but report being less dyspneic. Patients who met the reference standard also have different prevalence of comorbidities. For example, they are more likely to have hypertension, heart failure, and depression. Data for 6-minute-walk distance missing in 9% patients (9% and 10%) and dyspnea scores missing in 8% patients (8% and 9%) in those who met and did not meet the clinical trial reference standard, respectively.
*(*A* + *D* + *E* + *G*) and †(*B* + *C* + *F*) in Figure 2.

patient-reported physician diagnosis, and the clinical trial reference standard. These three case definitions identify overlapping, but largely different patient populations. Only 42% of patients were identified as having COPD by all three methods. Several demographic (race, education, body-mass index) and comorbidity (depression, diabetes, cancer) characteristics significantly differed between patients who met versus did not meet the trial reference standard.

Previous studies have reported that patients with COPD identified using ICD-9 diagnosis codes or patient-reported physician diagnosis may not have airflow obstruction on spirometry (17–21). Moreover, spirometry results may not available at the point of care. For example, we previously demonstrated that results of spirometry are available for only about one in five patients hospitalized for a COPD exacerbation (20). A study in five Latin American cities found that only 36% of patients who reported a physician diagnosis of COPD had airflow obstruction on spirometry (21). The current report adds to this existing literature by concurrently examining agreement between three case definitions (physician diagnosis based on ICD-9 codes, patient-reported physician diagnosis, clinical trial reference standard) in a large patient population across the United States. The poor agreement between the case definitions (κ = 0.20–0.25) raises concerns about the comparability of studies using different approaches to identifying patients with COPD.

A possible explanation for the low level of agreement is misdiagnosis of COPD. Overdiagnosis of COPD has been well documented in previous studies (22–24), probably because many patients with a clinical diagnosis of COPD never undergo

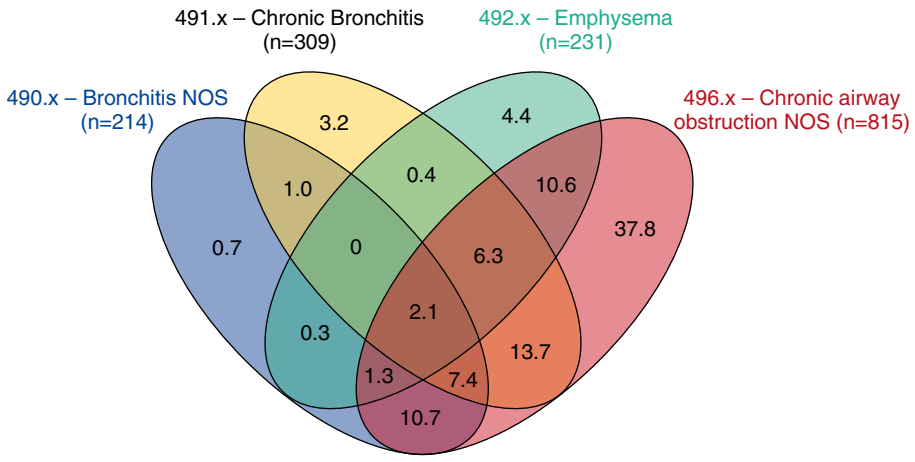

Figure 1. Percentage of participants identified by each International Classification of Diseases, Ninth Revision (ICD-9) code (n = 909). Most patients (84%) had multiple encounters, and ICD-9 codes may have varied across these encounters. A total of 54% of patients were identified by more than one ICD-9 code and 17% by three or more ICD-9 codes.

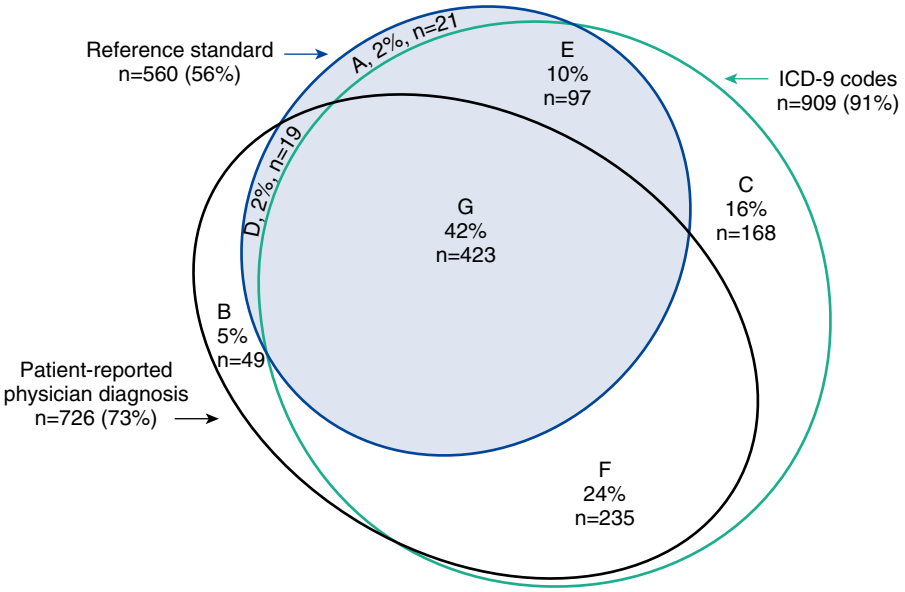

Figure 2. Groups identified as having chronic obstructive pulmonary disease by the different methods (total n = 998). In this study population, 56% met the clinical trial reference standard (*A* + *D* + *E* + *G*), whereas 44% did not (*B* + *C* + *F*). Only 42% met all three case definitions (*G*). Overall there was poor agreement between the case definitions for chronic obstructive pulmonary disease: (*1*) clinical trial reference standard (*A* + *D* + *E* + *G*) versus patient-reported physician diagnosis (*B* + *D* + *F* + *G*), κ (95% confidence interval) = 0.26 (0.20–0.31); (*2*) clinical trial reference standard versus International Classification of Diseases, Ninth Revision (ICD-9) codes (*C* + *E* + *F* + *G*), κ = 0.20 (0.15–0.24); and (*3*) patient-reported physician diagnosis versus ICD-9 codes, κ = 0.25 (0.15–0.31).

confirmatory spirometry (25). Results of our study indicate that overdiagnosis may be particularly common among patients who are black, have more than high-school education, are overweight or obese, and have depression or diabetes. Findings suggest the need for greater use of confirmatory spirometry, particularly in these populations.

Alternatively, patients who do not meet the clinical trial reference standard may have different COPD disease phenotype (26). Up to 40% of patients with radiographically evident emphysema do not have airflow obstruction when assessed using spirometry (27, 28). Moreover, the FEV_1/FVC ratio may fail to identify airflow obstruction in almost 10% of patients with mixed obstructive and restrictive pulmonary disease (29). These findings suggest the need for better characterization of phenotypes of COPD using lung volume measurements, diffusion capacity, and radiographic evaluation in patients with appropriate clinical findings for COPD but a normal or increased FEV_1/FVC ratio.

Our observations raise the question of the applicability of findings from clinical trials (which use the trial reference standard) to populations identified as having COPD using other case definitions and vice versa. For example, only about 60% of patients with COPD on the basis of ICD-9 diagnosis codes met the clinical trial reference standard. It is therefore unclear if the balance of benefits and risks of therapies observed in research populations enrolled in clinical trials are also seen in patients with COPD identified on the basis of ICD-9 codes or a patient-report of physician diagnosis in typical clinical settings.

Results of the current study therefore raise concerns about the appropriateness of performance improvement initiatives (which generally rely on administrative data, such as ICD-9 codes) to increase use of medications or other care paradigms that were established in clinical trial populations. In other words, quality improvement initiatives that seek to increase use of COPD guideline-recommended care (e.g., use of long-acting bronchodilators or pulmonary rehabilitation) in populations identified on the basis of ICD-9 codes alone (i.e., without confirmation of COPD diagnosis using spirometry and clinical risk factors) may or may not offer the benefits observed in clinical trials. Additionally, findings in this report suggest that epidemiology studies that rely exclusively on patient-report of a physician diagnosis may not accurately quantify the prevalence, risk factors, or prognosis of patients with COPD with airflow obstruction, given that only about 60% of

Table 3. Characteristics Associated with Meeting the Clinical Trial Reference Standard

Characteristics	Odds Ratio (95% CI)
Race (vs. white)	
Black	0.37 (0.26–0.53)*
Other	0.52 (0.27–1.00)
Education (vs. high school or less)	
College/professional degree	0.38 (0.26–0.56)*
Some college	0.68 (1.06–2.03)*
BMI, kg/m^2 (vs. normal)	
<18.5 (underweight)	4.00 (1.27–12.50)*
25–29.99 (overweight)	0.87 (0.58–1.30)
⩾30 (obese)	0.51 (0.35–0.75)*
Depression (yes vs. no)	0.53 (0.40–0.71)*
Diabetes (yes vs. no)	0.67 (0.48–0.93)*
Cancer (yes vs. no)	1.47 (1.05–2.08)*

Definition of abbreviations: BMI = body mass index; CI = confidence interval.
Clinical trial reference standard (*A* + *D* + *E* + *G*) versus others (*B* + *C* + *F*) in Figure 2. Multivariable logistic regression model that included characteristics listed in Tables 1 and 2 (characteristics significantly associated with meeting the trial reference standard). Results indicate that patients who are black (vs. white), with college or higher (vs. high school or less) education, obese (vs. normal weight), with depression, or diabetes are less likely to meet the trial reference standard. Patients with a history of cancer and underweight patients (vs. normal weight) are more likely to meet the trial reference standard. Hosmer-Lemeshow goodness-of-fit test (*P* value = 0.17) demonstrates adequate model fit.
*$P < 0.05$.

patients who reported a physician diagnosis of COPD met the clinical trial reference standard. Our findings provide justification for including measurements of airflow obstruction by spirometry in epidemiologic and health services research studies.

Patients who met and did not meet the clinical trial reference standard had a similar distribution of ICD-9 codes. Also, results of a sensitivity analysis using a post-bronchodilator FEV_1/FVC less than lower limit of normal in the clinical trial reference standard (rather than a fixed FEV_1/FVC ratio $<$70%) indicate limited overlap between case definitions that use spirometry-confirmed airflow obstruction, ICD-9 diagnosis codes, and patient-reported COPD diagnosis (*see* Figure E1B) (30). These findings indicate that it was not the selection of ICD-9 codes or the fixed ratio definition of airflow obstruction that accounted for the low level of agreement between the different case definitions.

Our study has multiple strengths. To our knowledge, this is the first study to concurrently examine the clinical trial reference standard, ICD-9 codes, and patient-reported physician diagnosis of COPD in the same population. Second, this multicenter study included nearly 1,000 patients at medical centers distributed across multiple regions of the United States. Third, our study identified specific demographic and clinical characteristics likely to be different in clinical trial populations and others identified as having COPD.

This study also has potential limitations. First, it is possible that patients who contributed data for the current report do not reflect the overall population of patients with COPD at each institution, because only about one-third of patients we attempted to contact completed the in-person study visit. Second, ICD-10 codes are likely to replace ICD-9 codes in the United States in October 2015 (31). Results of our study may or may not apply to case definitions that use ICD-10 codes for COPD. Third, although our study included eight institutions (four academic medical centers, two community medical centers, and two integrated health systems), it was not designed to compare differences in the performance characteristics of the various case definitions within and across the different types of healthcare institutions in the United States. The results of our study could be used to inform the development and conduct of adequately powered studies to answer such questions. Fourth, we did not have results of chest imaging studies (e.g., chest computed tomography), which could have helped to identify radiographic evidence of COPD in patients without evidence of airflow obstruction on spirometry. Last, our study used a cross-sectional design; longitudinal studies are needed to determine if functional outcomes (e.g., healthcare use, response to treatment) differ across the patient populations.

In summary, we found that in a multicenter US population of nearly 1,000 individuals, the clinical trial reference standard, ICD-9 codes, and patient-reported physician diagnosis identify three largely different populations of patients with COPD. Findings raise concerns about the comparability of studies using different COPD case definitions and the applicability of findings in COPD clinical trials to clinical populations identified by ICD-9 diagnosis codes and patient-reported physician diagnoses. It is unclear if the poor agreement between the different methods is caused by overdiagnosis or different COPD phenotypes (e.g., radiographic evidence of emphysema without concomitant airflow obstruction when measured using spirometry). Longitudinal studies are needed to determine if functional outcomes differ across the patient populations. ■

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