

Discriminative Accuracy of FEV₁:FVC Thresholds for COPD-Related Hospitalization and Mortality

Surya P. Bhatt, MD, MSPH; Pallavi P. Balte, PhD, MBBS; Joseph E. Schwartz, PhD; Patricia A. Cassano, PhD; David Couper, PhD; David R. Jacobs Jr, PhD; Ravi Kalhan, MD; George T. O'Connor, MD; Sachin Yende, MD; Jason L. Sanders, MD, PhD; Jason G. Umans, MD, PhD; Mark T. Dransfield, MD; Paulo H. Chaves, MD, PhD; Wendy B. White, PhD; Elizabeth C. Oelsner, MD, MPH

IMPORTANCE According to numerous current guidelines, the diagnosis of chronic obstructive pulmonary disease (COPD) requires a ratio of the forced expiratory volume in the first second to the forced vital capacity (FEV₁:FVC) of less than 0.70, yet this fixed threshold is based on expert opinion and remains controversial.

OBJECTIVE To determine the discriminative accuracy of various FEV₁:FVC fixed thresholds for predicting COPD-related hospitalization and mortality.

DESIGN, SETTING, AND PARTICIPANTS The National Heart, Lung, and Blood Institute (NHLBI) Pooled Cohorts Study harmonized and pooled data from 4 US general population-based cohorts (Atherosclerosis Risk in Communities Study; Cardiovascular Health Study; Health, Aging, and Body Composition Study; and Multi-Ethnic Study of Atherosclerosis). Participants aged 45 to 102 years were enrolled from 1987 to 2000 and received follow-up longitudinally through 2016.

EXPOSURES Presence of airflow obstruction, which was defined by a baseline FEV₁:FVC less than a range of fixed thresholds (0.75 to 0.65) or less than the lower limit of normal as defined by Global Lung Initiative reference equations (LLN).

MAIN OUTCOMES AND MEASURES The primary outcome was a composite of COPD hospitalization and COPD-related mortality, defined by adjudication or administrative criteria. The optimal fixed FEV₁:FVC threshold was defined by the best discrimination for these COPD-related events as indexed using the Harrell C statistic from unadjusted Cox proportional hazards models. Differences in C statistics were compared with respect to less than 0.70 and less than LLN thresholds using a nonparametric approach.

RESULTS Among 24 207 adults in the pooled cohort (mean [SD] age at enrollment, 63 [10.5] years; 12 990 [54%] women; 16 794 [69%] non-Hispanic white; 15 181 [63%] ever smokers), complete follow-up was available for 11 077 (77%) at 15 years. During a median follow-up of 15 years, 3925 participants experienced COPD-related events over 340 757 person-years of follow-up (incidence density rate, 11.5 per 1000 person-years), including 3563 COPD-related hospitalizations and 447 COPD-related deaths. With respect to discrimination of COPD-related events, the optimal fixed threshold (0.71; C statistic for optimal fixed threshold, 0.696) was not significantly different from the 0.70 threshold (difference, 0.001 [95% CI, -0.002 to 0.004]) but was more accurate than the LLN threshold (difference, 0.034 [95% CI, 0.028 to 0.041]). The 0.70 threshold provided optimal discrimination in the subgroup analysis of ever smokers and in adjusted models.

CONCLUSIONS AND RELEVANCE Defining airflow obstruction as FEV₁:FVC less than 0.70 provided discrimination of COPD-related hospitalization and mortality that was not significantly different or was more accurate than other fixed thresholds and the LLN. These results support the use of FEV₁:FVC less than 0.70 to identify individuals at risk of clinically significant COPD.

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Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Authors: Elizabeth C. Oelsner, MD, MPH, Division of General Medicine, Columbia University Medical Center, 630 W 168th St, Presbyterian Hospital Ninth Floor, Ste 105, New York, NY 10032 (eco7@cumc.columbia.edu); Surya P. Bhatt, MD, MSPH, Division of Pulmonary, Allergy, and Critical Care Medicine, University of Alabama at Birmingham, THH 422, 1720 Second Ave S, Birmingham, AL 35294 ([sbhatt@uabmc.edu](mailto:sbhhatt@uabmc.edu)).

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death worldwide.¹ In the United States, the prevalence of COPD is estimated to be 24 million, of which half remains undiagnosed.² Confusion regarding how to diagnose airflow obstruction, the major physiological feature of COPD, remains a major hurdle to improving care for patients with COPD.^{3,4}

Major respiratory society guidelines recommend diagnosing airflow obstruction when the ratio of the forced expiratory volume in the first second to the forced vital capacity (FEV₁:FVC) is less than a fixed threshold of 0.70.⁵⁻⁷ This approach is analogous to current clinical approaches to hypertension and diabetes, for which the identification of fixed disease thresholds has resulted in significant improvements in early detection and treatment.^{8,9} However, there remains no rigorous, population-based evidence to support the 0.70 threshold, which was set by expert opinion as the FEV₁:FVC threshold for defining clinically significant airflow obstruction.

The selection of a threshold for defining airflow obstruction has major implications for patient care and public health as the prevalence of airflow obstruction can vary by as much as 33% depending on which threshold is selected.¹⁰ To account for differences in FEV₁:FVC according to demographic factors, airflow obstruction can be defined by an FEV₁:FVC less than the lower limit of normal (LLN), which can be predicted from population-based normative data adjusted for age, sex, race, and height.^{11,12} However, in addition to pragmatic issues, concerns regarding the LLN approach include the premise that low absolute levels of lung function could be interpreted as normal in women, individuals who are not white, or elderly individuals.

The aim of this study was to determine the discriminative accuracy of various FEV₁:FVC fixed thresholds for predicting COPD-related hospitalization and mortality in a large, multiethnic, US general population-based sample of adults.

Methods

Study Population

The National Heart, Lung, and Blood Institute (NHLBI) Pooled Cohorts Study harmonized data from 9 US general population-based studies that collected spirometry data.¹³ The current report is limited to 4 cohorts that completed follow-up for COPD-related clinical events: the Atherosclerosis Risk in Communities Study (ARIC)¹⁴; Cardiovascular Health Study (CHS)¹⁵; Health, Aging and Body Composition Study (Health ABC)¹⁶; and the Multi-Ethnic Study of Atherosclerosis (MESA).¹⁷ CHS and Health ABC were designed to study older adults, whereas ARIC and MESA included both middle-aged and older adults (eTable 1 in the Supplement).¹⁷ All studies were approved by institutional review boards at participating institutions, and all participants provided written informed consent. Secondary data analysis for this work was approved by the Columbia University institutional review board.

Spirometry

Spirometry was performed using water-seal, dry-rolling seal or flow-sensing spirometers in accordance with the American

Key Points

Question What is the discriminative accuracy of various thresholds for the ratio of the forced expiratory volume in the first second to the forced vital capacity (FEV₁:FVC) for predicting chronic obstructive pulmonary disease (COPD)-related hospitalization and mortality?

Findings Among 24 207 participants from 4 US general population-based cohorts, the optimal fixed threshold for discriminating COPD-related events was 0.71 (C statistic for the optimal fixed threshold, 0.696). The discriminative accuracy of the 0.71 threshold was not significantly different than that of the 0.70 threshold (difference, 0.001) but it was more accurate than a lower-limit-of-normal threshold derived from population-based reference equations (difference between the optimal ratio threshold vs the model using the LLN threshold, 0.034). The 0.70 threshold provided optimal discrimination in a subgroup analysis of ever smokers and in adjusted models.

Meaning These results support the use of FEV₁:FVC less than 0.70 to identify individuals at risk of clinically significant COPD.

Thoracic Society criteria and quality controlled using 2005 criteria.¹⁸ To minimize measurement error, only participants with valid spirometry measurements were retained for analyses. Using the Global Lung Function Initiative approach, predicted values were calculated based on age, sex, race, and height, and the LLN for the FEV₁:FVC was defined as the 5th percentile of the distribution of the standard deviation (Z score).¹² National Health and Nutrition Examination Survey (NHANES) III spirometric reference equations were used in secondary analyses.¹¹

Outcomes

The primary outcome was a composite of COPD-related mortality and COPD-related hospitalization. A clinical events committee adjudicated COPD-related clinical events in Health ABC (hospitalizations and deaths) and CHS (deaths only). For hospitalizations and deaths in ARIC and MESA and for nonfatal hospitalizations in CHS, *International Classification of Diseases, Ninth Revision and International Classification of Diseases, Tenth Revision (ICD-9; ICD-10)* codes were used to classify COPD-related events (COPD: ICD-9, 496 and ICD-10, J44; chronic bronchitis: ICD-9, 490-491 and ICD-10 J40-J42; and emphysema: ICD-9, 492 and ICD-10, J43), following a previously validated protocol.¹³ The primary outcome, a COPD-related event, was defined as first hospitalization or death adjudicated as primarily or secondarily attributable to COPD or, if adjudication was lacking, events with COPD listed in any diagnosis field. In prior work in MESA, 82% of such administratively defined events were confirmed by a physician as evidence of clinical COPD.^{17,19}

In sensitivity analyses, COPD-related events were decomposed into COPD-related hospitalizations and COPD-related mortality. Also, only those events adjudicated or ICD coded as primarily caused by COPD were separately assessed. This end point was previously found to have a positive predictive value of 97% for physician-adjudicated exacerbations.¹⁹

Covariates

Age and sex were self-reported at enrollment. Race was self-reported according to fixed categories. The cohorts did not include a separate question regarding ethnicity, although MESA and Health ABC participants were asked to self-report as white, black, Asian/Pacific Islander, or Hispanic/Latino race/ethnicity (eTable 1 in the [Supplement](#)). Race/ethnicity was included as a covariate since this study aimed to evaluate discriminative accuracy in a multiethnic US general population setting, and race/ethnicity has been associated with lung function and COPD risk.²⁰ Current smoking status and pack-years were assessed at baseline by self-report, with biochemical verification in a subset.²¹ Lifetime smoking status was classified as never or ever by comparison of self-reported smoking status over all available examinations.¹³ Height was measured using standard methods. Due to the extensive quality control and harmonization efforts performed in the NHLBI Pooled Cohorts Study,¹³ missing covariate data at enrollment were rare (<1% [eFigure 1 in the [Supplement](#)]).

Statistical Analyses

The incidence density rate (IDR) of COPD-related events per 1000 person-years of follow-up was plotted by initial FEV₁:FVC, which was stratified by 0.01 increments over the range of 0.40 to 0.80, as was the IDR for all participants with FEV₁:FVC less than the LLN. The functional form of the relationship between the FEV₁:FVC and the IDR was explored by use of deviance statistics.

To evaluate the discriminative accuracy of different threshold-based definitions for airflow obstruction, airflow obstruction was dichotomized according to 11 fixed-ratio definitions (0.01 decrements over the interval of 0.75 to 0.65) and the LLN definition. Each fixed-threshold definition was modeled separately using Cox proportional hazards models. Time-to-event data were defined as time since measurement of FEV₁:FVC for each individual. Non-COPD mortality and loss to follow-up were treated as censoring events. The proportional hazards assumption was confirmed by Kaplan-Meier curves and residual plots.

The criterion for identifying the optimal fixed threshold was defined a priori as the threshold that generated the highest Harrell C statistic, which is a rank-correlation measure of the concordance between observed and predicted outcomes in the setting of censored survival data.^{22,23} The Harrell C statistic is an estimate of the area under the curve for a receiver operating characteristic curve that adjusts for censoring. C statistics were compared between the optimal ratio threshold model, the 0.70 threshold model, and the LLN threshold model. Formal statistical comparisons of C statistics (difference in C statistics from the model using the optimal ratio threshold vs the model using the 0.70 threshold and the difference in C statistics from the model using the optimal ratio threshold vs the model using the LLN threshold) were performed using a nonparametric approach to compare 2 correlated C statistics with right-censored survival outcomes.²⁴ Model fit was assessed by the Brier score.²⁵

The same unadjusted Cox proportional hazards models were used to calculate classification rates for each fixed thresh-

old and the LLN. Based on the sensitivity (true positive rate) and specificity (true negative rate) of each threshold, the Youden index (sensitivity + specificity - 1) was calculated.²⁶ In the primary analyses, which included a single binary predictor, maximizing the Harrell C statistic was equivalent to maximizing the Youden index. Because the Youden index assigns equal utility to sensitivity and specificity, which may not be consistent with clinical priorities, public health priorities, or both, a weighted Youden index was plotted across a range of potential relative weights for sensitivity and specificity.²⁷ Positive predictive value and negative predictive value were also calculated based on the observed event rates.

As sensitivity analyses, stratified models were performed according to smoking status and sex. Analyses were repeated for alternative outcome definitions: COPD-related hospitalization, COPD-related mortality, and events with adjudicated or ICD coded as primarily due to COPD. For comparison with the primary unadjusted approach, the incremental improvement in discrimination was evaluated when adding each ratio threshold to a Cox proportional hazards model adjusted for age at enrollment, sex, race/ethnicity, height, birth year, site, and cohort. Discrimination by the LLN-Global Lung Function Initiative was compared with that of the LLN-NHANES.

A 2-tailed alpha of .05 was considered significant for all analyses. Because of the potential for type 1 error due to multiple comparisons, findings for secondary analyses should be interpreted as exploratory. Beyond the exclusion of participants with missing or invalid spirometry and the censoring associated with loss to follow-up and non-COPD mortality, there were no missing data in the primary analyses. Secondary analyses that were stratified, adjusted for covariates, or both were restricted to complete case analyses. Analyses were completed using SAS, version 9.4 (Cary, North Carolina).

Results

Baseline Characteristics

After exclusions (eFigure 1 in the [Supplement](#)), there were 24 207 participants ([Table 1](#)). Mean age at spirometry was 63 years. Women constituted 54% of the cohort; 69% were non-Hispanic white, and 24% were black. Sixty-three percent were ever smokers and 37% were never smokers. Complete follow-up for COPD-related events was available for 97% of participants at 5 years, 85% at 10 years, and 77% at 15 years.

Prevalence of Airflow Obstruction

According to the LLN threshold, 3646 (15%) of participants had airflow obstruction (eFigure 2 in the [Supplement](#)). Compared with the LLN threshold, a fixed threshold of less than 0.66 yielded the most similar prevalence (3576 participants [15%]), but 540 (15%) of those with FEV₁:FVC less than 0.66 did not meet the LLN classification, and 610 (17%) of those meeting the LLN criterion were excluded.

There were 6261 (26%) participants with FEV₁:FVC less than 0.70, including all but 19 (0.5%) of participants meeting the LLN criterion (eFigure 2 in the [Supplement](#)). The IDR was

19.0 for participants with FEV₁:FVC less than 0.70 but greater than or equal to the LLN threshold. By comparison, the IDR was 17.2 for participants with FEV₁:FVC between 0.66 and 0.70 and less than the LLN threshold. A fixed ratio of less than 0.73 was required to capture 100% of participants below the LLN threshold (eTable 3 in the [Supplement](#)).

Incidence of COPD-Related Events

During a median follow-up of 15 years (interquartile range [IQR], 9 to 22), 3925 participants experienced COPD-related events over 340 757 person-years of follow-up (IDR, 11.5), including 3563 COPD-related hospitalizations (IDR, 10.5) and 447 COPD-related deaths (IDR, 1.3).

The IDR for COPD-related events was inversely related to the FEV₁:FVC (**Figure 1**). Initially, a cubic spline-smoothed curve, with smoothing parameter selected by the generalized cross-validation score, was used to describe the FEV₁:FVC and corresponding IDR relationship. The optimal functional form for the FEV₁:FVC and corresponding IDR relationship was a quadratic model over the interval (<0.40, 0.77) with a piecewise linear component over the interval (0.77, >0.80); this parametric model outperformed the cubic spline based on the deviance statistics for each. This suggested that participants with FEV₁:FVC of at least 0.77 had minimal COPD-related event risk; however, it did not indicate an inflection point over the remainder of the FEV₁:FVC range.

Discrimination of COPD-Related Events

In the primary analysis, the 0.71 threshold demonstrated the highest C statistic (0.696 [95% CI, 0.688 to 0.703]) (**Figure 2**). Discrimination by the 0.71 threshold was not significantly different than by the 0.70 threshold (difference, 0.001 [95% CI, -0.002 to 0.004]; *P* = .57), but was significantly more accurate than that of the LLN threshold (difference, 0.034 [95% CI, 0.028 to 0.041]; *P* < .001; **Table 2**). Taking all pairwise comparisons into account, C statistics were not significantly different vs the 0.70 threshold over the fixed threshold interval (0.70, 0.72) and were significantly more accurate than the LLN threshold over the fixed threshold interval (0.66, 0.74) (**Figure 2**). Brier scores were nominally lower for the LLN threshold (eTable 4 in the [Supplement](#)).

Sensitivity and Specificity for COPD-Related Events

The sensitivity for the LLN was 52%, and the specificity for the LLN was 89%, which approximated the results for a fixed 0.66 threshold (**Figure 3**). By comparison, for the 0.70 threshold, the sensitivity was 66%, and the specificity was 79%. Compared with the LLN, the weighted sum of sensitivity and specificity were greater for the 0.70 threshold under all conditions in which sensitivity was given equal or greater weight than specificity. The negative predictive value was at least 0.90 for fixed thresholds of 0.66 to 0.71, as well as for the LLN. The positive predictive value was 0.44 for the LLN threshold and 0.37 for the 0.70 threshold.

Sensitivity Analyses

In the majority of sensitivity analyses, as in the primary analysis, the C statistic for the optimal fixed threshold was not

Table 1. Baseline Characteristics

Total sample, No.	24 207
Total events follow-up, person-years, No.	340 757
Cohort	
ARIC	12 808 (52.9)
CHS	4814 (19.9)
Health ABC	2578 (10.7)
MESA	4007 (16.6)
Age, mean (SD), y	62.8 (10.5)
Age group, y	
45-55	6788 (28.0)
56-65	7827 (32.3)
66-75	6158 (25.4)
>75	3434 (14.2)
Men	11 217 (46.3)
Women	12 990 (53.7)
Body mass index, median (IQR) ^a	26.8 (24.0-30.3)
Race/ethnicity ^b	
Non-Hispanic white	16 794 (69.4)
Non-Hispanic black	5900 (24.4)
Hispanic/Latino	854 (3.5)
Asian/Pacific Islander	623 (2.6)
Other	36 (0.2)
Education status	
<High school	3124 (12.9)
High school	6663 (27.5)
Some college	3226 (13.3)
≥College	11 172 (46.2)
Lifetime current or former smoker	15 181 (62.7)
Pack-years in ever smokers, median (IQR)	22.3 (6.8, 40.5)
Medical history	
Hypertension ^c	13 303 (55.0)
Diabetes mellitus ^d	3404 (14.1)
Chronic obstructive pulmonary disease	2027 (8.4)
Coronary artery disease	1803 (7.5)
Asthma	1368 (5.7)
Baseline lung function, mean (SD)	
FEV ₁ percent predicted, %	92.4 (19.2)
FEV ₁ , L	2.5 (0.8)
FVC, L	3.4 (1.0)
FEV ₁ :FVC	0.73 (0.09)

Abbreviations: ARIC, Atherosclerosis Risk in Communities Study; CHS, Cardiovascular Health Study; FEV₁, forced expiratory volume in the first second; FVC, forced vital capacity; Health ABC, Health Aging and Body Composition; IQR, interquartile range; MESA, Multi-Ethnic Study of Atherosclerosis.

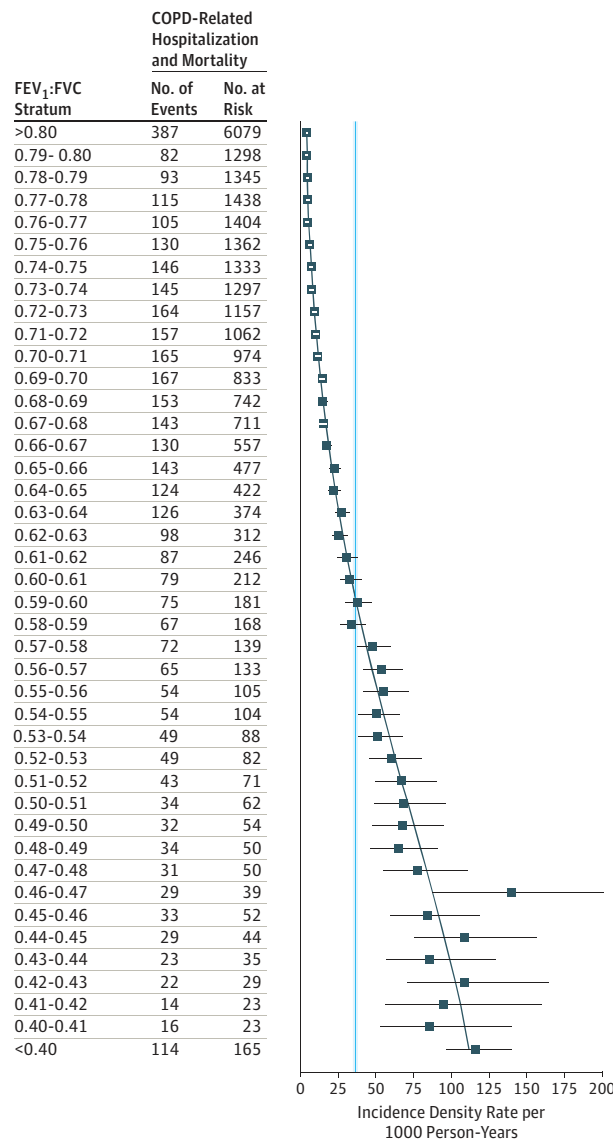
^a Calculated as weight in kilograms divided by height in meters squared.

^b Race was self-reported according to fixed, mutually exclusive categories that differed by cohort (ARIC: non-Hispanic white, non-Hispanic black, Asian Pacific Islander, or American Indian; CHS: non-Hispanic white, non-Hispanic black, Asian Pacific Islander, American Indian, or Other; Health ABC and MESA: non-Hispanic white, non-Hispanic black, Hispanic, or Asian [none asked about ethnicity at enrollment]). *Other* specifically includes the category of American Indian in ARIC and CHS.

^c Self-reported hypertension or systolic blood pressure (≥140 mm Hg) or diastolic blood pressure (≥90 mm Hg) or use of antihypertensive medications.

^d Self-reported diabetes or elevated fasting blood glucose levels (≥126 mg/dL) or use of oral hypoglycemic agents or insulin.

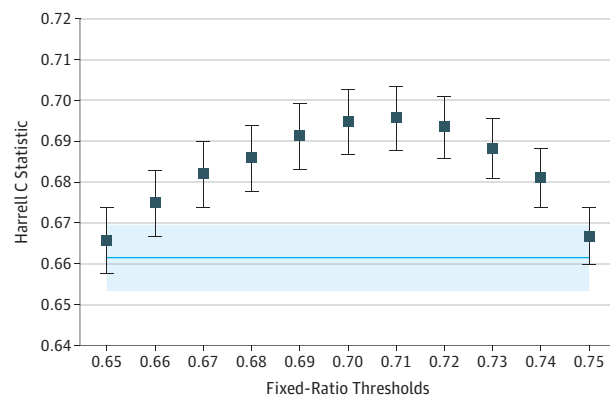
Figure 1. Incidence Density Rates for COPD-Related Hospitalization and Mortality According to Initial FEV₁:FVC



The incidence density rate (IDR) for chronic obstructive pulmonary disease (COPD)-related hospitalization and mortality was inversely related to the ratio of the forced expiratory volume in the first second to the forced vital capacity (FEV₁:FVC) without clear evidence of an inflection point. IDRs and 95% CIs were computed per 1000 person-years via Poisson regression in mutually exclusive, incremental categories of initial FEV₁:FVC. The predicted IDR (curved black line) is generated from the best function (quadratic 0.40 to 0.77; piecewise linear 0.77 to 0.80) describing the FEV₁:FVC and the corresponding IDR relationship. The blue line indicates IDR per 1000 person-years (95% CI indicated by blue shading), computed via Poisson regression, for all patients with an FEV₁:FVC less than the lower limit of normal per Global Lung Function Initiative reference equations.

significantly different from the C statistic for the model using a fixed-ratio threshold of 0.70 and was significantly better than the C statistic for the model using the LLN (Table 2). The 2 exceptions were in groups with relatively low event rates. First, a significant difference between using the C statistic for the optimal fixed threshold and the C statistic for the model using a

Figure 2. Discriminative Accuracy of Various Fixed FEV₁:FVC Thresholds for Airflow Obstruction With Respect to COPD-Related Hospitalization and Mortality



The C statistics (95% CI) for fixed-ratio thresholds (dots) were estimated separately in unadjusted Cox proportional hazards models that included only 1 dichotomous predictor (ie, whether a participant had a baseline ratio of forced expiratory volume in the first second to forced vital capacity [FEV₁:FVC] that was above or below a given ratio threshold). The C statistic for the lower-limit-of-normal (LLN) threshold is indicated by the solid blue horizontal line (95% CI indicated by blue shading). The optimal threshold based on highest C statistic was 0.71, but C statistics were not significantly different for 0.70 to 0.72. Fixed ratio thresholds 0.66 to 0.74 yielded C statistics that were significantly higher than the LLN threshold (*P* values <.05).

fixed-ratio threshold of 0.70 was observed in never smokers (IDR [4.04]; optimal fixed threshold [0.74]; eFigure 4 in the Supplement). Second, for COPD-related mortality (IDR [1.31]; optimal fixed threshold [0.69]; eFigure 5 in the Supplement), differences between using the C statistic for the optimal fixed threshold vs the C statistic for the model using a fixed-ratio threshold of 0.70 were statistically significant, and differences between using the C statistic for the optimal fixed threshold vs the C statistic for the model using the LLN were not significant. The optimal fixed threshold was 0.70 in ever smokers (eFigure 4 in the Supplement) and in men (eFigure 6 in the Supplement), 0.71 for COPD-related hospitalizations (eFigure 5 in the Supplement), and 0.69 for the events for which COPD was the primary or underlying cause (eFigure 7 in the Supplement).

The C statistic for the covariates-only base model was 0.680 (95% CI, 0.671 to 0.689; eFigure 8 in the Supplement). Addition of any ratio threshold to the covariates-only model significantly improved discrimination (*P* < .001 for all). The optimal fixed threshold, when added to the adjusted model, was 0.70 (C statistic for the optimal fixed threshold, 0.760 [95% CI, 0.752 to 0.768]), although discrimination was not significantly different over the fixed-threshold interval (0.66, 0.71). Whereas the LLN threshold yielded significantly less accurate discrimination than the optimal fixed threshold in the primary analysis, incremental discrimination by the LLN and 0.70 thresholds converged once models were adjusted for age (eFigure 9 in the Supplement), and discrimination by the LLN threshold was not significantly different from the optimal fixed threshold in the fully adjusted analysis (difference in the C statistic for the optimal fixed threshold vs LLN,

Table 2. Sensitivity Analyses for the Discriminative Accuracy of Various Fixed FEV₁:FVC Thresholds for COPD Event Risk^a

Model	No. at Risk/Events	IDR	Harrell C Statistic (95% CI)			C Statistic Difference (95% CI) ^c		
			Optimal Fixed Ratio Threshold ^b	Optimal Fixed Threshold	Model Using a Fixed Ratio Threshold of 0.70	Model Using an LLN Ratio Threshold	Optimal Fixed Threshold vs Model Using an LLN Ratio Threshold	
Primary analyses ^d	24 207/3925	11.54	0.71	0.696 (0.688 to 0.703)	0.695 (0.687 to 0.703)	0.661 (0.653 to 0.670)	0.001 (-0.002 to 0.004) ^e	0.034 (0.028 to 0.041)
Subgroup analyses								
Ever smoker	15 181/3389	16.34	0.70	0.67 (0.678 to 0.695)	NA ^f	0.663 (0.654 to 0.672)	NA ^f	0.024 (0.017 to 0.030)
Never smoker	9026/536	4.04	0.74	0.646 (0.624 to 0.668)	0.617 (0.595 to 0.640)	0.556 (0.538 to 0.573)	0.029 (0.009 to 0.048)	0.077 (0.054 to 0.100)
Men	11 217/2123	14.27	0.70	0.692 (0.681 to 0.703)	NA ^f	0.667 (0.655 to 0.678)	NA ^f	0.026 (0.07 to 0.034)
Women	12 990/1802	9.42	0.71	0.690 (0.688 to 0.702)	0.67 (0.675 to 0.702)	0.651 (0.639 to 0.663)	0.004 (-0.001 to 0.008) ^e	0.040 (0.031 to 0.049)
Alternative event definitions ^g								
COPD-related hospitalization	24 207/3563	10.47	0.71	0.685 (0.676 to 0.693)	0.683 (0.674 to 0.691)	0.647 (0.638 to 0.656)	0.002 (-0.002 to 0.005) ^e	0.037 (0.030 to 0.045)
COPD-related mortality	24 207/447	1.31	0.68	0.714 (0.641 to 0.787)	0.695 (0.622 to 0.768)	0.688 (0.614 to 0.762)	0.019 (0.007 to 0.032)	0.026 (-0.14 to 0.066) ^h
Hospitalization or mortality with COPD as primary/underlying cause	24 207/1129	3.16	0.69	0.756 (0.742 to 0.770)	0.755 (0.742 to 0.769)	0.736 (0.721 to 0.752)	0.00 (-0.004 to 0.007) ^e	0.020 (0.010 to 0.029)
Adjusted for covariates ⁱ	24 012/3793	11.16	0.70	0.760 (0.752 to 0.768)	NA ^f	0.762 (0.754 to 0.770)	NA ^f	-0.002 (-0.006 to 0.002)

Abbreviations: COPD, chronic obstructive pulmonary disease; IDR, incidence density rate per 1000 person-years

^a of follow-up; LLN, lower limit of normal per Global Lung Function Initiative reference equations;

NA, not applicable.

^b Cox proportional hazards models were used.

^c The optimal fixed threshold was defined as the one that generated the highest Harrell C statistic.

^d Formal statistical comparisons of C statistics were performed using a nonparametric approach to compare 2 correlated C statistics with right-censored survival outcomes.

^e The primary outcome was defined as first hospitalization or death adjudicated as primarily or secondarily attributable to COPD or, if adjudication was lacking, those with COPD listed in any diagnosis field.

^f Each fixed-threshold definition for airflow obstruction and LLN was added separately to a base model adjusted for age at enrollment, sex, race, height, birth year, site, and cohort.

^g C statistic for the optimal fixed threshold was not significantly different than the C statistic for 0.70.

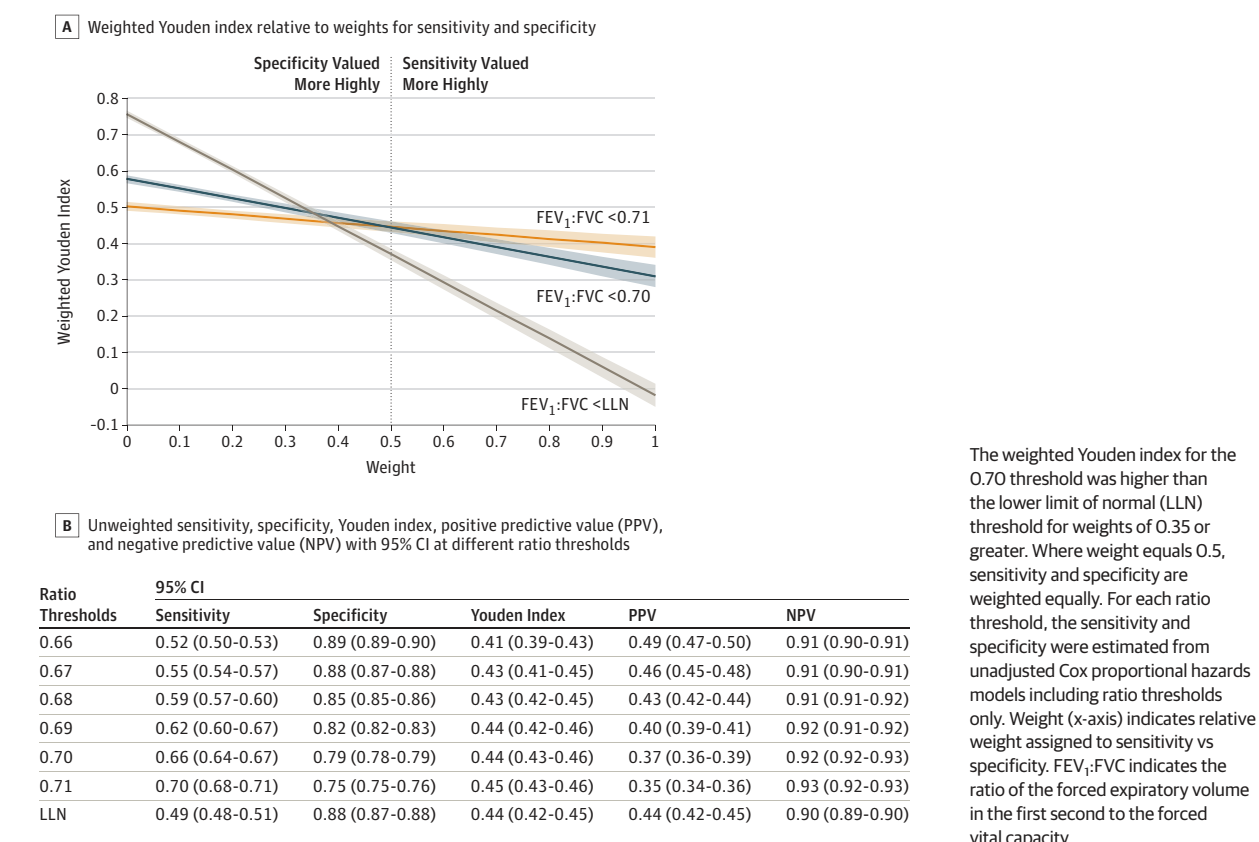
^h The optimal fixed threshold was 0.70; hence, the C statistic for the optimal fixed threshold is equal to the C statistic for the model using a fixed-ratio threshold of 0.70.

ⁱ In sensitivity analyses, the primary outcome was decomposed into COPD-related hospitalizations and COPD-related mortality. As another sensitivity analysis, the end point was restricted to incident hospitalizations and mortality adjudicated or coded as having COPD as the primary or underlying cause.

^j C statistic for the optimal fixed threshold was not significantly different than the C statistic for LLN.

^k Each fixed-threshold definition for airflow obstruction and LLN was added separately to a base model adjusted for age at enrollment, sex, race, height, birth year, site, and cohort.

Figure 3. Weighted Youden Index for Various FEV₁:FVC Thresholds Across a Range of Relative Weights for Sensitivity and Specificity



-0.002 [95% CI, -0.006 to 0.002]; Table 2). Consistent with agreement between predicted and observed outcomes, calibration plots of predicted to observed 10-year event risk showed overlapping predictive performance for LLN and 0.70 thresholds, and Brier scores were similar (eFigure 3 and eTable 6 in the Supplement). Results were similar after adjustment in stratified analyses and in analyses using alternative end points (eTable 5 in the Supplement).

Compared with the Global Lung Function Initiative definition for LLN, the NHANES definition for LLN attained a greater C statistic in unadjusted analyses (0.667 [95% CI, 0.658 to 0.675]), but the difference was small (0.005 [95% CI, 0.002 to 0.008]). Both the 0.70 and 0.71 thresholds were associated with significantly greater discriminative accuracy vs the NHANES LLN (difference in C statistic 0.70 vs NHANES, 0.028 [95% CI 0.022 to 0.034], and difference in C statistic 0.71 vs NHANES, 0.029 [95% CI, 0.023 to 0.035]).

Discussion

In this study based on pooled data from 4 US general population-based cohorts, a fixed threshold of 0.70 for the FEV₁:FVC provided discrimination of COPD-related hospitalization and mortality that was not significantly different or was more accurate than other fixed thresholds and

population-based reference equations. Hence, the present work provides population-based evidence to support 0.70 as the optimal FEV₁:FVC threshold for defining clinically significant airflow obstruction.

Until the findings of this research, the 0.70 fixed threshold to diagnose airflow obstruction was based on expert opinion. However, expert opinions have historically diverged. Over time, 2 distinct perspectives emerged. The first considers the age, sex, and race/ethnicity dependence of lung function as part of the normal variance and contends that reference equations drawn from the normal population should inform deviation from normality.^{11,12} This approach is, to some extent, similar to current definitions of osteoporosis,²⁸ yet even these are based on normative values for maximum bone density, not age-specific predictions. An alternative perspective is that the manner by which a certain lung size or degree of airflow limitation is achieved is immaterial, but that beyond this threshold of normal lung function, respiratory reserve is overcome and there are clinical consequences.³ This latter view, positing a fixed threshold for harm, is more consistent with current guidelines for high blood pressure and diabetes.^{8,9}

Establishing a diagnostic threshold that is easy to use is critical to improve adaptation of spirometry in primary care and to facilitate epidemiologic follow-up and multiregional clinical trials. Identifying individuals below the 5th percentile

of normal using population-based reference values may be statistically sound, but this approach assumes that the prevalence of airflow obstruction has to be at least 5%. It is also sensitive to population differences: this study found significantly better discrimination by the NHANES III LLN, which was developed from a US population, vs the Global Lung Function Initiative LLN. Furthermore, as populations demonstrate changing demographics such as obesity, which are not accounted for in the reference equations, different reference equations drawn from the same population over time can result in differing definitions of normal and abnormal.²⁹ There are also important differences in reference equations. For instance, the Global Lung Function Initiative equation for FEV₁:FVC adjusts for height, whereas the NHANES III LLN does not.

Although the aim of this study was to identify the optimal fixed FEV₁:FVC threshold to discriminate risk of COPD-related events in a general population-based context, a number of sensitivity analyses were performed. Of particular clinical interest was a subgroup analysis in ever smokers, who constitute the majority but far from all of COPD cases. Among ever smokers, the optimal ratio threshold was 0.70. In never smokers, the optimal ratio threshold was 0.74, but event rates were low and 0.70 still offered more accurate prediction compared with the LLN. No thresholds were significantly more accurate than 0.70 across strata of sex or in analyses adjusted for sociodemographic and anthropometric characteristics, which suggests that 0.70 may be applicable to all adults.

The selection of a diagnostic threshold requires trade-offs between sensitivity and specificity with important ramifications for underdiagnosis and overdiagnosis, and no ratio threshold is unassailable. Most reference equations assume uniformity of variance across patient ages, which means they are more likely to yield lower values for LLN and hence, underdiagnose airflow obstruction at older ages. Conversely, due to the age-related decline in lung function, the possible consequences of using a fixed threshold are overdiagnosis in older individuals (which could result in unnecessary medication) and underdiagnosis in younger individuals (which could lead to missed opportunities for recommending smoking cessation and early initiation of therapy).⁴ With respect to potential overdiagnosis by fixed thresholds, the prior literature has established that 7% to 23% of older adults meet the 0.70 threshold but not LLN criteria, yet longitudinal studies have mostly shown that these discordant participants have a greater degree of structural lung disease on computed tomography, worse quality of life, and greater health care utilization and mortality when compared with individuals without airflow obstruction by either criteria.^{2,30-34} With regards to potential underdiagnosis of younger individuals by a fixed threshold, evidence suggests this is of minimal importance: only 1% of young adults meeting the LLN criterion was missed by the fixed threshold of 0.70 in the Copenhagen General Population cohort; moreover, compared with those without airflow obstruction by any criteria, these individuals were no different in terms of COPD- or asthma-related exacerbations on follow-up.³⁵

Regardless of the threshold selected, the specificity and particularly sensitivity of airflow obstruction were modest, confirming recent observations that spirometry alone does not detect all individuals at risk of COPD-related events³⁶ and also confirming that some patients with airflow obstruction on spirometry may not report clinical symptoms. For cases in which the FEV₁:FVC value is borderline, especially in the absence of symptoms, it may be prudent to recommend close monitoring as recent data suggest the diagnosis of airflow obstruction in these individuals may not be stable.³⁷ Nonetheless, weighted analyses suggested that the 0.70 threshold would be preferred to lower fixed ratio thresholds and the LLN as long as sensitivity carries equal or greater weight than specificity.

Strengths of the current work include the use of a large, US general population-based sample, supporting the generalizability of our results. The sample also included a large number of never smokers and less than 10 pack-year smokers who are commonly excluded from major studies of COPD. Lung function was systematically harmonized, and outcomes were defined by adjudication or a validated protocol using administrative data.^{13,17}

Limitations

This study has several limitations. First, although the GOLD (Global Initiative for Chronic Obstructive Lung Disease) guidelines recommend using postbronchodilator values for confirming airflow obstruction,⁵ this study used prebronchodilator spirometry. Nonetheless, multiple studies have shown strong correlations between prebronchodilator and postbronchodilator spirometry measures, and both perform similarly in predicting respiratory outcomes.^{38,39} Furthermore, the LLN, the major comparator for this work, is calculated on prebronchodilator values only.

Second, no adjustments were made for medication use. Third, as participants were selected across cohorts, there are baseline differences in demographics and historical differences in disease management over time. Covariate-adjusted models included birth year, site, and cohort to alleviate potential biases due to this heterogeneity.

Fourth, although outcomes were longitudinal, the FEV₁:FVC threshold was determined at baseline. In cases of borderline lung function, it is possible that some participants do not consistently meet criteria for airflow limitation.³⁷

Fifth, there was loss to follow-up among participants, yet potential attrition biases were mitigated by use of survival models designed to account for censored data.

Sixth, the composite of COPD-related hospitalization and mortality was selected as the primary outcome; restricting the outcome to COPD mortality or to clinical events deemed to be primarily caused by COPD would be expected to exclude a large number of participants with mild-to-moderate disease who suffer exacerbations and in whom hospitalizations and mortality are more often due to cardiovascular causes than to respiratory.⁴⁰ Regardless, sensitivity analyses for events primarily caused by COPD yielded an optimal threshold (0.69) that was not significantly different with respect to discrimination compared with 0.70. COPD

hospitalization and mortality can be biased by preexisting knowledge of lung function, but physicians involved in classifying events were blinded to study spirometry,¹⁹ and clinical spirometry results are not often available in the medical record. This approach is analogous to that adopted by cardiovascular risk scores to predict events, but unlike cardiac events, respiratory events are not characterized by elevated levels of any biomarkers, and clinical diagnosis is the current criterion standard.

Conclusions

Defining airflow obstruction as an FEV₁:FVC of less than 0.70 provided discrimination of COPD-related hospitalization and mortality that was not significantly different than or was more accurate than other fixed thresholds and the LLN. These results support use of an FEV₁:FVC of less than 0.70 to identify individuals at risk of clinically significant COPD.

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Author Affiliations: Division of Pulmonary, Allergy, and Critical Care Medicine and the UAB Lung Health Center, University of Alabama at Birmingham (Bhatt, Dransfield); Division of General Medicine, Columbia University Medical Center, New York, New York (Balte, Schwartz, Oelsner); Division of Nutritional Sciences, Weill Cornell Medical College, Ithaca, New York (Cassano); Gillings School of Global Public Health, University of North Carolina, Chapel Hill (Couper); Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis (Jacobs); Division of Pulmonary and Critical Care Medicine, Northwestern University, Chicago, Illinois (Kalhan); Division of Pulmonary, Allergy, Sleep, and Critical Care, Boston University, Boston, Massachusetts (O'Connor); Department of Critical Care Medicine, University of Pittsburgh and Veterans Affairs Pittsburgh Healthcare System, Pittsburgh, Pennsylvania (Yende); Division of Pulmonary and Critical Care Medicine, Brigham and Women's Hospital, Boston, Massachusetts (Sanders); MedStar Health Research Institute, Hyattsville, Maryland (Umans); Benjamin Leon Center for Geriatric Research and Education, Florida International University, Miami (Chaves); Undergraduate Training and Education Center, Tougaloo College, Tougaloo, Mississippi (White); Department of Epidemiology, Mailman School of Public Health, Columbia University Medical Center, New York, New York (Oelsner).

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Concept and design: Bhatt, Oelsner.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Bhatt, Oelsner.

Critical revision of the manuscript for important intellectual content: All authors.

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Supervision: Oelsner.

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