Chronic Obstructive Pulmonary Disease in the Older Adult: What Defines Abnormal Lung Function?

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ABSTRACT

Background: The Global Initiative on Obstructive Lung Disease (GOLD) stages for chronic obstructive pulmonary disease (COPD) uses a fixed ratio of the post-bronchodilator forced expiratory volume in one second (FEV_1)/ forced vital capacity (FVC) of 0.70 as a threshold. Since the FEV_1/FVC ratio declines with age, using the fixed ratio to define COPD may "overdiagnose" COPD in older populations
Objective: To determine morbidity and mortality among older adults whose FEV_1/FVC is less than 0.70 but greater than the lower limit of normal (LLN).
Methods: We classified the severity of COPD in 4,965 participants age 65 years and older in the Cardiovascular Health Study using these two methods and determined the age-adjusted proportion of the population that died or had a COPD-related hospitalization in up to 11 years of follow-up.
Results: 1621(32.6%) subjects died and 935 (18.8%) had at least one COPD-related hospitalization during the follow-up period. People (n=1134) whose FEV_1/FVC fell between the LLN and the fixed ratio had an increased adjusted risk of death (hazard ratio [HR] 1.3, 95% confidence interval [CI] 1.1, 1.5) and COPD-related hospitalization (HR 2.6, 95% CI 2.0, 3.3) during follow-up compared to asymptomatic individuals with normal lung function.
Conclusion: In this cohort, subjects classified as "normal" using the LLN but abnormal using the fixed ratio were more likely to die and to have a COPD-related hospitalization during follow-up. This suggests that a fixed FEV_1/FVC < 0.70 may identify at-risk patients, even among older adults.

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is an internationally important cause of morbidity and mortality [1;2]. The definition of COPD has evolved over time from one based on a clinical diagnosis of chronic bronchitis or anatomic findings of emphysema to one based on the presence of abnormal lung function [3;4].

The Global Initiative on Obstructive Lung Disease (GOLD) has developed criteria to aid both the diagnosis and epidemiologic study of COPD [3;5] that have been, in large part, adopted by the American Thoracic Society and the European Respiratory Society [6]. The GOLD criteria classify obstructive lung disease based on the post-bronchodilator lung function into the following categories: Stage 1 (Mild, $FEV_1/FVC < 0.70$ and $FEV_1 >= 80\%$), stage 2 (Moderate, $FEV_1/FVC< 0.70$ and $FEV_1 >= 50$ to $< 80\%$ predicted), stage 3 (Severe, $FEV_1/FVC < 0.70$ and $FEV_1 >= 30\%$ to $< 50\%$ predicted), and Stage 4 (Very Severe, $FEV_1/FVC < 0.70$ and $FEV_1 < 30\%$ predicted). In addition, people with chronic respiratory symptoms with an $FEV_1/FVC >= 0.70$ are classified as GOLD Stage 0 (at risk)[3].

An area of controversy in the GOLD guidelines relates to the use of the fixed FEV_1/FVC ratio of 0.70 as the threshold for defining stage 1 or more severe COPD. This decision was a pragmatic one, based on the desire for simplicity, since perception of the complexity of spirometry and its interpretation has been one of the barriers to more widespread uptake of this simple clinical tool. This threshold, while easy to remember, does not take into account the age-related decline in the FEV_1/FVC ratio. Thus, a ratio of 0.65 might be considered "normal" in a 75 year old if one uses the population "norms" to classify individuals. This concept is shown graphically in figure 1, which shows the LLN for the FEV_1/FVC ratio derived from "healthy" female never smokers in the Third National Health and Nutrition Examination Survey [7]. From these data, the age at which the LLN crosses 0.70 is 52 in white females. (Comparable ages for other race-gender groups are 41 years for white males, 54 years for black females, and 48 years for black males). The hatched part of figure 1 depicts people who would be diagnosed as having COPD using the fixed ratio but not using the LLN, a group which some might consider "over-diagnosed"[8]. Using the same logic, the fixed ratio potentially "under-diagnoses" COPD in younger adults (Figure 1). The recently published ATS/ERS guidelines for the interpretation of spirometry recommends that the LLN be used to classify "obstruction" on spirometry [9]. These recommendations come from an examination of cross-sectional data. A hallmark of COPD is the presence of obstruction, but patients may have obstruction in the absence of COPD, although in this paper we'll consider the presence of "obstruction" and COPD as the same. Missing from discussions of whether to use the fixed ratio versus the LLN is how these different classifications relate to outcomes. This information is crucial in making recommendations for the clinical use of spirometry.

This paper uses data from a large cohort of U.S. adults aged 65 and older at baseline and followed for up to 11 years in order to look at outcomes in individuals who fell below the fixed ratio threshold of 0.70 at baseline but whose ratios were above the LLN. We compare their outcomes against those of a healthy cohort of a similar age that was free of respiratory symptoms and had "normal" lung function ($FEV_1/FVC >= 0.70$ and $FVC > 80\%$ predicted) at baseline.

METHODS

Study Background and Population

Study subjects were members of the Cardiovascular Health Study (CHS), a cohort of 5,201 men and women, aged 65years and older, who were recruited from four communities in 1989 [10]. Our analysis was limited to CHS participants of white or black race who underwent pulmonary function testing during their baseline clinical examination. For this analysis participants were followed for up to 11 years to determine all-cause mortality and COPD-related hospitalizations. Study protocols were approved for protection of human subjects [10].

Pulmonary Function Data

Spirometry was conducted using a volume displacement, water-sealed spirometer. At least three acceptable spirograms were obtained from a minimum of five forced expirations. Quality assurance was provided by the CHS Pulmonary Function Center, and the procedures followed the then contemporary American Thoracic Society guidelines [11]. We used the race- and sex-specific prediction equations developed by Hankinson et al. to determine the predicted values for the FEV_1, FVC and the lower limit of normal for the FEV_1/FVC [7].

Variable Definition

Age, sex, race and smoking status were self-reported. Age was stratified into 6 categories, race was classified as white or black, and baseline smoking status was classified as current, former or never.

We used modified GOLD criteria [3] to classify an individual's lung function, adding a "restricted" category ($FEV_1/FVC >= 0.70$ and FVC < 80% predicted). Subjects were then classified as GOLD 0 if they had "normal" lung function ($FEV_1/FVC >= 0.70$ and FVC >= 80% predicted) and at least one respiratory symptom. (Do you usually have a cough?; Do you usually bring up phlegm from your chest?; Does your chest ever sound wheezy or whistling apart from colds?; Do you have to walk slower than people of your age on the level because of breathlessness?) In addition, we stratified GOLD categories 1, 2 and 3-4 according to whether the FEV_1/FVC ratio was also less than the LLN (Table 1).

Table 1. Description of modified Global Initiative on Obstructive Lung Disease (GOLD) categories. The Bolded categories comprise the "potentially over-diagnosed" group of individuals.

Category	Description
Normal	FEV_1/FVC *>= 0.7 and FVC,% > 80 and asymptomatic
GOLD 0	FEV_1/FVC >= 0.7 and FVC,% >= 80 and symptomatic
Restricted	FEV_1/FVC >= 0.7 and FVC,% < 80
GOLD 1 (>= LLN)	**FEV_1/FVC<0.7 and FEV_1,% >= 80 and FEV_1/FVC >= LLN**
GOLD 1 (< LLN)	FEV_1/FVC<0.7 and FEV_1,% >= 80 and FEV_1/FVC<LLN
GOLD 2 (>= LLN)	**FEV_1/FVC<0.7 and 80>FEV_1,% >= 50 and FEV_1/FVC >= LLN**
GOLD 2 (< LLN)	FEV_1/FVC<0.7 and 80>FEV_1,% >= 50 and FEV_1/FVC<LLN
GOLD 3 or 4 (>= LLN)	**FEV_1/FVC<0.7 and FEV_1,%<50 and FEV_1/FVC >= LLN**
GOLD 3 or 4 (< LLN)	FEV_1/FVC<0.7 and FEV_1,%<50 and FEV_1/FVC<LLN

* FEV_1 is the forced expiratory volume in one second and FVC is the forced vital capacity. LLN refers to lower limit of normal for the FEV_1/FVC

Deaths

Death information coded in the CHS database was obtained from death certificates, although cause of death was not made available in our file to protect the participants' confidentiality. We used the time of survival from the baseline examination to either death or the date last known to be alive as the time metric.

Hospitalizations

Hospitalization data were searched and events coded for any hospitalizations that mentioned COPD in the time period following the baseline examination. We used the time from the spirometry to either the COPD hospitalization, death or the date last known to be alive as the time metric.

Analysis

All analyses were conducted with SAS version 8.2 (SAS Institute, Cary, NC), SUDAAN version 8.0 (RTI, Research Triangle Park, NC) and SPSS version 10 (SPSS Inc, Chicago, IL, USA). Our primary outcomes of interest in the survival models were death and COPD hospitalizations, and the main predictor of interest in our analysis was lung function . Cox proportional hazard regression models were developed using the SUDAAN procedure SURVIVAL to account for differential follow up in cohort participants. Plots of the log-log survival curves for each covariate were produced to ensure that the proportional hazards assumptions were satisfied. Time of follow up was used as the underlying time metric. For deaths, the exit date was the date of death reported on the death certificate and, for survivors, the exit date was the date the participant was last known to be alive. For COPD hospitalizations, the exit date was the date of COPD hospitalization, and for those not hospitalized the exit date was the date of death reported on the death certificate or the date the participant was last known to be alive. Age, sex, race, and smoking status were included in the adjusted models.

RESULTS

The studied CHS cohort consisted of 5,201 subjects. We excluded 30 subjects who were not of white or black race, 154 subjects missing pulmonary function data and an additional 52 individuals who were missing data on covariates included in the analysis or missing follow-up data, leaving 4,965 subjects in our analytic cohort.

The demographic characteristics of the studied population are displayed in Table 2. The cohort was 95% white and 57% female, and only 11.6% were current smokers. The bolded categories in the modified GOLD classification scheme represent those individuals who would not have been classified as having COPD had we used the LLN in place of the fixed ratio to define an abnormal ratio. In all, 54% (1134) of the 2090 individuals who met the current GOLD threshold for COPD would not have been identified as having COPD based on the LLN criterion. This included 74.9% of those with GOLD stage 1, 38.6% of those with GOLD stage 2 and 2.4% of those with GOLD stage 3 or 4 disease.

During the follow-up period, there were 1621 deaths (32.6%) and 935 (18.8%) individuals with at least one COPD-related hospitalization (Table 2). As would be expected, increasing age was associated with a higher death rate, as was sex and smoking status. Smoking status and age were, similarly, predictors of COPD-related hospitalization, whereas age was not.

Table 2 – Demographic distribution of study participants and proportion of people who died or had a COPD-related hospitalization during follow-up. From the Cardiovascular Health Study (CHS) and follow-up.

	N	Dead by Year 11 N (% of row)	COPD Hospitalization by Year 11 N (% of row)
Total	4965	1621	935
Age Group			
65-71	439	77 (17.5)	74 (16.9)
72-75	1682	337 (20.0)	268 (15.9)
76-79	1169	336 (28.7)	241 (20.6)
80-83	860	346 (40.2)	184 (21.4)
84-87	510	285 (55.9)	107 (21.0)
88 and older	305	240 (78.7)	61 (20.0)
Sex			
Female	2810	728 (25.9)	457 (16.3)
Male	2155	893 (41.4)	478 (22.2)
Race			
White	4735	1538 (32.5)	893 (18.9)
Black	230	83 (36.1)	42 (18.3)
Smoking Status			
Current Smoker	574	236 (41.1)	245 (42.7)
Former Smoker	2112	734 (34.8)	443 (21.0)
Never Smoker	2279	651 (28.6)	247 (10.8)
GOLD Category*			
GOLD 3 or 4 (< LLN)	243	134 (55.1)	158 (65.0)
GOLD 3 or 4 (>= LLN)	**6**	**2 (33.3)**	**2 (33.3)**
GOLD 2 (< LLN)	424	167 (39.4)	182 (42.9)
GOLD 2 (>= LLN)	**266**	**106 (39.9)**	**70 (26.3)**
GOLD 1 (< LLN)	289	123 (42.6)	84 (29.1)
GOLD 1 (>= LLN)	**862**	**315 (36.5)**	**143 (16.6)**
GOLD 0	921	272 (29.5)	93 (14.2)
Restricted	653	196 (30.0)	115 (12.5)
Normal	1301	306 (25.3)	88 (6.8)
Total	4965	1621 (32.7)	935 (18.8)

* See table 1

When evaluated using Cox proportional hazard models, the "potentially over-diagnosed" individuals (i.e., those for whom the FEV_1/FVC ratio was less than 0.7 but greater than the LLN) appear to be at increased risk of both death and COPD-related hospitalization. The unadjusted hazard ratio, relative to the "normal" group, for all cause mortality was significantly greater than 1 for those with both stage 1 and stage 2 disease (small sample size precluded meaningful analysis of those with stage 3 or 4 disease), and

this remained statistically significant in the adjusted analysis for those with stage 2 disease (Table 3).

Table 3 Risk of lung function impairment for death using Cox Proportional Hazard models. From the Cardiovascular Health Study and follow-up.

GOLD Category*	Unadjusted Model Hazard Ratio (95% Confidence Interval)	Adjusted Model† Hazard Ratio (95% Confidence Interval)
GOLD 3 or 4 (< LLN)	3.0 (2.5, 3.7)	3.0 (2.4, 3.7)
GOLD 3 or 4 (>= LLN)	**1.8 (0.4, 8.8)**	**3.0 (0.6, 14.3)**
GOLD 2 (< LLN)	1.9 (1.6, 2.3)	1.7 (1.4, 2.0)
GOLD 2 (>= LLN)	**1.9 (1.5, 2.4)**	**2.2 (1.7, 2.7)**
GOLD 1 (< LLN)	2.1 (1.7, 2.6)	1.4 (1.1, 1.7)
GOLD 1 (>= LLN)	**1.7 (1.5, 2.0)**	**1.1 (0.96, 1.3)**
GOLD 0	1.3 (1.1, 1.6)	1.2 (1.03, 1.4)
Restricted	1.3 (1.1, 1.6)	1.9 (1.6, 2.3)
Normal	1.0	1.0

* See table 1

† Adjusted for age, sex, race and smoking status

Furthermore, for all "potentially over-diagnosed" subjects combined the adjusted risk of death was 1.3 (95% CI = 1.1, 1.5). For COPD-related hospitalizations the estimated risks were consistently greater and more statistically significant (Table 4), with an adjusted risk for all "potentially over-diagnosed" subjects combined of 2.6 (95% CI = 2.0, 3.3)

Table 4 Risk of lung function impairment for COPD-related hospitalization using Cox Proportional Hazard models. From the Cardiovascular Health Study and follow-up.

GOLD Category*	Unadjusted Model Hazard Ratio (95% Confidence Interval)	Adjusted Model† Hazard Ratio (95% Confidence Interval)
GOLD 3 or 4 (< LLN)	17.2 (13.2, 22.4)	15.1 (11.5, 19.8)
GOLD 3 or 4 (>= LLN)	**8.5 (2.0, 35.2)**	**9.5 (2.5, 36.1)**
GOLD 2 (< LLN)	8.7 (6.8, 11.2)	6.4 (4.9, 8.4)
GOLD 2 (>= LLN)	**4.7 (3.5, 6.5)**	**4.9 (3.6, 6.7)**
GOLD 1 (< LLN)	5.3 (4.0, 7.1)	3.5 (2.6, 4.7)
GOLD 1 (>= LLN)	**2.8 (2.2, 3.7)**	**2.0 (1.6, 2.7)**
GOLD 0	2.0 (1.5, 2.6)	1.9 (1.4, 2.5)
Restricted	2.3 (1.7, 3.1)	2.8 (2.1, 3.8)
Normal	1.0	1.0

* See table 1

† Adjusted for age, sex, race and smoking status

The Kaplan-Meier curves depicting time to the first COPD-related hospitalization, stratified by baseline lung function level, are depicted in Figure 2.

The preceding analyses indicate that individuals with restrictive disease and those with GOLD stage 0 (i.e., symptomatic but with normal lung function) are also at increased risk of both all cause mortality and COPD-related hospitalizations. Those with restrictive disease appear to have a risk between that of individuals with stage 1 and stage 2 disease. The "potentially over-diagnosed" group with ratios above the LLN tend to be at somewhat less risk than those whose ratios are less than the LLN.

DISCUSSION

In this large cohort of an elderly population, lung function at the baseline examination predicted both death and COPD-related hospitalizations during the follow-up period. People whose FEV_1/FVC fell between the LLN and the fixed ratio, who some might consider as "over-diagnosed", had an increased adjusted risk of death (HR 1.3, 95% CI 1.1, 1.5) and COPD-related hospitalization (HR 2.6, 95% CI 2.0, 3.3) during follow-up.

While we saw the above noted effects in the overall "potentially over-diagnosed" group, these effects varied, predictably, by the FEV_1 percentage predicted category at baseline (Tables 3 and 4). This resulted in a much stronger effect being seen among subjects with FEV_1s less than 80% predicted (GOLD Stage 2 or higher) than those above this threshold.

We included in this analysis separate categories for subjects with restrictive disease and those who reported respiratory symptoms at baseline in the absence of pulmonary function impairment (GOLD Stage 0). Our inclusion of people who report any respiratory symptom (cough, sputum production, wheezing, or dyspnea) goes beyond what the GOLD criteria use to classify GOLD Stage 0 (Chronic symptoms of cough and sputum production)[3], but we have shown previously that this more inclusive and sensitive classification predicts adverse outcomes [12]. This finding was confirmed in this analysis, with subjects in the GOLD Stage 0 category at baseline having a higher adjusted risk of death (HR1.2, 95% CI 1.03, 1.4) and COPD-related hospitalization (HR 1.9, 95% CI 1.4, 25) during follow-up.

Although the current GOLD criteria[3] do not include a category for restrictive disease, we have previously shown that a variety of different disease processes, including congestive heart failure, diabetes mellitus, and obesity, predict this spirometric pattern and that this spirometric pattern is a predictor of death [13]. Kohler et al. reported recently about 14% of patients in their "COPD clinic" were in this category[14]. In the current analysis, being in this category at baseline predicted both death and COPD-related hospitalizations in follow-up. Whether this represents a misdiagnosis, a phenotype of COPD, or an overlap between COPD and other comorbid disease is unclear.

Central to this paper is the debate over what constitutes "normal" in a population and how that may change over time and with aging. For example, the body mass index (BMI) of the population of the United States has been increasing in recent years [15]. Using population "norms" to classify people in the upper 5th percentile of BMI, rather than using a fixed BMI threshold to classify an at risk group, would misclassify people at risk if the population is growing more obese [16]. More analogous to what is seen with lung function in an aging population, visual acuity declines with age [17]. Standards for what constitutes adequate vision to, for example, obtain a driver's license, are not linked to age; if a person's vision is below a certain fixed threshold they are not issued a license.

This analysis has certain limitations. The strict classification using GOLD criteria requires the use of a post-bronchodilator FEV_1, which was not available in this study [3]. There is evidence that 20% to 30% of a population classified as "obstructed" prebronchodilator will not meet this criteria after an inhaled bronchodilator [18]. It is unclear, however, what proportion of these people meet true reversibility criteria, and how this change affects outcomes. In our analysis, misclassifying "normal" subjects as obstructed would have biased our findings towards the null. We did not have data on total lung capacity, which is needed for the strict definition of restrictive lung disease, [19] so it is possible that some people we classified as restrictive may have had other pathology or normal lung volumes [20]. Again, this potential misclassification would bias our findings towards the null. In this analysis we did not reclassify our "potentially overdiagnosed" subjects into either our "restrictive" category or GOLD Stage 0. This was done to simplify the analysis and to allow the results to be more easily interpreted.

The current GOLD standards for the diagnosis of COPD use the fixed FEV_1/FVC of 0.70 to define COPD, potentially "over-diagnosing" some elderly patients whose ratio is below this threshold but above their LLN value. Data from this analysis suggests that patients in this group have risk of death and COPD-related hospitalizations that is higher than that seen in "normal" subjects but lower than that seen in subjects with values below the LLN. Thus, using the LLN to classify lung disease in the elderly may miss a part of the population more likely to have complications and, possibly, able to benefit from intervention. Overall, this suggests that concerns about "over-diagnosis" of COPD using the fixed ratio that stem from cross-sectional data deserve closer scrutiny from other cohort studies that can evaluate outcomes to see if their analyses replicate ours.

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Legend

Figure 1. This depicts the decline of the lower limit of normal (LLN) of the forced expiratory volume in one second (FEV_1)/ forced vital capacity (FVC) with aging, among white never smoking females in the Third National Health and Nutrition Examination Survey [7]. The hatched portion depicts elderly subjects who are "potentially over-diagnosed" and the shaded portion depicts younger adults who are "potentially under-diagnosed" with obstructive lung disease.

Figure 2 . Kaplan-Meier survival curves of COPD-related hospitalization. From the Cardiovascular Health Study (CHS) and follow-up through 1999.

* FEV_1 is the forced expiratory volume in one second and FVC is the forced vital capacity. GOLD stage 3 or 4 ($FEV_1/FVC < 0.70$ and $FEV_1 < 50\%$ predicted), GOLD stage 2 ($FEV_1/FVC < 0.70$ and $FEV_1 >= 50$ to $< 80\%$ predicted), GOLD Stage 1 ($FEV_1/FVC < 0.70$ and $FEV_1 >= 80\%$), restricted ($FEV_1/FVC >= 0.70$ and $FVC < 80\%$ predicted), GOLD stage 0 (presence of respiratory symptoms in the absence of any lung function abnormality), and no lung disease. GOLD Stages are further split into those with subjects below and above (bolded) the lower limit of normal (LLN) for the FEV_1/FVC.

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