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Global Initiative on Obstructive Lung Disease (GOLD) classification of lung disease and mortality: findings from the Atherosclerosis Risk in Communities (ARIC) study

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Summary
Objective: To determine whether a modified Global Initiative on Obstructive Lung Diseases (GOLD) classification of chronic obstructive pulmonary disease (COPD) predicts mortality in a cohort of subjects followed for up to 11 years.
Methods: We analyzed data from 15,759 adult participants, aged 43–66 years at baseline, in the Atherosclerosis Risk in Communities (ARIC) study. All baseline and follow-up data were available for 15,440 (97.9%) of the initial participants. We classified subjects using a modification of the GOLD criteria for COPD (prebronchodilator forced expiratory volume in 1 s (FEV_1) stratification of disease severity), and added a "restricted" category ($FEV_1/FVC > 70\%$ and $FVC < 80\%$ predicted). We used Cox proportional hazard models to determine the risk of impaired lung function on subsequent mortality, after adjusting for age, race, sex and smoking status.
Results: 1242 (8.0%) subjects died by the end of 1997. The overall rate of death was 8.9 per 1000 person years, but varied from 5.4/1000 among normal subjects to 42.9/1000 among subjects with GOLD Stage 3 or 4 COPD. After adjusting for covariates, all GOLD categories, along with the restricted category, predicted a higher risk of death: GOLD Stage 3 or 4, hazard ratio (HR) 5.7, 95% confidence interval (CI) 4.4, 7.3; GOLD Stage 2 HR 2.4, 95% CI 2.0, 2.9; GOLD Stage 1 HR 1.4, 95% CI 1.1, 1.6; GOLD Stage 0 HR 1.5, 95% CI 1.3, 1.8; and restricted HR 2.3, 95% CI 1.9, 2.8.

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Conclusion: The modified GOLD classification system of COPD predicts mortality in this cohort of middle-aged Americans followed for up to 11 years.

Introduction

Chronic obstructive pulmonary disease (COPD) is an important cause of morbidity and mortality in the US.[1] Restrictive lung disease, which may have several different etiologies, is also an important cause of disability, morbidity and mortality in the US.[2,3] Although tobacco smoking is the most important risk factor for both the development and progression of COPD, it is not the only one, with asthma,[4] exposure to ambient pollutants in the home and workplace,[5] and respiratory infections[6,7] also being important.

A large proportion of the morbidity and mortality that occurs in people with lung disease is not pulmonary[8,9] which raises the possibility that the presence of lung disease may be an indicator of either susceptibility to the development of other diseases or may be associated with systemic inflammation, which may then lead to these other diseases.[10–13] Impaired lung function has been previously shown to predict mortality,[14–20] but none of these studies used the recently developed international Global Initiative on Obstructive Lung Disease (GOLD) guidelines for the staging of COPD severity.[21] The GOLD guidelines, however, do not define restrictive disease.

We used a modification of the GOLD classification criteria, incorporating a classification for restrictive disease, to examine the relation between impaired lung function and mortality in a large cohort of US adults aged 43–66 at baseline and followed for up to 11 years.

Methods

Study population

The Atherosclerosis Risk in Communities (ARIC) study was initiated in 1986 as a longitudinal, population-based study of the etiology and clinical sequelae of atherosclerosis. The ARIC cohort includes 15,759 subjects aged 43–66 years at baseline from four US communities: Forsyth County, NC; Jackson, MS; suburbs of Minneapolis, MN; and Washington County, MD. ARIC participants were selected from the entire population by probability sampling in the communities other than Jackson, where probability sampling was used to select African Americans only. ARIC participants underwent pulmonary function testing during a baseline clinical examination and provided information on history of respiratory symptoms and diagnoses, BMI, smoking history, and medical history. Study protocols were approved for protection of human subjects. Details of the ARIC study are published elsewhere.[22]

Subjects

Our analysis was limited to ARIC participants who provided baseline information on respiratory symptoms and diagnoses, who underwent pulmonary function testing at the baseline examination, and for whom follow-up data were available ($n = 15,440$).

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. The best single spirogram was identified by computer and confirmed by a technician. Quality assurance was provided by the ARIC Pulmonary Function Center, and the procedures followed contemporary American Thoracic Society guidelines.[23] Several measures of lung function were used: the forced expiratory volume in 1 s (FEV_1), the forced vital capacity (FVC), and the FEV_1/FVC ratio. Linear regression models were used to create prediction equations for FEV_1 and FVC based on age, sex, race, and height among asymptomatic never-smokers who did not have a diagnosis of any lung disease (asthma, chronic bronchitis, or emphysema). These prediction equations (based on race, gender, age, and height) follow standard methods[24] for creating spirometric reference values as follows: For African-American males: $FEV_1 = -1.473+0.089 \times \text{height} - 0.028 \times \text{age}$ ($n = 311$), $FVC = -3.703+0.131 \times \text{height} - 0.024 \times \text{age}$ ($n = 311$); for African-American females: $FEV_1 = -1.029+0.072 \times \text{height} - 0.024 \times \text{age}$ ($n = 1076$), $FVC = -2.333+0.104 \times \text{height} - 0.027 \times \text{age}$ ($n = 1077$); for White males: $FEV_1 = -2.599+0.116 \times \text{height} - 0.031 \times \text{age}$ ($n = 913$), $FVC = -5.179+0.169 \times \text{height} - 0.030 \times \text{age}$ ($n = 913$); for White females: $FEV_1 = -0.6861+0.0755 \times \text{height} - 0.028 \times \text{age}$ ($n = 2257$), $FVC = -2.377+0.114 \times \text{height} - 0.027 \times \text{age}$ ($n = 2257$).

Variable definition

Using a modification of the criteria developed by the GOLD,[21] we classified subjects according to their GOLD stages of COPD: GOLD stage 3 or 4 ($FEV_1/FVC < 0.70$ and $FEV_1 < 50\%$ predicted), GOLD stage 2 ($FEV_1/FVC < 0.70$ and $FEV_1 \geqslant 50$ to $< 80\%$ predicted), GOLD Stage 1 ($FEV_1/FVC < 0.70$ and $FEV_1 \geqslant 80\%$), restricted ($FEV_1/FVC \geqslant 0.70$ and $FVC < 80\%$ predicted), GOLD stage 0 (presence of respiratory symptoms in the absence of any lung function abnormality), and no lung disease. Bronchodilator response was not evaluated in this survey so classification is based on the ''prebronchodilator'' level.

Respondents with positive responses to ''Have you ever smoked cigarettes?'' and ''Do you now smoke cigarettes?'' were classified as ''ever smokers'' and ''current smokers,'' respectively. Pipe or cigar smokers were also considered as ''smokers''. Pack-years of cigarettes smoked were calculated for current and former smokers. BMI was calculated as weight divided by height squared (kg/m^2).[25] Education level was categorized as less than high school, completion of high school, or more than high school.

We defined a subject as having a respiratory symptom if he responded positively to any of the following questions: 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?; Are you too breathless to leave the house or breathless on dressing or undressing?

Deaths

Cause of death was obtained from death certificates. We used the International Classification of Disease, Ninth Revision (ICD-9) codes to classify death as respiratory (ICD-9 490–496), lung cancer (ICD-9 162), cardiovascular (ICD-9 410–429), or other (all others).

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 outcome of interest was death, and the main predictor of interest in our analysis was lung function and the presence of respiratory symptoms at the baseline examination. Cox proportional hazard regression models were developed using the SUDAAN procedure SURVIVAL to account for differential follow-up in cohort participants. 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. Plots of the log–log survival curves for each covariate were used to show that the proportional hazards assumptions were met. Age, sex, race, smoking status, education level, body mass index, pack-years of cigarette smoking, and years since last smoked were included in the adjusted models and the models were evaluated for interactions. We also used alternative classifications of lung function (including our ''restricted'' group in either the Normal or GOLD 0 groups) to examine how the ''restricted'' category influenced the results.

Results

The entire ARIC cohort consisted of 15,792 subjects. We excluded 287 subjects who were of race other than white or black and an additional 65 subjects who were missing data on one of the other variables in our analysis, leaving 15,440 subjects in our analytic cohort. Excluded subjects did not vary significantly with regard to age, sex, or smoking status from included subjects ($P > 0.05$ for all comparisons).

The demographic characteristics of the studied population are displayed in Table 1. Overall, 271 (1.8%) of participants had GOLD stage 3 or 4 COPD and 1484 (9.6%) had GOLD stage 2 at baseline. One thousand two hundred and forty-two subjects died during the follow-up period, which was a mean of 9.0 years and a maximum of 11.1 years for the population. Subjects with lung function impairment or respiratory symptoms had a higher mortality during follow-up than normal subjects (Table 1, Fig. 1). Cause of death by GOLD category at baseline is displayed in Table 2.

A higher proportion of subjects with lung function impairment reported at least one respiratory symptom compared to normal subjects, and there was evidence that people with lower lung function report more symptoms (Table 3).

After adjusting for covariates, all GOLD categories, along with the restricted category, predicted a higher risk of death: GOLD 3 or 4, hazard ratio (HR) 5.7, 95% confidence interval (CI) 4.4, 7.3; GOLD 2 HR 2.4, 95% CI 2.0, 2.9; GOLD 1 HR 1.4, 95% CI 1.1, 1.6; GOLD 0 HR 1.5, 95% CI 1.3, 1.8; and restricted HR 2.3, 95% CI 1.9, 2.8. GOLD staging of lung function and the presence of respiratory

Table 1 Demographic distribution and outcomes of study participant.

	N	Deaths (%)	Person years	Death rate/1000 person years
Age group				
43–49	4120	139 (3.4)	37,775	3.7
50–54	4012	223 (5.6)	36,694	6.1
55–59	3772	350 (9.3)	33,888	10.3
60–66	3536	530 (15.0)	30,823	17.2
Sex				
Male	6925	709 (10.2)	61,816	11.5
Female	8515	533 (6.3)	77,364	6.9
Race				
White	11311	756 (6.7)	102,984	7.3
Black	4129	486 (11.8)	36,197	13.4
Smoking status				
Current smoker	4409	552 (12.5)	38,770	14.2
Former smoker	4972	380 (7.6)	45,003	8.4
Never smoker	6059	310 (5.1)	55,407	5.6
Pack years				
60+	756	162 (21.4)	6359	25.5
40–59	1342	200 (14.9)	11,707	17.1
20–39	2982	296 (9.9)	26,606	11.1
1–19	3593	211 (17.0)	32,777	6.4
Unknown	257	28 (10.9)	2253	12.4
0	6510	345 (5.3)	59,478	5.8
Body mass index				
<20	139	27 (19.4)	1176	23.0
20–24	4970	377 (7.6)	44,836	8.4
25–29	6067	457 (7.5)	54,931	8.3
$\geqslant 30$	4264	381 (8.9)	38,238	10.0
Education level				
<12	3671	518 (14.1)	32,195	16.1
12	4996	336 (6.7)	45,249	7.4
$\geqslant 12$	6773	388 (5.7)	61,737	6.3
GOLD category*				
GOLD 3 or 4	271	92 (34.0)	2143	42.9
GOLD 2	1484	232 (15.6)	12,852	18.1
GOLD 1	1679	137 (8.1)	15,031	9.1
GOLD 0	2244	204 (9.1)	20,191	10.1
Restricted	1101	150 (13.6)	9644	15.6
Normal	8661	427 (4.9)	79,317	5.4
Total	15440	1242 (8.0)	139,180	8.9

From the Atherosclerosis Risk in Communities (ARIC) study 1986–1989 and follow-up through 1997.

*GOLD stage 3 or 4 ($FEV_1/FVC<0.70$ and $FEV_1<50\%$ predicted), GOLD stage 2 ($FEV_1/FVC<0.70$ and $FEV_1\geqslant 50$ to $<80\%$ predicted), GOLD Stage 1 ($FEV_1/FVC<0.70$ and $FEV_1\geqslant 80\%$), restricted ($FEV_1/FVC\geqslant 0.70$ and $FVC<80\%$ predicted), GOLD stage 0 (presence of respiratory symptoms in the absence of any lung function abnormality), and no lung disease.

symptoms were related to an increased risk of mortality both before and after adjustment for the covariates of age, sex, race, smoking status, pack-years of cigarettes, body mass index, and educational level (Table 4). At each GOLD stage, subjects reporting at least one respiratory symptom had a higher risk of death than those without symptoms (Fig. 2 for GOLD stage 3 or 4, other figures available from author). Including the ''Restricted'' subjects in either the GOLD 0 or normal categories did not significantly change the results (data not shown but available from the author).

Discussion

In this analysis of a large cohort of middle-aged adults in the US, we have demonstrated the GOLD stages of COPD are associated with higher mortality in up to 11 years of follow-up. Additionally, we have demonstrated that the presence of respiratory symptoms predicts higher mortality at every level of lung function impairment, including subjects with "normal" lung function. These findings are similar to those we reported previously in a US population followed for up to 22 years.[9] In that study, the adjusted HR for subjects with GOLD stage 3 or 4 COPD was 2.7 (95% CI 2.1, 3.5). In that study, though, the age range of the baseline population was much wider (25–75 years old vs. 43–66 years old) and the proportion of current smokers was much higher (42% vs. 28%) than the current study.

Several other studies have demonstrated that lower levels of lung function lead to higher mortality.[15,16,18,20,26] This higher mortality is related to pulmonary related mortality, lung cancer, and cardiovascular disease.[9,27,28] Factors such as chronic muscle wasting, autonomic dysfunction, systemic inflammation, or oxidative stress may be responsible for this increased risk.[29–34]

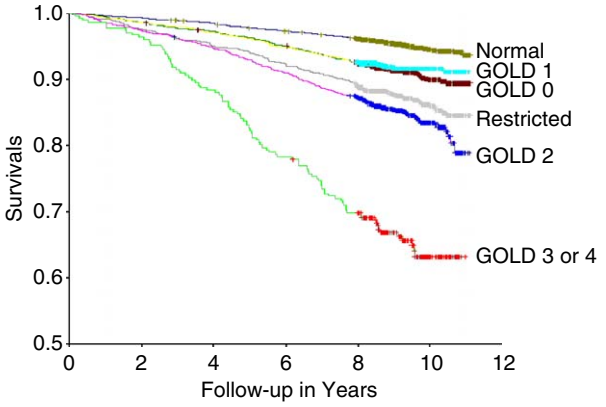

Figure 1 Kaplan–Meier survival curves for subjects included in the study, stratified by lung function level at baseline. From the Atherosclerosis Risk in Communities (ARIC) study 1986–1989 and follow-up through 1997.

Table 3 Proportion of subjects reporting at least one chronic respiratory symptom.

	N	Percentage reporting respiratory symptoms
GOLD 3 or 4*	271	81.9
GOLD 2	1484	52.0
GOLD 1	1679	29.6
Restricted	1101	35.4
Normal/GOLD 0†	10,905	20.5
Total	15,440	26.7

From the Atherosclerosis Risk in Communities (ARIC) study 1986–1989 and follow-up through 1997.

*GOLD stage 3 or 4 ($FEV_1/FVC < 0.70$ and $FEV_1 < 50\%$ predicted), GOLD stage 2 ($FEV_1/FVC < 0.70$ and $FEV_1 \geq 50$ to $< 80\%$ predicted), GOLD Stage 1 ($FEV_1/FVC < 0.70$ and $FEV_1 \geq 80\%$), restricted ($FEV_1/FVC \geq 0.70$ and $FVC < 80\%$ predicted), GOLD stage 0 (presence of respiratory symptoms in the absence of any lung function abnormality), and no lung disease.

†Normal and GOLD 0 are included in the same row to show the prevalence of respiratory symptoms in subjects with neither obstructed nor restricted lung function.

Table 2 Underlying cause of death among 1242 decedents in the study.

	Deaths	Underlying cause of death (%)*			
		Respiratory	Lung cancer	Cardiac	Other
GOLD 3 or 4†	92	31.5	23.9	13.0	31.5
GOLD 2	232	3.5	25.4	27.6	43.5
GOLD 1	137	0.7	18.3	24.8	56.2
Restricted	150	1.3	7.3	39.3	52.0
GOLD 0	204	0.5	8.3	35.3	55.9
Normal	427	0.5	6.3	30.2	63.0
Total	1242	3.5	13.0	29.8	53.8

From the Atherosclerosis Risk in Communities (ARIC) study 1986–1989 and follow-up through 1997.

*Based on International Classification of Disease, Ninth Revision (ICD-9) codes to classify death as respiratory (ICD-9 490-496), lung cancer (ICD-9 162), cardiovascular (ICD-9 410-429), or other (all others).

†GOLD stage 3 or 4 ($FEV_1/FVC < 0.70$ and $FEV_1 < 50\%$ predicted), GOLD stage 2 ($FEV_1/FVC < 0.70$ and $FEV_1 \geq 50$ to $< 80\%$ predicted), GOLD Stage 1 ($FEV_1/FVC < 0.70$ and $FEV_1 \geq 80\%$), restricted ($FEV_1/FVC \geq 0.70$ and $FVC < 80\%$ predicted), GOLD stage 0 (presence of respiratory symptoms in the absence of any lung function abnormality), and no lung disease.

Table 4 Results of Cox proportional Hazard Models predicting survival.

	Symptoms	*N*	Unadjusted hazard ratio (95% confidence interval)	Adjusted hazard ratio (95% confidence interval)
GOLD 3 or 4*	Yes	222	9.2 (7.3, 11.7)	4.5 (3.5, 5.8)
	No	49	4.0 (2.1, 7.7)	1.9 (0.97, 3.6)
GOLD 2	Yes	772	3.9 (3.2, 4.7)	2.1 (1.7, 2.6)
	No	712	2.9 (2.3, 3.6)	1.6 (1.3, 2.1)
GOLD 1	Yes	497	2.5 (1.9, 3.3)	1.6 (1.2, 2.1)
	No	1182	1.4 (1.1, 1.7)	1.0 (0.8, 1.3)
Restricted	Yes	390	4.1 (3.2, 5.2)	2.8 (2.2, 3.7)
	No	711	2.3 (1.8, 2.9)	1.8 (1.4, 2.3)
GOLD 0	Yes	2244	1.9 (1.6, 2.2)	1.6 (1.3, 1.9)
Normal	No	8661	Referent	Referent

Results are both unadjusted and adjusted for age, sex, smoking status, body mass index, race, pack-years of smoking, race, and educational level. From the Atherosclerosis Risk in Communities (ARIC) study 1986–1989 and follow-up through 1997.

*GOLD stage 3 or 4 ($FEV_1/FVC < 0.70$ and $FEV_1 < 50\%$ predicted), GOLD stage 2 ($FEV_1/FVC < 0.70$ and $FEV_1 \geq 50$ to $< 80\%$ predicted), GOLD Stage 1 ($FEV_1/FVC < 0.70$ and $FEV_1 \geq 80\%$), restricted ($FEV_1/FVC \geq 0.70$ and $FVC < 80\%$ predicted), GOLD stage 0 (presence of respiratory symptoms in the absence of any lung function abnormality), and no lung disease.

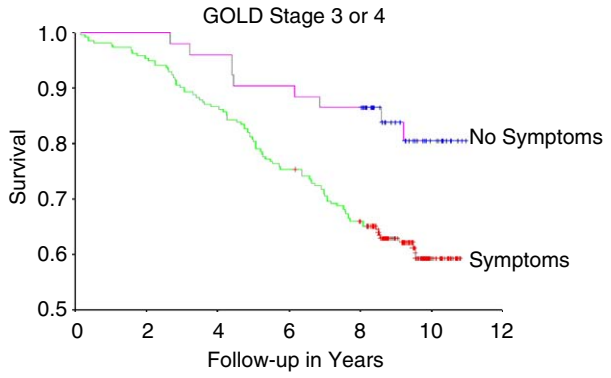

Figure 2 Kaplan–Meier survival curves for subjects included in the study with GOLD Stage 3 or 4 chronic obstructive pulmonary disease ($FEV_1/FVC < 0.70$ and $FEV_1 < 50\%$ predicted), stratified by respiratory symptoms at baseline. From the Atherosclerosis Risk in Communities (ARIC) study 1986–1989 and follow-up through 1997.

In this analysis we separated out individuals with "restricted" spirometry, as we have done in previous analyses.[9,28] These subjects are not currently addressed in the GOLD criteria,[35] yet they may comprise an important phenotype of COPD or represent patients with comorbid disease that contributes to morbidity and mortality.

Respiratory symptoms, particularly chronic mucous hypersecretion and dyspnea, have been shown to be related to higher mortality in COPD patients.[36,37] New in our study is the finding that GOLD stage 0 COPD, which is respiratory symptoms in the absence of lung function impairment, had an increased risk of mortality. One study has shown that GOLD stage 0 COPD (defined only by the symptom of coughing up phlegm 3 months a year) did not predict progression of disease, but mortality was not evaluated in that study.[38] Our study differed from that one in that we looked at all respiratory symptoms and had mortality as an endpoint.

This analysis has certain limitations. Smoking status, which is an important predictor of mortality, was not independently validated with biomarkers. Respiratory symptoms were all self-reported and not independently validated. The strict classification using GOLD criteria requires the use of a post-bronchodilator FEV_1, which was not available in this study.[21] We did not have data on total lung capacity, which is needed for the strict definition of restrictive lung disease,[39] available, so it is possible that some people we classified as restrictive may have had other pathology or normal lung volumes.[40]

In conclusion, we found that in this large prospectively followed cohort of middle-aged adults in the US both lung function impairment, determined using a modification of the GOLD criteria for COPD, and respiratory symptoms result in increased risk of mortality in up to 11 years of follow-up. These findings provide a further stimulus for finding out why lung function impairment is such a powerful predictor of mortality, and further emphasizes the potential value of spirometry in assessing overall health status. The finding also emphasizes the predictive value of respiratory symptoms and reminds us that symptoms have important predictive value in assessing health status.

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Appendix A. Supplementary Materials

The online version of this article contains additional supplementary data. Please visit doi:10.1016/j.rmed.2005.03.035.

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