RESPIRATORY CARE Paper in Press. Published on "October 29, 2019 as DOI: 10.4187/respcare.07012

FEV_1 as a Standalone Spirometric Predictor and the Attributable Fraction for Death in Older Persons

Carlos A Vaz Fragoso, Peter H Van Ness, and Gail J McAvay

BACKGROUND: Commonly used thresholds for staging FEV_1 have not been evaluated as standalone spirometric predictors of death in older persons. Specifically, the proportion of deaths attributed to a reduced FEV_1, when staged by commonly used thresholds in L, percent of predicted (% pred), and Z scores, has not been previously reported. METHODS: In 4,232 white persons ≥ 65 y old, sampled from the Cardiovascular Health Study, FEV_1 was stratified as stage 1 (FEV_1 ≥ 2.00 L, ≥80% pred, and Z score ≥−1.64), stage 2 (FEV_1 1.50–1.99 L, 50–79%pred, and Z score −2.55 to −1.63), and stage 3 (FEV_1 < 1.50 L, < 50% pred, and Z score < −2.55). Notably, a Z score threshold of −1.64 defines normal-for-age lung function as the lower limit of normal (ie, 5th percentile of distribution), and accounts for differences in age, sex, height, and ethnicity. Next, adjusted odds ratios and average attributable fractions for 10-y all-cause mortality were calculated, comparing FEV_1 stages 2 and 3 against stage 1, expressed in L, % pred, and Z scores. The average attributable fraction estimates the proportion of deaths attributed to a predictor by combining the prevalence of the predictor with the relative risk of death conferred by that predictor. RESULTS: FEV_1 stage 2 and 3 in L, % pred, and Z scores yielded similar adjusted odds ratios of death: 1.40–1.51 for stage 2 and 2.35–2.66 for stage 3. Conversely, FEV_1 stages 2 and 3 in L, % pred, and Z scores differed in prevalence: 12.8–28.6% for stage 2 and 6.4–17.5% for stage 3, and also differed in the adjusted average attributable fraction for death: 3.2–6.4% for stage 2 and 4.5–9.1% for stage 3. CONCLUSION: In older persons, the proportion of deaths attributed to a reduced FEV_1 is best stratified by Z score staging thresholds because these yield a similar relative risk of death but a more age- and sex-appropriate prevalence of FEV_1 stage. *Key words: aging; spirometry; relative risk; average attributable fraction; death.* [Respir Care 0;0(0):1–•. © 0 Daedalus Enterprises]

Introduction

The spirometric evaluation of lung function frequently includes FEV_1 and FVC because these establish normal-for-age spirometry and the impairments of restrictive-pattern and air-flow obstruction.[1-5] In older persons, however, values for FVC are less likely to meet quality control testing criteria than values for FEV_1.[6] This is because FVC is more effort-dependent, requiring a maximal and sustained forced exhalation from full inspiration to the lowest residual lung volume, whereas FEV_1 is the expired volume in the first second of the FVC maneuver.[1]

Accordingly, the spirometric evaluation of older persons may be limited to FEV_1.[6] Such an approach, wherein FEV_1 is interpreted as a standalone spirometric measure, has value for at least 3 reasons. First, because it predicts the maximum attainable ventilation during exercise, a low FEV_1 establishes a reduced ventilatory capacity.[7] Second, a low FEV_1 in older persons is associated with dyspnea and slow gait speed, and these, in turn, lead to several adverse outcomes, including an increased risk of death.[8-11]

Drs Vaz Fragoso, Van Ness, and McAvay are affiliated with Yale University School of Medicine, Department of Internal Medicine, New Haven, Connecticut. Dr Fragoso is also affiliated with Veterans Affairs Connecticut Healthcare System, Clinical Epidemiology Research Center, West Haven, Connecticut.

The authors were partially supported by a grant from the Claude D Pepper Older Americans Independence Center at Yale University School of Medicine (#P30AG021342 NIH/NIA). The authors have disclosed no other conflicts of interest.

Correspondence: Carlos A Vaz Fragoso MD, 950 Campbell Ave, West Haven, CT 06516. E-mail: carlos.fragoso@yale.edu.

DOI: 10.4187/respcare.07012

RESPIRATORY CARE Paper in Press. Published on "October 29, 2019 as DOI: 10.4187/respcare.07012

Third, in middle-aged and older persons, a low FEV_1 is associated with adverse cardiovascular outcomes.[12-15]

In clinical practice, threshold values are used to stratify the severity of a spirometric impairment. Regarding FEV_1, the most commonly applied thresholds are expressed in 3 ways: in liters, as in the preoperative evaluation of patients undergoing lung resection (ie, 2.00 and 1.50 L); in percent of predicted (% pred), as in the staging of air-flow obstruction by the Global Initiative for Chronic Obstructive Lung Disease (ie, 80% and 50% pred); or in Z scores, also in the staging of air-flow obstruction and previously validated in multiple cohorts of middle-aged and older persons (ie, Z scores of −1.64 and −2.55).[5,8,16-20] Whether these thresholds are clinically meaningful when FEV_1 is a standalone spirometric predictor has not been established in older persons. In particular, because of age-related changes in lung function, the commonly used thresholds for staging FEV_1 may yield different associations with health outcomes.[3-5,12,18-20]

In primary analyses of older white subjects from the Cardiovascular Health Study (CHS),[21] we have therefore evaluated associations between commonly used thresholds for FEV_1 and the most definitive health outcome of all-cause mortality. Specifically, we staged FEV_1 as a standalone, 3-level measure of severity in L, % pred, and Z scores, and we calculated adjusted odds ratios (ORs) and average attributable fractions (AAFs) for death, respectively. Importantly, the AAF estimates the proportion of deaths attributed to a predictor by combining the prevalence of the predictor with the relative risk of death conferred by that predictor.[22,23] In addition, unlike other measures of attributable fraction, the AAF is additive in that the sum of the contribution of each predictor to the outcome does not exceed 100%.[22,23]

Based on prior work,[24] we note that commonly used thresholds for FEV_1 may not be equivalently low or high across the adult lifespan and in females versus males. Hence, in secondary analyses of healthy never-smokers from the Global Lung Function Initiative (GLI),[4] we have evaluated age and sex differences in the calculation of a commonly used threshold, namely the lower limit of normal (LLN) for FEV_1, expressed in L, % pred, and Z scores. Also based on prior work,[15] associations with mortality may differ for FEV_1 versus FVC. Hence, to further inform comparisons with FEV_1, we have evaluated FVC, using the same statistical methods as described earlier.

We posit that the results of this study will further inform the role of FEV_1 as a standalone spirometric predictor in geriatric risk stratification.

QUICK LOOK

Current knowledge

The proportion of deaths attributed to the FEV_1 when staged by commonly used thresholds (ie, 2.0 L and 1.50 L), percent predicted (ie, 80% and 50%), and Z scores (−1.64 and −2.55) has not been previously reported in older persons. Notably, a Z score threshold of −1.64 defines normal-for-age lung function as the lower limit of normal (5th percentile of distribution) and accounts for differences in age, sex, height, and ethnicity. In addition, the average attributable fraction calculates the proportion of attributed deaths by combining the prevalence of the predictor with its relative risk of death.

What this paper contributes to our knowledge

In a large sample of white persons aged ≥ 65 y, the commonly used thresholds for staging FEV_1 (ie, liters, percent predicted, and Z scores) yielded a similar relative risk of death but differed in the prevalence of FEV_1 stage and, thus, in the average attributable fraction for death. Hence, the proportion of deaths attributed to a reduced FEV_1 is best stratified by Z score staging thresholds because these yield a similar relative risk of death but a more age- and sex-appropriate prevalence of FEV_1 stage.

Methods

Study Population

The CHS is a longitudinal study of persons aged ≥ 65 y, identified from a random sample of Medicare eligibility lists in 4 communities in the United States.[21] For our analytical sample, we included CHS subjects from the initial 1989–1990 cohort, as only this group completed clinical and spirometric evaluations at the same visit (ie, at study entry). Moreover, consistent with prior work involving older persons,[5,18,24,25] we required a spirometric test quality control grade of C or better, which included at least 2 acceptable FEV_1 values matching within 200 mL.[25] Lastly, because the proportion of African Americans was too small to support our analyses (5.3%), we evaluated only white participants. Therefore, our analytical sample included 4,232 white subjects (81.4% of the initial cohort). The institutional review boards from the Veterans Affairs Connecticut Healthcare System and Yale University approved this study.

Baseline Characteristics

Baseline characteristics included age, gender, body mass index, smoking status, and adjudicated cardiovascular conditions, as follows: hypertension (ie, systolic blood pressure ≥ 160 mm Hg or diastolic blood pressure ≥ 95 mm Hg, or history of hypertension requiring medication), dyslipi-

RESPIRATORY CARE Paper in Press. Published on "October 29, 2019 as DOI: 10.4187/respcare.07012

demia (ie, low-density lipoprotein cholesterol ≥ 160 mg/dL or high-density lipoprotein cholesterol < 40 mg/dL), diabetes mellitus (ie, taking insulin or oral hypoglycemic, or fasting glucose ≥ 126 mg/dL), cardiovascular disease (ie, myocardial infarction, angina, heart failure, or claudication), and cerebrovascular disease (ie, stroke or transient ischemic attack).[21]

Spirometry

Spirometry was performed in the seated position, using a water-sealed, Collins Survey II spirometer and contemporary protocols from the American Thoracic Society.[21,25] The spirometric performance was reviewed by the CHS Pulmonary Function Reading Center,[25] which assigned quality control grades for FEV_1.

Based on the highest measured FEV_1 in L, we calculated % pred and Z score values for FEV_1. % pred was calculated as ([measured FEV_1]/[predicted mean for FEV_1]) × 100. The predicted mean was established with regression equations from the GLI, which are based on reference populations of healthy never-smokers and include the predictor variables of age, height (measured standing), sex, and ethnicity.[2,17] Z scores were calculated using the LMS (λ-μ-Sigma) method, also using GLI regression equations.[3,4] Specifically, in addition to the predicted mean (μ), the LMS method included the coefficient of variation (Sigma), representing the spread of reference values (variability in spirometric performance), and skewness (λ), representing the departure from normality.[3]

Next, using the earlier described thresholds, FEV_1 was stratified as stage 1 (FEV_1 ≥ 2.00 L, ≥80% pred, and Z score ≥ −1.64), stage 2 (FEV_1 1.50–1.99 L, 50–79%pred, and Z score −2.55 to −1.63), and stage 3 (FEV_1 < 1.50 L, < 50% pred, and Z score < −2.55).[5,8,16-20] Regarding Z scores, −1.64 corresponded to the 5th percentile of distribution (defining the LLN), whereas −2.55 corresponded to the 0.5th percentile of distribution.[5,8,18-20]

To inform comparisons with FEV_1 in subjects who achieved FEV_1 acceptability criteria, we evaluated FVC in L, % pred, and Z scores. In these analyses, FVC was staged as a standalone, 3-level measure of severity, using the same thresholds as described for FEV_1.

Vital Status

Vital status was available on all participants, ascertained over a 10-y follow-up period, with 1,438 confirmed deaths (34% of the analytical sample).

Statistical Analysis

Baseline characteristics of the CHS sample were first summarized as means and standard deviations, or as counts and percentages, and included frequency distributions for FEV_1 stage 1–3 in L, % pred, and Z scores. To inform comparisons with FEV_1, frequency distributions were also calculated for FVC stage 1–3 in L, % pred, and Z scores.

In primary analyses, using pooled logistic regression models and CHS data, adjusted ORs and 95% CIs for 10-y all-cause mortality were calculated for FEV_1 stage 2 and 3, relative to stage 1. Covariates of interest were age ≥ 75 y (a group at high risk of death),[27] male sex, body mass index ≥ 30 kg/m^2, current smoker, ≥ 10 pack-years, and cardiovascular conditions. Goodness-of-fit was assessed by analysis of residuals. Because missing data were modest (4.2%), complete case analysis was conducted.

Next, using CHS data and the same covariates, adjusted AAFs for 10-y all-cause mortality were calculated for FEV_1 stage 2 and 3, relative to stage 1. Notably, the AAF is symmetrical with the probability of the outcome based on all combinations of predictors observed in the data and with final values for individual AAFs obtained by averaging across these observed combinations.[22,23] In addition, for the point estimate of each AAF, 5,000 bootstrap samples were generated to establish 95% CIs.

In secondary analyses, using data from GLI, age and sex differences in the LLN for FEV_1 when expressed in L, % pred, and Z scores were evaluated in a white individual of average height (white female: average height = 163 cm; white male: average height =178 cm) at ages 25, 45, 65, and 85 y. In these analyses, the LLN (5th percentile of distribution) was calculated from GLI regression equations that are based on reference populations of healthy never-smokers and account for differences in age, height, sex, and ethnicity.[2-4]

Lastly, to inform comparisons with FEV_1, associations of FVC in L, % pred, and Z scores with 10-y all-cause mortality were evaluated, using CHS data and the same statistical methods as described earlier. In addition, using data from GLI, the LLN for FVC in L, % pred, and Z scores was calculated in a white female and male of average height, as described earlier.

SAS/STAT 14.2 software (SAS Institute, Cary, North Carolina) was used for estimating the survival models, and MATLAB software (The MathWorks, Natick Massachusetts) was used to compute the AAFs.

Results

Primary Analyses (CHS Sample)

Table 1 reports baseline characteristics of the CHS sample: mean age was 72.6 y, 43.1% were male, mean body mass index was 26.2 kg/m^2, and 54.5% were former or current smokers (average 18.9 pack-years). Cardiovascular conditions were prevalent, including hypertension (41.3%), dyslipidemia (36.7%), diabetes (14.7%), cardio-

RESPIRATORY CARE Paper in Press. Published on "October 29, 2019 as DOI: 10.4187/respcare.07012

Table 1. Baseline Characteristics of Cardiovascular Health Study Sample*

Characteristic	Baseline Data
Age, y	72.6 ± 5.3
Age > 75 y†	1,411 (33.3)
Males	1,825 (43.1)
Body mass index, kg/m^2	26.2 ± 3.9
Smoking history	
Never	1,925 (45.5)
Former	1,827 (43.2)
Current	477 (11.3)
Pack-years	18.9 ± 27.5
Cardiovascular conditions	
Hypertension‡	1,746 (41.3)
Dyslipidemia§	1,540 (36.7)
Diabetes mellitus¶	618 (14.7)
Cardiovascular disease‖	818 (19.3)
Cerebrovascular disease**	225 (5.3)

	FEV_1	FVC
Spirometry		
Liters	2.09 ± 0.66	2.99 ± 0.86
≥ 2.00: Stage 1	2,186 (53.9)	3625 (89.4)
1.50–1.99: Stage 2	1,158 (28.6)	334 (8.2)
< 1.50: Stage 3	711 (17.5)	96 (2.4)
% of predicted††	86.5 ± 21.0	94.1 ± 17.8
≥ 80: Stage 1	2,718 (67.0)	3259 (80.4)
50–79: Stage 2	1,078 (26.6)	743 (18.3)
< 50: Stage 3	259 (6.4)	53 (1.3)
Z score‡‡	−0.77 ± 1.20§§	−0.37 ± 1.07‖‖
≥ −1.64: Stage 1	3,206 (79.1)	3607 (89.0)
−2.55 to −1.63:	518 (12.8)	324 (8.0)
Stage 2		
< −2.55: Stage 3	331 (8.2)	124 (3.0)

Data are presented as *n* (%) or mean ± SD. *N* = 4,232.
* Of 4,232 subjects in this sample, 177 (4.2%) had missing data on nonspirometric predictors.
† An age group at high risk of cardiovascular death.
‡ Systolic blood pressure ≥ 160 mm Hg, diastolic blood pressure ≥ 95 mm Hg, or history of hypertension requiring antihypertensive medication.
§ Low-density lipoprotein cholesterol ≥ 160 mg/dL or high-density lipoprotein cholesterol < 40 mg/dL.
¶ If taking insulin or oral hypoglycemic, or fasting glucose ≥ 126 mg/dL.
‖ Myocardial infarction, angina, heart failure, or claudication.
** Stroke or transient ischemic attack.
†† Calculated as [measured/predicted mean] × 100.
‡‡ Calculated from regression equations from the Global Lung Function Initiative.
§§ Z score of −0.77 corresponds to 22nd percentile of distribution, which is well above the lower limit of normal (defined as the 5th percentile of distribution).
‖‖ Z score of −0.37 corresponds to the 36th percentile of distribution, which is well above the lower limit of normal (defined as the 5th percentile of distribution).

vascular disease (19.3%), and cerebrovascular disease (5.3%).

Table 1 also reports baseline FEV_1: mean values were 2.09 L, 86.5% pred, and Z score of −0.77 (denoting 22nd percentile, well above the LLN [5th percentile]). Regarding FEV_1 stage 1–3, frequency distributions varied when expressed in L, % pred, and Z scores. For FEV_1 stage 1, the Z score threshold identified the largest group (79.1% vs 53.9% and 67.0% for L and % pred, respectively). For FEV_1 stage 2, the L and % pred thresholds identified the largest groups (28.6% and 26.6% for L and % pred, respectively, vs 12.8% for Z scores). For FEV_1 stage 3, the L threshold identified the largest group (17.5% vs 6.4% and 8.2% for % pred and Z scores, respectively). Compared with FEV_1, Table 1 also shows that FVC had greater representation in stage 1 but lower representation in stages 2 and 3, whether in L, % pred, or Z scores. For example, based on Z scores ≥ −1.64 (stage 1), 89.0% of participants had normal-for-age FVC (≥ LLN) versus only 79.1% having normal-for-age FEV_1 (≥ LLN). Conversely, based on Z scores < −1.64 (combined stages 2 and 3), only 11.0% had abnormal-for-age FVC (< LLN) versus 21.0% having abnormal-for-age FEV_1 (< LLN).

Figure 1 graphs adjusted survival over 10 y by FEV_1 stage. Although variable separation of survival curves is shown in the first 5 y of follow-up, the adjusted 10-y survival was similar across L, % pred, and Z scores, ranging from 0.70–0.71 for FEV_1 stage 1, 0.60–0.62 for FEV_1 stage 2, and 0.46–0.51 for FEV_1 stage 3, respectively. Compared with FEV_1, and whether in L, % pred, or Z scores, Figure 2 shows that the adjusted 10-y survival was similar for FVC stage 1 (0.68–0.69) but lower and more varied for stages 2 and 3 (0.45–0.54 and 0.34–0.45, respectively). Notably, survival in FVC stage 3 as % pred decreased abruptly at 3 y into follow-up, but this included a baseline sample of only 124 subjects.

Table 2 reports adjusted ORs and AAFs for 10-y all-cause mortality of FEV_1 stages 2 and 3, relative to stage 1. Our results indicate that FEV_1 in L, % pred, and Z scores yielded similar increases in the adjusted OR of death, ranging from 1.40–1.51 for stage 2 to 2.35–2.66 for stage 3. Otherwise, FEV_1 in L, % pred, and Z scores varied in the adjusted AAF of death, ranging from 3.2–6.4% for stage 2 (46–92 attributable deaths) to 4.5–9.1% for stage 3 (65–131 attributable deaths). Compared with FEV_1, Table 2 also shows that FVC in L, % pred, and Z scores yielded higher adjusted ORs of death, ranging from 1.71–1.92 for stage 2 to 2.55–3.37 for stage 3. However, FVC stage 3 as % pred, despite having the highest adjusted OR of death (3.37), yielded the lowest adjusted AAF for death (1.2%) and the lowest number of attributable deaths (n = 17), a consequence of the very low prevalence of 1.3% for FVC stage 3 as % pred (see Table 1); similar results were shown for FVC stage 3 in L and Z scores. Additionally, for combined stages 2 and 3 defined by Z scores < −1.64 (< LLN), only 80 deaths were attributed to abnormal-for-age FVC, whereas 118 deaths were attributed to abnormal-for-age FEV_1; similar results were shown for combined stages 2 and 3 when in L and Z scores.

RESPIRATORY CARE Paper in Press. Published on "October 29, 2019 as DOI: 10.4187/respcare.07012

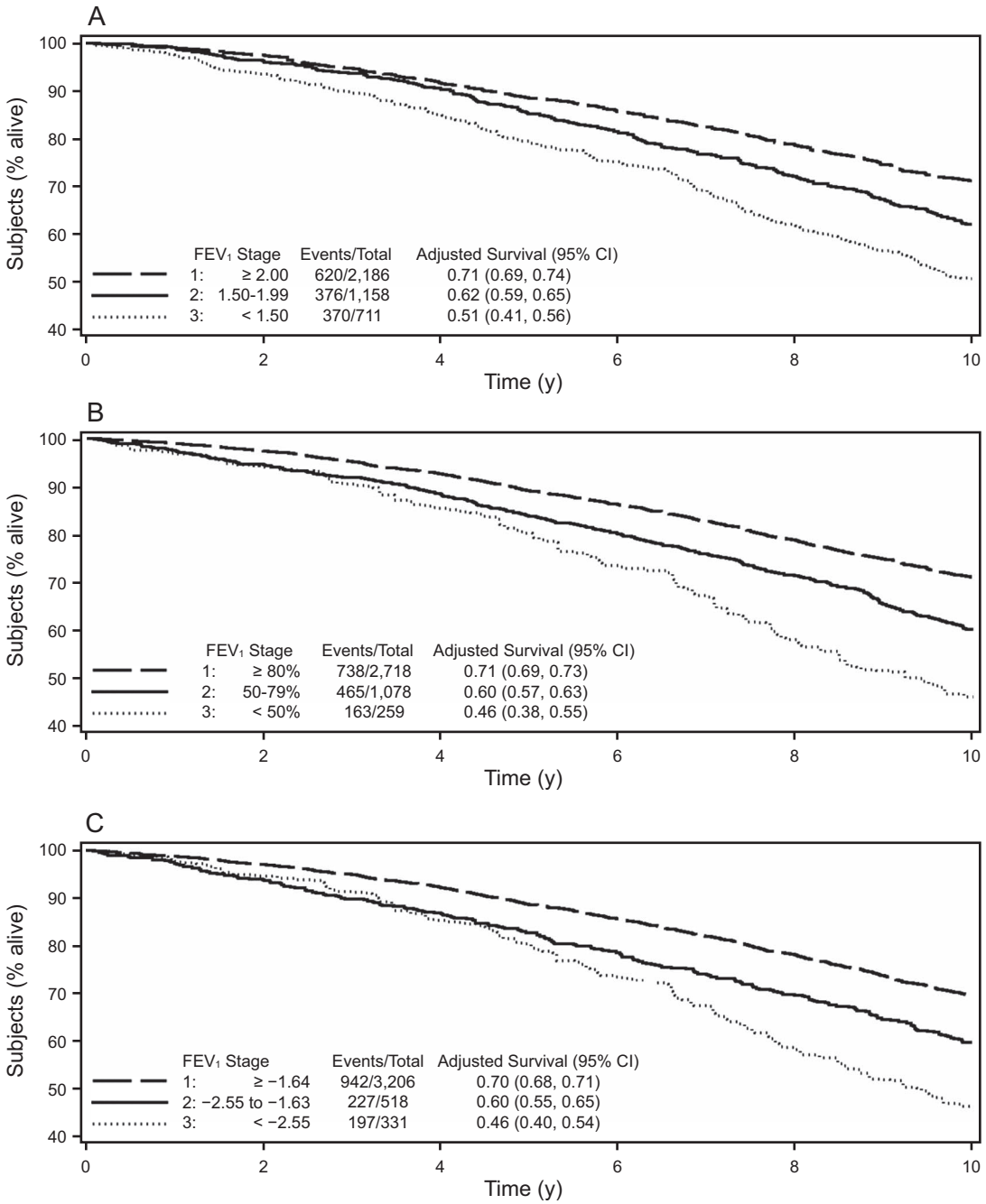

Fig. 1. Adjusted survival curves over 10 y of follow-up, stratified by FEV_1 stage in (A) liters, (B) % predicted, and (C) Z scores, using data from the Cardiovascular Health Study sample. Based on estimates from 3 separate pooled logistic regression models (FEV_1 in liters, % predicted, and Z score, respectively), adjusted for age ≥75 y, male sex, body mass index ≥ 30, current smoker, ≥ 10 pack-years, and cardiovascular conditions.

Secondary Analyses (GLI Sample)

Table 3 reports age and sex differences in the LLN for FEV_1 in a GLI sample of healthy never-smokers. Specifically, in a white female and a white male of average height, FEV_1 at the LLN decreased across the adult lifespan when in L and % pred, but not Z scores, and was lower in females versus males only when in L. Similar to FEV_1, Table 3 also shows that FVC at the LLN decreased across the adult lifespan when in L and % pred, but not in Z scores, and was lower in females versus males only when in L.

RESPIRATORY CARE Paper in Press. Published on "October 29, 2019 as DOI: 10.4187/respcare.07012

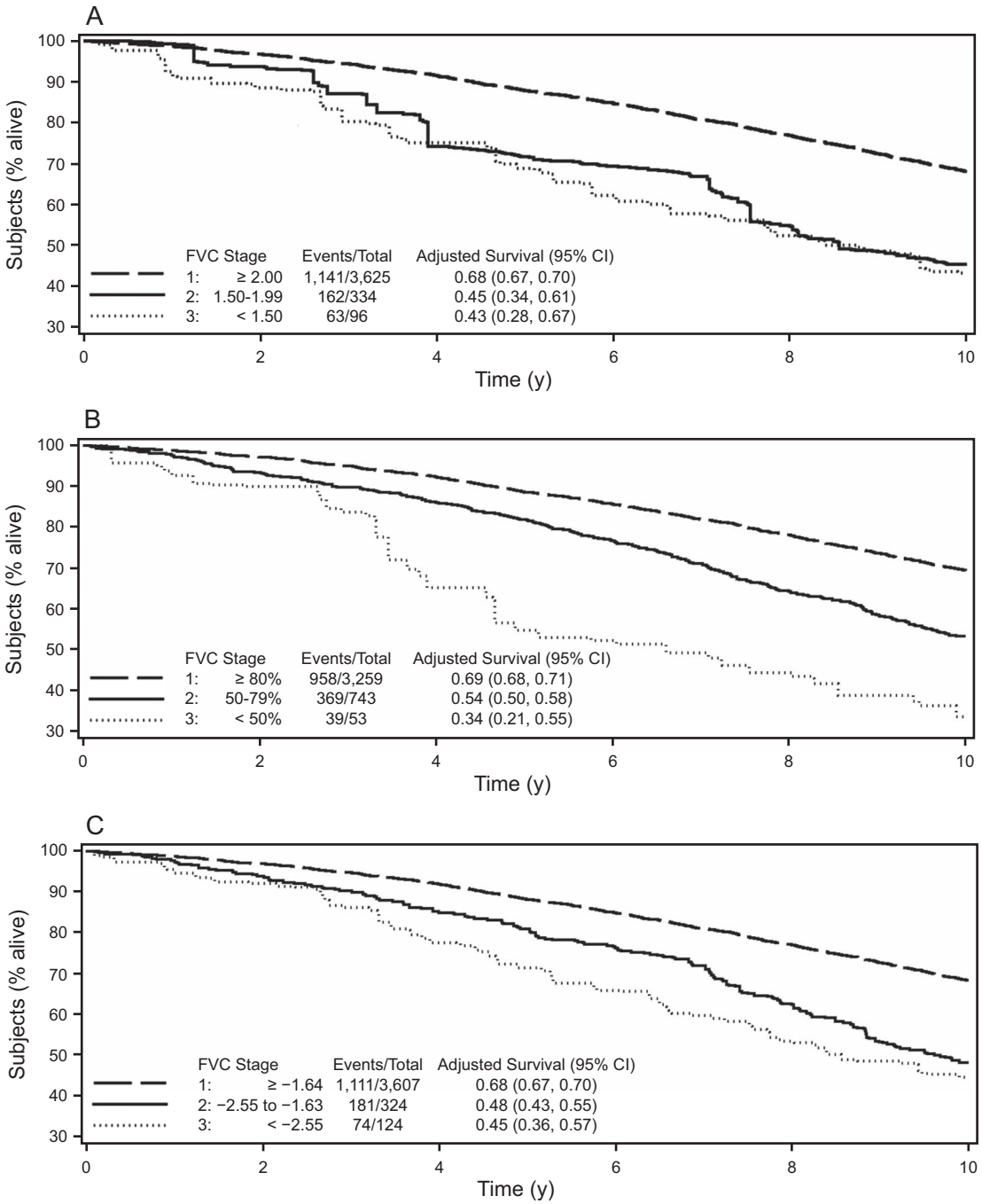

Fig. 2. Adjusted survival curves over 10 y of follow-up, stratified by FVC stage in (A) liters, (B) % predicted, and (C) Z scores, using data from the Cardiovascular Health Study sample. Based on estimates from 3 separate pooled logistic regression models (FVC in liters, % predicted, and Z score, respectively), adjusted for age ≥75 y, male sex, body mass index ≥ 30, current smoker, ≥ 10 pack-years, and cardiovascular conditions.

Discussion

In older white subjects from CHS,[21] our results indicate that FEV_1, staged by commonly used thresholds in L, % pred, and Z scores, yielded similar adjusted ORs of death (Table 2). Thus, commonly used thresholds for staging FEV_1 similarly stratified the relative risk of death, because these thresholds similarly compared lung function across three levels of severity.

In contrast, adjusted AAFs for 10-y all-cause mortality varied when FEV_1 was staged by commonly used thresholds in L, % pred, and Z scores. For example, the adjusted

RESPIRATORY CARE Paper in Press. Published on "October 29, 2019 as DOI: 10.4187/respcare.07012

Table 2. Adjusted Odds Ratio and Average Attributable Fraction for 10-Y All-Cause Mortality*

Spirometry Staging†	Odds Ratio (95% CI)‖		Average Attributable Fraction			
			Percent Contribution (95% CI)¶		Deaths, *n***	
	FEV_1	FVC	FEV_1	FVC	FEV_1	FVC
Liters						
≥ 2.00: Stage 1			Reference Group			
1.50–1.99: Stage 2	1.40 (1.20–1.62)	1.71 (1.25–1.62)	4.6 (2.4–6.7)	2.8 (1.7–4.0)	66	40
< 1.50: Stage 3	2.35 (2.00–2.76)	2.85 (2.14–3.79)	9.1 (7.2–11.1)	1.8 (1.2–2.6)	131	26
% of predicted‡						
≥ 80: Stage 1			Reference Group			
50–79: Stage 2	1.50 (1.32–1.70)	1.81 (1.59–2.06)	6.4 (4.2–8.5)	7.0 (5.2–8.8)	92	101
< 50: Stage 3	2.66 (2.21–3.22)	3.37 (2.36–4.82)	4.5 (3.4–5.8)	1.2 (0.7–1.8)	65	17
Z score§						
≥ −1.64: Stage 1			Reference Group			
−2.55 to −1.63: Stage 2	1.51 (1.29–1.77)	1.92 (1.62–2.28)	3.2 (1.8–4.6)	3.6 (2.5–4.8)	46	51
< −2.55: Stage 3	2.39 (2.00–2.83)	2.55 (1.97–3.29)	5.0 (3.7–6.4)	2.0 (1.3–2.9)	72	29

* N = 4,232 subjects from the Cardiovascular Health Study. Of 4,232 subjects, 177 (4.2%) had missing data on nonspirometric predictors (ie, cardiovascular conditions).
† Measured at study entry and staged as a 3-level measure of lung function (ie, stage 1 had the highest level of lung function, stage 2 had an intermediate level of lung function, and stage 3 had the lowest level of lung function).
‡ Calculated as [measured/predicted mean] × 100.
§ Calculated from regression equations from the Global Lung Function Initiative.
‖ Estimated using 3 separate pooled logistic regression models (ie, FEV_1 and FVC in liters, % of predicted, and Z score, respectively) and adjusted for age ≥ 75 y, male sex, body mass index ≥ 30 kg/m^2, current smoker, ≥ 10 pack-years, and cardiovascular conditions.
¶ Percentage contribution of each predictor (FEV_1 and FVC stages 2 and 3, respectively) to the outcome of death, based on estimates from pooled logistic regression models and adjusted for age ≥ 75 y, male sex, body mass index ≥ 30 kg/m^2, current smoker, ≥ 10 pack-years, and cardiovascular conditions.
** Calculated as the adjusted average attributable fraction × total number of deaths over 10 y of follow-up (ie, 1,438 deaths).

Table 3. Age and Sex Differences in the LLN Spirometric Values* in Subjects of Average Height†

Age, y	L				% of Predicted‡§				Z Score‖			
	Female		Male		Female		Male		Female		Male	
	FEV_1	FVC	FEV_1	FVC	FEV_1	FVC	FEV_1	FVC	FEV_1	FVC	FEV_1	FVC
25	2.65	3.07	3.74	4.49	80.4	79.9	80.6	80.9			−1.64	
45	2.30	2.85	3.22	4.06	79.0	79.2	78.8	78.9				
65	1.76	2.25	2.52	3.35	74.3	74.4	73.9	75.3				
85	1.25	1.66	1.86	2.66	68.6	68.6	67.9	71.1				

* Calculated at the 5th percentile of distribution, as determined in a GLI reference population of healthy never-smokers.
† Average height of a white female = 163 cm; average height of a white male = 178 cm.
‡ For FEV_1: % of predicted = [FEV_1 at the LLN in L/predicted mean FEV_1 in L] × 100. In a GLI reference population of healthy never-smokers, the respective predicted mean values for FEV_1 in L at ages 25, 45, 65, and 85 y were 3.30, 2.91, 2.37, and 1.82 L in a white female of average height and 4.64, 4.09, 3.41, and 2.74 L in a white male of average height.
§ For FVC: % of predicted = [FVC at the LLN in L/predicted mean FVC in L] × 100. In a GLI reference population of healthy never-smokers, the respective predicted mean values for FVC in L at ages 25, 45, 65, and 85 y were: 3.84, 3.60, 3.03, and 2.42 L in a white female of average height and 5.55, 5.14, 4.46, and 3.74 L in a white male of average height.
‖ Calculated from GLI regression equations, as the Z score value at the 5th percentile of distribution.
LLN = lower limit of normal
GLI = Global Lung Function Initiative

AAF for death was 6.4% for FEV_1 stage 2 as % pred, but only 4.6% and 3.2% for FEV_1 stage 2 in L and Z scores, respectively (Table 2). As discussed earlier, the AAF estimates the proportion of deaths attributed to a predictor (FEV_1 stage 2) by combining the prevalence of the predictor with the relative risk of death (adjusted OR) conferred by that predictor.[22,23] Given that adjusted ORs of death were similar (Table 2), the variability in the adjusted AAF for death was therefore due to differences in the prevalence of the FEV_1 stage 2 predictor when expressed in L, % pred, and Z scores (Table 1). A similar pattern of AAF variability was seen with FEV_1 stage 3 when expressed in L, % pred, and Z scores (Table 2).

In healthy never-smokers from GLI,[4] our results indicate that commonly used FEV_1 thresholds are only age- and sex-appropriate when expressed as Z scores, but not when expressed in L or % pred. This is shown in Table 3 by calculating the LLN for FEV_1 in L, % pred, and Z scores.

RESPIRATORY CARE Paper in Press. Published on "October 29, 2019 as DOI: 10.4187/respcare.07012

Specifically, in white individuals of average height, FEV_1 at the LLN decreased across the adult lifespan, including in older persons (≥ 65 y) and when expressed in L and % pred, and it was lower in females versus males but only when expressed in L. We further note that the 80% pred threshold for FEV_1, which distinguishes stage 1 from stage 2, is often proposed as an estimate of the LLN, but this is only appropriate in young adults, as shown in our study and in prior work.[3,4] Otherwise, across the adult lifespan and in females and males, the Z score value at the LLN remains the same because it is a fixed percentile distribution that accounts for age- and sex-related changes in lung function.

Accounting for age-related changes is a crucial step in interpreting lung function. In particular, the FEV_1 declines across the adult lifespan, principally due to increased stiffness of the chest wall and decreased elastic recoil of the lung.[3-5] Advancing age also leads to variability in spirometric performance, increasing the coefficient of variation (ie, the spread of reference values).[3,4] Likewise, sex, height, and ethnicity must be considered because these predict the FEV_1.[3,4] Notably, the LMS approach for GLI calculation of spirometric Z scores accounts for age-related changes in lung function and variability in spirometric performance, as well as the predictors of sex, height, and ethnicity.[3,4] In contrast, the % pred approach does not account for age-related changes in spirometric performance, and the L approach does not account for age-related changes in lung function or spirometric performance, nor for the predictors of sex, height, and ethnicity.

Accordingly, a major limitation of using FEV_1 thresholds in L and % pred is most evident when distinguishing normal-for-age lung function (≥ LLN) from respiratory disease (< LLN).[2] To illustrate, we compared a measured (observed) FEV_1 in L and % pred with the LLN value expressed in L and % pred. As shown in Table 3, wherein all reported values correspond to the LLN, we find that a white male of average height with a measured FEV_1 of 2.0 L would be above the LLN value of 1.86 L at age 85 y (thus having normal-for-age FEV_1), but below the LLN values of 2.52, 3.22, and 3.74 L at ages 65, 45, and 25 y, respectively (thus potentially having respiratory disease). Similarly, a white male of average height with a measured FEV_1 of 70% pred will be above the LLN value of 67.9% pred at age 85 y (thus having normal-for-age FEV_1), but below the LLN values of 73.9, 78.8, and 80.6% pred at ages 65, 45, and 25 y, respectively (thus potentially having respiratory disease). Similar results occur in a white female of average height.

A related limitation of using FEV_1 thresholds in L and % pred is the staging of severity. This is because FEV_1 in L and % pred assumes incorrectly that a threshold value is equivalently low or high across the adult lifespan and in females or males. For example, by age and sex alone, an 85-y-old female with a measured FEV_1 of 1.40 L is classified as having FEV_1 stage 3 when expressed in L, despite having FEV_1 > LLN (Table 3). Similarly, by age alone, an 85-y-old female or male with FEV_1 of 70% pred is classified as having FEV_1 stage 2 when expressed as % pred, despite having FEV_1 > LLN (Table 3). This misclassification leads to a miscalculation of the prevalence of FEV_1 stage and, in turn, to a miscalculation of the AAF. Consequently, the proportion of deaths attributed to a reduced FEV_1 is best stratified by Z score staging thresholds because these yield a similar relative risk of death but a more age- and sex-appropriate prevalence of FEV_1 stage.

Prior work has suggested that associations with mortality are stronger for FVC than for FEV_1.[15] Hence, to inform comparisons with FEV_1, we evaluated FVC, using the same statistical methods for mortality and LLN as described earlier. Our results suggest that FEV_1 compares favorably with FVC for 2 major reasons. First, based on the LLN, FEV_1 identified a larger at-risk population than FVC. For example, for combined stage 2 and stage 3 defined by Z scores < −1.64 (< LLN), 21.0% had abnormal-for-age FEV_1 but only 11.0% had abnormal-for-age FVC. Second, the number of attributable deaths was substantially higher for FEV_1 than for FVC. In particular, for combined stage 2 and stage 3 defined by Z scores < −1.64 (< LLN), 118 deaths were attributed to abnormal-for-age FEV_1, whereas only 80 deaths were attributed to abnormal-for-age FVC. Another comparison that merits emphasis is the capacity to complete a given test.[6] As discussed earlier, prior work in older subjects has shown that values for FEV_1 are more likely to meet quality control testing criteria, as compared with FVC.[6]

Our study has several strengths. We evaluated FEV_1 as a predictor of death, using adjusted ORs and AAFs and data from a well-established cohort of older persons (ie, CHS). In addition, we staged the severity of FEV_1 based on thresholds that are commonly used in the preoperative assessment of lung resection and when stratifying lung function in COPD.[5,8,16-20]

Our study also has several limitations. First, our CHS sample included only white subjects aged ≥ 65 y. Second, we did not evaluate less commonly used spirometric approaches, such as FEV_1 indexed to the residual standard deviation, to height (squared or cubed), or to the sex-specific lowest first percentile (ie, the FEV_1 quotient), nor did we evaluate the forced expiratory volume in 6 s (FEV_6) as a proxy for FVC.[28,29] These alternative approaches have merit but are not commonly used in clinical practice, have not applied the LMS method, or lack regression equations for predictive values in those aged > 80 y.[5,8,16-20,29] Third, we did not apply an alternative, 5-level Z score staging for FEV_1, although we do note that the latter stratification did not have a corresponding threshold specifically set at the LLN (ie, Z score of −1.64).[30] As discussed earlier, the

RESPIRATORY CARE Paper in Press. Published on "October 29, 2019 as DOI: 10.4187/respcare.07012

LLN is a standard criterion for establishing normal-for-age lung function and, therefore, is a crucial threshold for staging FEV_1.[2]

Our focus on FEV_1 as a standalone measure may be also considered as a limitation, given that a combined evaluation of FEV_1 and FVC is required to distinguish normal-for-age spirometry from a spirometric impairment.[2] This, however, may be a minor limitation. In our study, for example, of the 3,206 subjects with a normal-for-age FEV_1 ($\geq$ LLN), we found that 2,933 (91.5%) had normal-for-age spirometry (FEV_1/FVC $\geq$ LLN and FVC $\geq$ LLN), whereas only 229 (7.1%) had mild air-flow obstruction (FEV_1/FVC $<$ LLN but $FEV_1 \geq$ LLN) and only 44 (1.4%) had restrictive pattern (FEV_1/FVC $\geq$ LLN but FVC $<$ LLN).[5,18-20,26] Prior work has shown that mild air-flow obstruction represents an early stage of disease and that the FVC criterion for restrictive-pattern ($<$ LLN) may represent a suboptimal effort in the setting of a normal-for-age FEV_1.[6,18] Nonetheless, in the setting of respiratory symptoms (eg, dyspnea) and risk factors (eg, smoking history), further pulmonary evaluation may be required, given that normal-for-age spirometry or FEV_1 cannot definitively exclude respiratory disease.[5]

Finally, clinical practice often uses thresholds to stratify physiologic impairments (eg, FEV_1, left ventricular ejection fraction, and creatinine clearance). However, lung function and many clinical phenomena occur in a continuum, precluding definitive cut points.[31-33] Despite this limitation, staging spirometric severity has high value in clinical decision making and public health policy, given that patient care is improved by prioritizing severe over milder physiologic impairments, particularly in older persons with multimorbidity and polypharmacy.[35,36] Regarding the staging of spirometric severity according to Z score thresholds, the latter have a strong mathematical, physiological, and clinical rationale, previously evaluated in multiple cohorts of middle-aged and older persons[3-5,8,12,18-20,23,26,34,35] and now, in this study, evaluated as a standalone FEV_1 predictor.

Conclusions

In a large sample of older white subjects and in a reference population of healthy never-smokers, we have shown that Z score staging thresholds best stratify the proportion of deaths attributable to a reduced FEV_1 because these yielded a similar relative risk of death but a more age- and sex-appropriate prevalence of FEV_1 stage. Moreover, based on frequency distributions and the number of attributable deaths, our results suggest that FEV_1 compares favorably with FVC as a standalone spirometric predictor of death. Hence, FEV_1 as a standalone spirometric predictor has a strong rationale in geriatric risk stratification, potentially having broad applicability in patient care and public health policy, given that measuring FEV_1 is also more likely to meet quality control testing criteria in older persons.[6]

REFERENCES

1. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J 2005;26(1):319-338.
2. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, et al. Interpretative strategies for lung function tests. Eur Respir J 2005;26(5):948-968.
3. Stanojevic S, Wade A, Stocks J, Hankinson J, Coates AL, Pan H, et al. Reference ranges for spirometry across all ages. Am J Respir Crit Care Med 2008;177(3):253-260.
4. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3-95 year age range: the global lung function 2012 equations. Eur Respir J 2012; 40(6):1324-1343.
5. Vaz Fragoso CA, Gill T. Respiratory Impairment and the aging lung: a novel paradigm for assessing pulmonary function. J Gerontol Med Sci 2012;67(3):264-275.
6. Allen SC, Yeung P. Inability to draw intersecting pentagons as a predictor of unsatisfactory spirometry technique in elderly hospital inpatients. Age and Ageing 2006;35(3):304-306.
7. Weisman IM, Beck KC, Casaburi R, Cotes JE, Crapo RO, Dempsey JA, et al. ATS/ACCP statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med 2003;167(2):211-277.
8. Vaz Fragoso CA, Beavers DP, Hankinson JL, Flynn G, Berra K, Kritchevsky SB, et al.; on behalf of the Lifestyle Interventions and Independence in Elder Study Group. Respiratory impairment and dyspnea and their associations with physical inactivity and mobility in sedentary community-dwelling older persons. J Am Geriatr Soc 2014;62(4):622-628.
9. Miner B, Tinetti ME, Van Ness PH, Han L, Leo-Summers L, Newman AB, et al. Dyspnea in community-dwelling older persons: a multifactorial geriatric health condition. J Am Geriatr Soc 2016; 64(10):2042-2050.
10. Studenski S, Perera S, Patel K, Rosano C, Faulkner K, Inzitari M, et al. Gait speed and survival in older adults. JAMA 2011;305(1): 50-58.
11. Tessier JF, Nejjari C, Letenneur L, Filleul L, Marty ML, Gateau PB, Dartigues JF. Dyspnea and 8-year mortality among elderly men and women: The PAQUID cohort study. Eur J Epidemiol 2001;17(3): 223-229.
12. Vaz Fragoso CA, McAvay G, Van Ness PH, Metter EJ, Ferrucci L, Yaggi HK, et al. Aging-related considerations when evaluating the forced expiratory volume in 1-second (FEV_1) over time. J Gerontol A Biol Sci Med Sci 2016;71(7):929-934.
13. Marcus EB, Curb JD, MacLean VJ, Reed DM, Yano K. Pulmonary function as a predictor of coronary heart disease. Am J Epidemiol 1989;129(1):97-104.
14. Hole DJ, Watt GCM, Davey-Smith G, Hart CL, Gillis CR, Hawthorne VM. Impaired lung function and mortality risk in men and women: findings from the Renfrew and Paisley prospective population study. BMJ 1996;313(7059):711-716.
15. Min KB, Min JY. Reduced lung function, C-reactive protein, and increased risk of cardiovascular mortality. Circ J 2014;78(9):2309-2316.
16. Bapoje SR, Whitaker JF, Schulz T, Chu ES, Albert RK. Preoperative evaluation of the patient with pulmonary disease. Chest 2007;132(5): 1637-1645.
17. Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, Bourbeau J, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease 2017 re-

port. GOLD executive summary. Am J Respir Crit Care Med 2017; 195(5):557-582.
18. Vaz Fragoso CA, McAvay G, Van Ness PH, Casaburi R, Jensen RL, MacIntyre N, et al. Phenotype of spirometric impairment in an aging population. Am J Respir Crit Care Med 2016;193(7):727-735.
19. Vaz Fragoso CA, Cain HC, Casaburi R, Lee PJ, Iannone L, Leo-Summers LS, Van Ness PH. Spirometry, static lung volumes, and diffusing capacity. Respir Care 2017;62(9):1137-1147.
20. Vaz Fragoso CA, Concato J, McAvay G, Van Ness PH, Gill TM. Respiratory impairment and COPD hospitalization: a competing risk analysis. Eur Respir J 2012;40(1):37-44.
21. Fried LP, Borhani NO, Enright P, Furberg CD, Gardin JM, Kronmal RA, et al; on behalf of the Cardiovascular Health Study Research Group (CHS). The Cardiovascular Health Study: design and rationale. Ann Epidemiol 1991;1(3):263-276.
22. Murphy TE, McAvay G, Carriero NJ, Gross CP, Tinetti ME, Allore HG, Lin H. Deaths observed in Medicare beneficiaries: average attributable fraction and its longitudinal extension for many diseases. Statist Med 2012;31(27):3313-3319.
23. Vaz Fragoso CA, Van Ness PH, Murphy TE, McAvay G. Spirometric impairments, cardiovascular outcomes, and noncardiovascular death in older persons. Respir Med 2018;137:40-47.
24. Miller MR. Does the use of per cent of predicted have any evidence base? Eur Respir J 2015;45:322-323.
25. Griffith KA, Sherrill DL, Siegel EM, Manolio TA, Bonekat HW, Enright PL. Predictors of loss of lung function in the elderly: the cardiovascular health study. Am J Respir Crit Care Med 2001;163(1): 61-68.
26. Vaz Fragoso CA, McAvay G, Van Ness PH, Casaburi R, Jensen RL, MacIntyre N, et al. Phenotype of normal spirometry in an aging population. Am J Respir Crit Care Med 2015;192(7):817-825.
27. Rich MW, Chyun D, Skolnick AH, Alexander KP, Forman DE, Kitzman DW, et al. Knowledge gaps in cardiovascular care of older adults: a scientific statement from the American Heart Association, American College of Cardiology, and American Geriatrics Society. J Amer Geriatr Soc 2016;64(11):2185-2192.
28. Miller MR, Pedersen OF. New concepts for expressing forced expiratory volume in 1 s arising from survival analysis. Eur Respir J 2010;35(4):873-882.
29. Hankinson JL, Crapo RO, Jensen RL. Spirometric reference values for the 6-s FVC maneuver. Chest 2003;124(5):1805-1811.
30. Quanjer PH, Pretto JH, Brazzale DJ, Boros PW. Grading the severity of airways obstruction: new wine in new bottles. Eur Respir J 2014; 43(2):505-512.
31. Feinstein A. The inadequacy of binary models for the clinical reality of three-zone diagnostic decisions. J Clin Epidemiol 1990;43:109-113.
32. Quanjer PH, Ruppel G, Brusasco V, Pérez-Padilla R, Vaz Fragoso CA, Culver BH, et al. COPD [confusion over proper diagnosis] in the zone of maximum uncertainty (letter). Eur Respir J 2015;46: 1523-1524.
33. Cook NR. Use and misuse of the receiver operating characteristic curve in risk prediction. Circulation 2007;115:928-935.
34. Vaz Fragoso CA, Concato J, McAvay G, Van Ness PH, Rochester CL, Yaggi HK, Gill TM. The ratio of FEV1 to FVC as a basis for establishing chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2010;181:446-451.
35. Vaz Fragoso CA, Gill TM, McAvay G, Quanjer PH, Van Ness PH, Concato J. Respiratory impairment in older persons: when less means more. Am J Med 2013;126:49-57.
36. Fried TR, Vaz Fragoso CA, Rabow MW. Caring for the older person with chronic obstructive pulmonary disease. JAMA 2012;308(12): 1254-1263.