Difference in Mortality Risk in Elderly People with Bronchial Obstruction Diagnosed Using a Fixed Cutoff or the Lower Limit of Normal of the FEV₁/FVC Ratio

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Keywords

Bronchial obstruction · Elderly · Lower limit of normal · Fixed cutoff

Abstract

Background: Whether a fixed cutoff or the lower limit of normal of the FEV₁/FVC ratio should be used to diagnose bronchial obstruction is still a matter of debate. This issue is particularly important for elderly people. **Objectives:** We used equations applicable up to 90 years of age to evaluate the mortality of elderly people diagnosed with bronchial obstruction using either a fixed cutoff of 0.7 or the lower limit of normal (LLN). **Methods:** Participants in the SaRA (Salute Respiratoria nell'Anziano, Italian for "Respiratory Health in the Elderly") study were grouped as follows: FEV₁/FVC ≥ 0.7 and ≥ LLN ($n = 535$: F⁺/L⁻), FEV₁/FVC < 0.7 but ≥ LLN ($n = 118$: F⁺/L⁻), and FEV₁/FVC < 0.7 and < LLN ($n = 229$: F⁺/L⁺). We estimated the mortality risk in the three groups over 15 years of follow-up. **Results:** The mean age was 73 years (58% men). The hazard ratio (HR) for mortality was 1.427 (95% CI: 1.09–1.868) in the F⁺/L⁻ group and 2.143 (95% CI: 1.13–1.995) in the F⁺/L⁺ group. After adjustment for potential confounders,

we found no increased mortality in the F⁺/L⁻ group (HR: 1.007, 95% CI: 0.755–1.342), while the HR in the F⁺/L⁺ group was still sizeable (1.474, 95% CI: 1.136–1.911). **Conclusions:** As expected, using a fixed cutoff translates in a larger number of people to be classified as having bronchial obstruction. In our sample the increased mortality in the F⁺/L⁻ group is due to the confounding effect of age and sex. Our study lends support to the use of LLN in elderly people.

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Introduction

The diagnosis of bronchial obstruction is based on the evidence of reduction of the forced expiratory volume in the first second (FEV₁) to forced vital capacity (FVC) ratio (Tiffeneau-Pinelli index) [1]. There is debate, however, on what is the best threshold to identify a reduced FEV₁/FVC. A FEV₁/FVC < 0.7 has been traditionally used as a cutoff value. However, the use of a fixed cutoff (FC) seems to be too simplistic, and it does not take into account the different rate of decline of FEV₁ and FVC [2]. The most important consequence of using the FC is an

overdiagnosis of airflow limitation in elderly people [3] and a hazardous underdiagnosis in younger subjects [4]. Considering this problem, an alternative strategy has been proposed, based on the use of the lower limit of normal (LLN) of FEV_1/FVC calculated on the basis of prediction equations [5, 6]. Even if this approach can consider the different trend of FEV_1 and FVC through the ageing process, it is only valid to the extent to which the equations used to calculate the LLN are valid. Most importantly, the equation used must have been developed in samples including an adequate number of patients of the same age as the subject under study. Furthermore, most prediction equations assume a constant variability of this parameter across ages, and this assumption may be unrealistic, especially in elderly people. Finally, the validity of the prediction equation may be hampered by differences in the characteristics of the population studied compared to the population in which the standards have been developed.

In comparison to the FC, the LLN-based strategy may not detect a substantial proportion of people with significant airflow limitation [3, 7], but it is still unclear whether people with $FEV_1/FVC < 0.7$ have a more rapid decline compared to those with $FEV_1/FVC < LLN$.

Scanty data are available on the difference in mortality risk of people diagnosed with bronchial obstruction according to either method, compared to people without bronchial obstruction. This issue is particularly relevant in elderly people, in which the discrepancy between the two methods is likely to be more evident due to age-related functional changes. Mannino et al. [4] analyzed the Cardiovascular Health Study data in which one-third of patients were older than 80 years. This study, however, used the then available prediction equations derived from National Health and Nutrition Examination Surveys III (NHANES) data [8] that have an upper age bound of 80 years and that only included 90 Caucasian men in the age group of 66–80 years. Another study by the same author on this topic used NHANES data and did not report data on the subset of elderly participants [9]. While these studies reported an increased mortality in the group with $FEV_1/FVC < 0.7$ but not obstructed according to the LLN, Luoto et al. [10] recently reported no increase of mortality at 5 years in this group. This latter study used recently issued reference equations that are appropriate for people up to 90 years of age [11]; however, it had a follow-up time of only 5 years, while both studies by Mannino et al. [8, 9] had a follow-up time of about 10 years.

On these premises, we took the opportunity of using the estimating equations recently issued by the Global

Lung Initiative [11, 12] that are applicable to people up to 90 years of age, to evaluate the 15-year mortality rate of elderly people with bronchial obstruction diagnosed using a FC of 0.7 or the LLN.

Methods

Study Population and Follow-Up

Between January 1996 and July 1999 a total of 1,970 participants were recruited from 24 Departments of Geriatrics or Respiratory Medicine within the context of the SaRA (Salute Respiratoria nell'Anziano, "Respiratory Health in the Elderly") study. Details on the SaRA project are available elsewhere [13]. This is a multi-center Italian project investigating various aspects of chronic airway diseases in the elderly population (age ≥ 65 years) attending pulmonary or geriatric outpatient clinics for any reason. All participants were in stable conditions when the spirometry was performed. Researchers had an extensive training in both respiratory function study of the elderly and multidimensional geriatric assessment. Enrolment was on a consecutive basis. Data from individual centers were collected by a coordinating center at the *Cattedra di Malattie dell'Apparato Respiratorio* of the University of Palermo, which was also responsible for the quality control, the retrieval, and the final processing of data. The study design was approved by the Ethics Committee of the coordinating center (#276/2012). From this dataset, we selected 1,296 participants with post-bronchodilator spirometry with no missing anthropometric values. We then excluded subjects with a history of asthma ($n = 224$). Of the remaining participants, information on vital status as of December 2010 was available for 882. Causes of death were derived from death certificates, and were available for 74% of participants. Compared to the subjects included in the analysis, those lost to follow-up had comparable age (74 vs. 73 years, respectively), prevalence of men (52 vs. 58%), mean distance walked in 6 min (117 vs. 128 m), mean post-bronchodilator FEV_1 (86 vs. 88%), and mean BODE index (1.9 vs. 1.7).

Pulmonary Function Tests and Case Definition

All the centers were equipped with an identical fully computerized water-sealed Stead-Wells spirometer (Baires System; Biomedin, Padua, Italy) that met the standards of the American Thoracic Society (ATS) recommendations for diagnostic spirometry [14]. Tests were performed with a standardized technique in all centers, and a quality control process was successfully implemented: all the centers achieved a high-quality performance in spirometry [13]. We identified three groups of participants: $FEV_1/FVC \geq 0.7$ and $\geq LLN$ (60.7%, F^-/L^-), $FEV_1/FVC < 0.7$ but $\geq LLN$ (13.4%, F^+/L^-), and $FEV_1/FVC < 0.7$ and $< LLN$ (26%, F^+/L^+). None of the participants had $FEV_1/FVC \geq 0.7$ and $< LLN$. The LLN was calculated on the basis of the equations developed by the Global Lung Initiative [11, 12], as they are applicable to very old people and also allow for age-related changes in FEV_1/FVC variability [15].

Analytic Approach

The demographic and clinical characteristics of the three groups were compared using descriptive statistics along with analysis of variance for continuous variables and χ^2 test for categorical variables. In this analysis we included the 6-min walking test [16]

Table 1. Characteristics of the sample by group

	F ⁻ /L ⁻ (n = 535)	F ⁺ /L ⁻ (n = 118)	F ⁺ /L ⁺ (n = 229)	p value
Age, years	73 (6)	75 (6)	73 (5)	0.001
Male sex, %	44	80	79	<0.001
Distance walked in 6 min (normal for height)	134 (49)	124 (42)	116 (46)	<0.001
Weight (normal for height)	26 (4)	26 (4)	25 (4)	0.002
mMRC ≥2, %	8	18.6	55	<0.001
Post-BD FEV ₁ , L	2.303 (0.634)	2.234 (0.585)	1.461 (0.561)	<0.001
Post-BD FEV ₁ , %	1.01 (0.176)	0.887 (0.179)	0.578 (0.196)	<0.001
Post-BD FVC, L	2.938 (0.822)	3.365 (0.863)	2.983 (0.868)	<0.001
Post-BD FVC, %	0.99 (0.173)	1.015 (0.199)	0.898 (0.202)	<0.001
BODE index	1 (1.3)	1.3 (1.6)	3.4 (2.5)	<0.001
Smoking, pack-years	12.5 (22.5)	31.5 (35.5)	42.7 (36.1)	<0.001
Ischemic heart disease, %	10	10	14	0.157
Heart failure, %	4	9	8	0.013
Peripheral artery disease, %	5	3	9	0.54
Ischemic stroke, %	7	3	4	0.119

Values are means (SD), unless otherwise specified. BD, bronchodilator.

and comorbid diseases such as ischemic heart disease, heart failure, and stroke. Smoking was analyzed as cumulative exposure (pack-years). To evaluate the baseline risk of death we calculated the BODE index [17], that has been shown to predict mortality in elderly people [18]. The risk of dying after 15 years was estimated using the Kaplan-Meier method, and differences in the survival curves were evaluated using the log-rank test. The relative hazard of dying of subjects with bronchial obstruction was estimated using a Cox proportional hazard model. The assumptions of such a model were checked by testing the statistical significance of the interaction between time and group. In these analyses, we were interested in investigating two different things: first, to estimate the increase in mortality risk in subjects classified as having bronchial obstruction using either method compared to those without obstruction; second, to estimate the difference in the mortality risk in the F⁺/L⁻ group compared to the F⁺/L⁺ group. Accordingly, in a first model a single reference group was used (subjects without obstruction), while in a second, each category was contrasted with the preceding (i.e., F⁺/L⁻ vs. F⁻/L⁻ and F⁺/L⁺ vs. F⁺/L⁻). The models were then adjusted for potentially confounding variables: distance covered during the 6-min walking test, dyspnea (mMRC >2), ischemic heart disease, heart failure, and pack-years smoked. This model is suited to investigate the effect of FEV₁ < LLN, as the LLN is inherently adjusted for age and sex, but leave residual confounding for the effect of FEV₁ < 0.7. Therefore, a third model including age and sex was also evaluated.

In case of a linear relationship between mortality and FEV₁/FVC reduction, we would expect higher mortality rates in F⁺/L⁺ patients compared to F⁺/L⁻ patients. However, the assumption underpinning our hypothesis that the diagnostic cutoff (either fixed or based on predictive equations) may be used to obtain prognostic information is that a threshold exists, after which mortality risk starts to increase. In order to verify this assumption, we inspected the survival curves of our sample stratified by 5% decrements of

FEV₁/FVC in the 0.4–0.8 range. Furthermore, we compared the likelihood ratio χ^2 statistics and the score statistics of Cox models in which the FEV₁/FVC ratio was kept linear or transformed assuming no effect until the threshold value (FC or LLN) and then linear. In these models, when FEV₁/FVC was greater than the cut-off value it was set to 0, otherwise it was set to FEV₁/FVC < 0.7 or FEV₁/FVC < LLN, as appropriate.

Results

The mean age of the population was 73 years (SD: 6; 58% women). The three groups had a similar mean age, while men were less prevalent in the group without bronchial obstruction. The mean LLN for FEV₁/FVC was 63.2%. As expected, FEV₁ declined from the F⁻/L⁻ to the F⁺/L⁻ group (101 and 88.7% of the predicted value, respectively), and more evidently in the F⁺/L⁺ group (57.8% of the predicted value). Physical function measured by the 6-min walking test paralleled this trend, with walked distances of 134, 124, 116 m in the F⁻/L⁻, F⁺/L⁻, and F⁺/L⁺ groups, respectively. No other meaningful differences were noted across groups, except for a slightly higher prevalence of ischemic heart disease in the F⁺/L⁺ group (Table 1).

The cumulative follow-up time was 9,075 years, with a median of 13 years. The 15-year mortality was 53.7% overall and 45.7, 58.1, 70.2% in the F⁻/L⁻, F⁺/L⁻, and F⁺/L⁺ groups, respectively.

Table 2. Hazard ratio associated with different cutoffs of FEV₁/FVC

	Unadjusted model	Adjusted model 1 ^a	Adjusted model 2 ^b
F ⁻ /L ⁻	–	–	–
F ⁺ /L ⁻	1.427 (1.09–1.868)	1.349 (1.018–1.789)	1.007 (0.755–1.342)
F ⁺ /L ⁺ (vs. F ⁺ /L ⁻)	1.502 (1.13–1.995)	1.092 (0.799–1.493)	1.305 (0.948–1.796)

^a Adjusted for walked distance, dyspnea, ischemic heart disease, heart failure, pack-years. ^b Same as previous, plus age and sex.

Fig. 1. Cumulative survival by group.

Figure 1 shows the survival curves of the three groups. Up to 1 year, no difference in survival is apparent across groups, then subjects with bronchial obstruction (defined in either way) start to show an increased mortality rate compared with subjects without obstruction. At 2 years, the curves of the F⁺/L⁻ and F⁺/L⁺ groups diverge, and the relative distances between the groups remain constant until the end of follow-up, indicating a proportionality of hazards in time. Compared to the F⁻/L⁻ group, the hazard ratio for mortality in the F⁺/L⁻ group was 1.427 (95% CI: 1.09–1.868), while it was 1.502 (95% CI: 1.13–1.995) in the F⁺/L⁺ group compared to the F⁺/L⁻ group, and 2.143 compared to the F⁻/L⁻ group (Table 2, first column). After adjustment for potential confounders, but not for age and sex, the association between obstruction and mortality was attenuated, especially in the F⁺/L⁺ group, but it remained clinically sizeable and statistically significant. The increase in risk in the F⁺/L⁺ group, however, was not con-

firmed in this analysis (Table 2, second column). When we added to this model age and sex, no increase in mortality was observed in the F⁺/L⁻ group (Table 2).

The most frequent causes of death were cardiovascular diseases (43.1%), while respiratory conditions and malignancies accounted for 13.5 and 26.1% of all deaths, respectively. There was no difference in the proportion of cardiovascular deaths across the three groups, while the mortality for pulmonary causes was 8.4% in the F⁻/L⁻ group, 12.8% in the F⁺/L⁻ group, and 20.1% in the F⁺/L⁺ group ($p = 0.364$ for the comparison between F⁺/L⁻ and F⁺/L⁺). It must be noted, however, that we observed only 6 respiratory events in the F⁺/L⁻ group. Mortality due to malignancies was slightly more common in the F⁺/L⁻ (34%) compared to the F⁻/L⁻ group (27.5%) and the F⁺/L⁺ group (21.6%).

Table 3 (left panel) shows two measures of model adequacy, the likelihood ratio test and the score test, for three Cox models with different transformations of the Tiffeneau index as the independent variable, with and without adjustment for age and sex. The first model assumes a linear relationship between FEV₁/FVC and mortality hazard, so the index is modeled as a continuous variable. The second model assumes that the mortality risk does not increase until the FEV₁/FVC falls below 0.7, and then start to increase in a linear fashion; compared to the first model, the model adequacy was only marginally increased. In contrast, an unadjusted model assuming that the mortality hazard remains stable until the FEV₁/FVC ratio falls below the LLN and then increases linearly seems to be less adequate, as expressed by lower values of the likelihood ratio and Wald tests. These data are confirmed in the first part of Figure 2, in which each curve represents the overall survival of participants stratified according to 5% increments of the Tiffeneau index: starting at about 1.5 years there is a clear difference in the group of curves for FEV₁/FVC ≥ 0.7 compared to those for FEV₁/FVC < 0.7 . After inclusion of age and sex, however, the best model was the one using the LLN (Table 3, right panel).

Fig. 2. Mortality across strata of FEV₁/FVC (0.05 increments).

Table 3. Model adequacy statistics

	Unadjusted model		Adjusted model ^a	
	model LR	score	model LR	score
Tiffeneau linear	76.3	87.8	184.2	198.6
Risk increasing below 0.7	74.4	97.1	190.8	216.7
Risk increasing below LLN	64.0	87.9	194.3	223.6

LR, likelihood ratio. ^a Adjusted for age and sex.

Discussion

Using equations that are expected to reliably predict pulmonary function in the elderly, we showed that mortality risk starts to increase for FEV₁/FVC values below 0.7 but still above the LLN. The presence of a linear trend across groups seems to confirm a linear relationship between FEV₁/FVC reduction and mortality, as also shown by others [19]. The increased mortality in the F⁺/L⁻ group, however, seems to be due to the confounding effect of age and sex. This finding indicates that for prognostic purposes the FC may provide information on the mortality risk, but only inasmuch as it is influenced by these demographic variables. The LLN, instead, is able to identify subjects at increased risk independent of age, sex, comorbid diseases, and smoking exposure [20].

Our results reflect the known fact that FEV₁ decreases more rapidly than FVC with age [2], and therefore a FC incorporates the effect of age and sex on lung volumes [11]. In other words, a slight reduction in the FEV₁/FVC ratio may well be due to ageing as well as respiratory conditions. The LLN, instead, includes age and sex in its definition, and therefore there is an inherent adjustment for these variables. Indeed, relatively few participants were classified in the F⁺/L⁻ group, and none in the F⁻/L⁺ group, confirming the role of age and sex in the differences between the two cutoff. This explains why when age and sex are taken into account, the increase in mortality of the F⁺/L⁻ group is no longer apparent, and the model that best describes the data is the one including a threshold effect at the LLN.

It may be inferred from this result that a reduction of FEV₁/FVC below the FC may be a “generic” marker of increased mortality risk, while a reduction below the LLN may identify people at higher risk for mortality due to respiratory causes. This hypothesis is in line with the finding that people in the F⁺/L⁻ group do not have an accelerated FEV₁ decline, in contrast to people in the F⁺/L⁺ group [21], and also that people in the latter group have decreased lung clearance index compared to the F⁻/L⁻ group [22]. In partial contrast, we found an increased mortality for respiratory causes in the F⁺/L⁻ group, with a point estimate that is slightly greater than the one observed for all-cause mortality. In this group, however, we only had 6 events for the cause-specific analysis, and therefore the estimate of risk is rather imprecise, not allowing specific conclusions.

We found that people diagnosed with bronchial obstruction using either the FC or the LLN do not differ significantly with respect to demographic characteristics, comorbid diseases, or BODE index. Thus, the two cutoff levels seem to be equivalent with respect to the identification of patients with an increased burden of disease. By definition, participants in the F⁺/L⁺ group had significantly lower FEV₁, but the difference in the distance walked in 6 min compared to the participants in the F⁺/L⁻ group was of only 8 m, well below the minimal clinically important difference for this test (54 m) [23]. However, it must be kept in mind that our study is focused on the prognostic significance of the different approaches to diagnose bronchial obstruction, not on the best way to diagnose bronchial obstruction. With respect to this issue, both the FC and the LLN may have advantages and disadvantages, as reported by others [20].

In our sample, models allowing for a bi-modal relationship between FEV₁/FVC and mortality and adjusted

for age and gender had better discriminative capacity compared to an adjusted model including FEV₁/FVC as a linear variable, especially when the LLN was used. Thus, it seems reasonable to allow for a threshold in the FEV₁ at the LLN. In support of this conclusion, investigating the relationship between pulmonary function and cardiovascular mortality, Sin et al. [24] showed that the mortality risk was similar in the fifth and fourth quintile of FEV₁, and started to increase only from the third quintile.

In line with our results, another study [4] showed that patients classified as “normal” using the LLN but abnormal using the fixed ratio were more likely to die during follow-up and that this characteristic was not maintained after correction for age, sex, and smoking habits, except for GOLD class 2. In addition to confirming the results of that study, our study adds more information on the adequacy of prediction based on LLN and FC, and on the effect of demographic variables on the mortality risk estimation. Results from another study on this topic [25] partly differed from ours because they showed increased mortality in the F⁺/L⁺ group, but did not find an increased risk in the F⁺/L⁻ group. This study, however, was performed in a sample markedly different from ours, including only men born in 1914 and of 55 years of age at the time of the study. Finally, we are unable to adequately compare our results with those reported by Luoto et al. [10], as only an adjusted analysis is reported in that study, showing no increase in mortality in the F⁺/L⁻ group.

This study is limited by the fact that ours was a convenient sample, i.e., people attending respiratory and geriatric ambulatories. Thus, the studied population likely was only to some extent representative of the general pop-

ulation. On the other hand, this study has important strengths: spirometry was performed by highly skilled operators with standardized equipment and with a high-quality procedure [13]. Furthermore, the 15 year follow-up allows to assess the prognostic implications of bronchial obstruction over a long period and to identify time-dependent differences, if any. Indeed, as time goes on, a survivor effect is expected, with inherent increased importance of age as compared to other risk factors. The fact that the prognostic implication of bronchial obstruction is yet evident at 15 years confirms the biological importance of bronchial obstruction as a prognostic marker even in a geriatric population.

In conclusion, we found that the increased mortality seen in people with FEV₁/FVC below the FC is associated with mortality only through the confounding effect of age and sex, and the LLN may be more useful to identify people with increased mortality risk. Thus, the LLN seems to be preferable not only to avoid overdiagnosis and over-treatment, but also in order to identify persons at higher risk of death. Further studies are needed to evaluate the rate of disease progression in terms of lung function, symptoms, and health status in people classified according to either strategy.

Financial Disclosure and Conflicts of Interest

This is an original work and it is not under consideration for publication elsewhere. All the authors of this paper have contributed significantly to its drafting and revision. All the contributors have been included in the author list. None of the authors has any conflict of interest to disclose.

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