Can the New Global Lung Initiative Equations Better Stratify the Risk of Death in Elderly People with Chronic Obstructive Pulmonary Disease?

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Key Words

Chronic obstructive pulmonary disease · Spirometry ·
Global Lung Initiative · Prediction equations · Mortality risk

Abstract

Background: The forced expiratory volume in the first second (FEV₁) is commonly expressed as percentage of its value predicted by equations. The most commonly used equations are poorly applicable to elderly people. Recently, a set of equations (Global Lung Initiative, GLI) has been released that is expected to be more appropriate in this population. **Objectives:** We evaluated the agreement of the GLI, European Respiratory Society (ERS), and National Health and Nutrition Examination Survey (NHANES) equations for prediction of FEV₁ and compared their discriminative capacity with respect to mortality, taking as reference the prediction equation developed in the population from which our sample was drawn (SARA). **Methods:** We studied 264 patients with chronic obstructive pulmonary disease aged ≥70 years. Agreement was evaluated using the Bland-Altman method, discriminative capacity using incidence rate ratios for mortality calculated across quartiles of each measure. **Results:** The mean age of the sample was 75.8 years (72.7% men). In women, the mean FEV₁ERS/FEV₁SARA, FEV₁NHANES/

FEV₁SARA, and FEV₁GLI/FEV₁SARA were 0.81, 0.91, and 0.966, respectively. The corresponding values in men were 0.959, 0.963, and 1.02, respectively. The overall discriminative capacity with respect to death was equally poor for all equations. **Conclusion:** The GLI equations for predicting FEV₁ provide similar estimates compared to an equation developed in a healthy subset of the population in which they are applied, and higher values compared to the ERS equation, especially in women. However, the use of the GLI equation does not improve the stratification of the risk of mortality in elderly people compared to ERS or NHANES equations.

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Introduction

Despite its high prevalence [1], chronic obstructive pulmonary disease (COPD) often remains underdiagnosed and undertreated [2]. Spirometry is the fundamental examination for the diagnosis of bronchial obstruction, that is based on the ratio of the forced expiratory volume in the first second (FEV₁) and forced (www.goldcopd.com) or slow [3] vital capacity. The FEV₁ is also the main parameter used to classify the severity of obstruction, and it is customary to express it as a percent of the value pre-

dicted on the basis of the subject's gender, age and height (FEV_1 percent predicted, $FEV1PP$). FEV_1 has been shown to predict mortality regardless of bronchial obstruction [4]. Predicted values are usually obtained using equations that are based on statistical assumptions (e.g., homogeneous variance of the error term of the model) that may be untenable, especially in the elderly population, introducing a significant age-related bias. Furthermore, predictions are only valid when applied to subjects that are adequately represented in the population in which the equation has been developed, and despite the advancing age of COPD patients [5], the most commonly used equations only include a relatively small fraction of elderly people. For example, the reference equations of the European Respiratory Society (ERS) [6] are only valid for people aged up to 70 years, while those based on the National Health and Nutrition Examination Survey (NHANES) [7] are valid up to 80 years of age, but included relatively few elderly people. The Global Lung Initiative (GLI) has recently issued predictive equations that cover a wide age span (3–95 years) and were developed using modern statistical techniques able to overcome some of the limits of the traditional regression models [8–10]. Accordingly, these equations should be preferred, especially in the elderly population. It is not known, however, whether $FEV1PP$ calculated using the GLI equation can predict mortality better than $FEV1PP$ calculated using other reference equations. The objectives of our study are to evaluate the agreement of the GLI, ERS, and NHANES equations for prediction of FEV_1 with respect to a population-specific predicting equation (SARA, Salute Respiratoria nell'Anziano – Respiratory Health in the Elderly) in a sample of people aged 70 years or older, and to compare the discriminative capacity of $FEV1PP$ calculated using these equations with respect to 5-year mortality.

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 study. Details on the SARA project are available elsewhere [11]. 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 patients 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. Enrollment was done 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 904 patients aged 70 years or older with post-bronchodilator spirometry and valid anthropometric data. Of these, information on vital status as of December 2010 was available for 737.

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. 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 [11]. We identified patients with COPD on the basis of presence of bronchial obstruction, defined as post-bronchodilator $FEV_1/FVC < 5$ th percentile measured on a subset of participants in this study without respiratory diseases or smoking exposure (0.65 in men and 0.67 in women) [12]. The final sample size was 264.

Analytic Approach

We evaluated the agreement between the FEV_1 predicted by the SARA equation ($FEV1SARA$), [13] with that predicted by the ERS ($FEV1ERS$) [6], NHANES ($FEV1NHANES$) [7], and GLI ($FEV1GLI$) [8] equations using the Bland-Altman method [14]. As the variance of the difference was not uniform across FEV_1 values, to obtain less biased 95% agreement interval, the analysis was performed on the log scale. In this way, the difference between results obtained by the two methods compared corresponds to their ratio on the natural scale. Post-bronchodilator FEV_1 was expressed as percent predicted according to $FEV1SARA$ ($FEV1PP_{SARA}$), $FEV1ERS$ ($FEV1PP_{ERS}$), $FEV1NHANES$ ($FEV1PP_{NHANES}$), or $FEV1GLI$ ($FEV1PP_{GLI}$).

To evaluate the discriminative capacity of FEV_1 , we estimated incidence rate ratios (IRR) for mortality calculated across quartiles of $FEV1PP$ obtained using the different reference equations. The overall diagnostic performance was evaluated using the C statistic [15]. The C statistic can be interpreted in the same way as the area under the ROC curve, with higher values indicating better discriminative capacity (1 indicates perfect discriminative capacity). We also analyzed the agreement of the classification of patients into Global initiative on Obstructive Lung Disease (GOLD, <http://www.goldcopd.com>) classes obtained using the three different reference standards. Finally, using Cox proportional hazard models, we estimated the hazard ratio for mortality across $FEV1PP$ quartiles adjusting for other variables known to impact mortality in COPD (body mass index, dyspnea, distance covered at the 6-min walking test, and smoking exposure expressed as pack-years).

Results

The mean age of the sample was 75.8 years; men made up 72.7% of the sample. Table 1 shows the characteristics of the study sample, while the distribution of FEV_1 predicted

Fig. 1. Distribution of the FEV₁ predicted by the SARA, ERS, NHANES, and GLI equations.

according to SARA, ERS, NHANES, and GLI is reported in figure 1 and table 2. In our sample, 43 would not have been considered obstructed using the lower limit of normal (LLN) for FEV₁/FVC based on the ERS equation, 27 using the NHANES-based LLN, and 45 using the GLI-based LLN.

In figure 2, we report the agreement between FEV₁ predicted by the ERS and GLI equations. On average, the ratio between the FEV₁ERS and FEV₁SARA was 0.916 (95% agreement interval: 0.765–1.097). In women, the mean ratio was 0.81, indicating that in this group the SARA equation yields predicted values on average greater by 19% compared to the ERS equation, with 95% agreement intervals spanning from 0.683 to 0.961. In men, there was more agreement between measures, with a mean ratio of 0.959, indicating an average underestimation by the ERS equation of 4.1%, with 95% confidence agreement between 0.908 and 1.012.

Figure 3 shows that in general, the agreement between NHANES and SARA estimation was similar to that of

Table 1. Characteristics of the sample

Mean age (SD), years	75.8 (4.9)
Men, %	73
Mean post-bronchodilator FEV ₁ (SD)	1.5 (0.6)
Mean Barthel index (SD)	92.8 (8.1)
Mean pack-years smoked (SD)	35.5 (35.9)
Mean MMSE score (SD)	26.5 (3.8)
Mean GDS score (SD)	3.9 (3.3)
Stroke, %	4
Angina, %	8
Myocardial infarction, %	10
Heart failure, %	10

ERS and SARA, with a mean ratio of 0.948 (95% agreement interval: 0.851–1.057). Compared to the ERS equation, however, in women, the NHANES estimation was in better agreement with the SARA estimation (mean ratio: 0.91) and with slightly less variability (95% agreement

Fig. 2. Bland-Altman plot showing the agreement between the ERS and SARA equations in predicting FEV₁.

Table 2. Distribution of FEV₁ percent predicted, by gender

	Women						Men					
	minimum	1st quartile	median	mean	3rd quartile	maximum	minimum	1st quartile	median	mean	3rd quartile	maximum
SARA	0.93	1.71	1.94	1.89	2.11	2.55	1.77	2.35	2.56	2.56	2.77	3.3
ERS	0.67	1.29	1.61	1.55	1.8	2.37	1.58	2.21	2.46	2.46	2.7	3.36
NHANES	0.69	1.52	1.77	1.74	1.99	2.55	1.42	2.2	2.47	2.48	2.76	3.52
GLI	1.23	1.64	1.82	1.82	2	2.43	1.93	2.4	2.59	2.61	2.81	3.4

interval: 0.812–1.02). In men, the mean ratio was 0.963 (95% CI: 0.881–1.053).

Finally, the GLI and SARA equations showed an excellent agreement overall, with a mean ratio of 1.005 and 95% agreement interval of 0.928–1.088, with a slight underestimation in women and a slight overestimation in men (fig. 4).

According to the GOLD classification system, 18.2% participants were in class A, 10.6% in class B, 30.7% in class C, and 40.5% in class D using the SARA reference equations. Using the FEV1PP_{ERS}, 4 patients changed class (from D to B), while 5 patients changed class using the FEV1PP_{NHANES} (1 from C to A and 4 from D to B), and 3 using the FEV1PP_{GLI} (2 from B to D and 1 from D to B).

Fig. 3. Bland-Altman plot showing the agreement between the NHANES and SARA equations in predicting FEV_1 .

Table 3. IRR for mortality according to quartiles of FEV_1 percent predicted by different standards

	SARA	ERS	NHANES	GLI
Best quartile	Reference	Reference	Reference	Reference
III quartile	1.6 (0.78–3.44)	0.99 (0.49–2.01)	1.43 (0.7–3.01)	1.09 (0.52–2.31)
II quartile	2.36 (1.21–4.87)	1.38 (0.73–2.69)	2.07 (1.07–4.19)	1.98 (1.05–3.92)
Worst quartile	2.98 (1.56–6.09)	2.33 (1.29–4.37)	2.7 (1.43–5.38)	2.64 (1.43–5.14)
C statistic	0.434	0.419	0.435	0.425

Table 3 shows that the mortality rate is increased in patients in the worst two quartiles of FEV_1 PP expressed according to the SARA, NHANES, and GLI equations. Using the ERS equations, instead, an increased mortality was observed only in the fourth quartile. Overall, however, the discriminative capacity was poor, as reflected by a C statistic of 0.434, 0.419, 0.435, and 0.425 for quartiles of FEV_1 expressed as percent of SARA, ERS,

NHANES, and GLI predicted values, respectively (see also fig. 5).

After correction for body mass index, dyspnea, smoking, and distance walked at the 6-min walking test, the association between FEV_1 PP was weakened, and an increased risk of mortality was seen only in participants in the worst quartile of FEV_1 PP_{SARA} (HR: 2.14, 95% CI: 0.99–4.64) (table 4).

Fig. 4. Bland-Altman plot showing the agreement between the GLI and SARA equations in predicting FEV₁.

Table 4. Adjusted hazard ratio for mortality according to quartiles of FEV₁ predicted by different standards

	SARA	ERS	NHANES	GLI
Best quartile	Reference	Reference	Reference	Reference
III quartile	1.86 (0.87–4.01)	0.66 (0.32–1.37)	0.53 (0.25–1.14)	0.54 (0.26–1.12)
II quartile	1.77 (0.83–3.77)	0.66 (0.32–1.37)	0.85 (0.41–1.79)	0.61 (0.29–1.26)
Worst quartile	2.14 (0.99–4.64)	0.63 (0.34–1.16)	0.78 (0.43–1.41)	0.76 (0.42–1.37)

Adjusted for body mass index, dyspnea, distance covered at the 6-min walking test, and exposure to cigarette smoking.

Discussion

Our data show that prediction of FEV₁ according to the GLI equation has an excellent agreement with predictions made using an equation developed in a subset of our study population without respiratory diseases, which qualifies as the theoretical 'gold standard'. The agreement in women was less satisfactory compared to that in men

and also had wider agreement intervals. On the opposite end, the ERS equation underestimated the theoretical FEV₁ compared to the SARA equation by 9% on average and by 19% in women. The agreement between the SARA and the NHANES prediction was somewhat better, with an average underestimation of 5% overall and 9% in women.

Fig. 5. Probability of surviving, by quartiles of FEV1PP.

The finding that the ERS equation yields lower values compared to the GLI equation is in contrast with the finding by Sluga et al. [16], which reported lower predicted values obtained by the GLI equation. The sample of their study, however, had a mean age of 63 years, that is, more

than 10 years younger than ours. Furthermore, their ERS predicted values were corrected by a factor of 1.08, as recommended by Dutch guidelines. On the contrary, it has repeatedly been reported that the ERS equations tend to yield lower predicted values compared to other estimat-

ing equations, probably because of methodological issues and characteristics of the population in which the ERS equations have been developed [17–20]. This is also true for the ERS-GLI comparison: Quanjer et al. [21] reported larger predicted FEV₁ compared to ERS, although the discrepancy was smaller than the one we observed. Furthermore, the difference between estimated FEV₁ values was similar in men and women. It should be noted, however, that the population studied by Quanjer et al. [21] was younger, including about 50% of subjects aged <60 years. In the same study, in line with our results, there was little difference between the GLI and NHANES predicted values.

The clinical significance of the underestimation of FEV₁ by ERS and NHANES equations deserves discussion. On the one hand, it may cause a larger proportion of patients to get treatment, especially among women, and this is relevant in the elderly population where the benefit/risk ratio of respiratory drugs tends to be smaller [22] and some of the potential side effects, such as fractures [23] or pneumonia [24], can have a dramatic impact on the health status. On the other hand, however, this overestimation is more evident at levels of FEV₁ that are already relatively low, and therefore it does not necessarily change the decision about treatment. Furthermore, it is now generally accepted that the severity of COPD, and hence its treatment, should not be based only on the degree of FEV₁ reduction, but also on other clinical variables. Indeed, using a severity index such as the new GOLD classification, that also takes into account symptoms and exacerbation frequency, we found no difference in staging obtained using the different equations.

The overall capacity of predicting mortality on the base of FEV₁ reduction was low regardless of the reference equation used, with C statistics ranging from 0.41 for

FEV1PP_{ERS} and FEV1PP_{NHANES} to 0.43 for FEV1PP_{GLI}. The prognostic role of FEV1PP, regardless of the equation used, is further reduced when other variables with known impact on mortality (body mass index, dyspnea, functional capacity, and smoking exposure) are taken into account. This finding was not unexpected, as it has already been shown that the predictive capacity of FEV1PP is poor compared to alternative methods to express FEV₁, such as FEV₁ divided by height cubed or the FEV₁ quotient, that is FEV₁ divided by the sex-specific first centile of FEV₁ [25, 26]. Our data indicate that, with respect to prognosis, the GLI equation has not overcome the problems inherent in using FEV1PP, even if known biases – especially nonconstant variability of the estimate across the whole age range – has been addressed by the statistical method used to develop these equations. A limitation of this study is that we used FVC, not VC, in the calculation of the Tiffeneau-Pinelli index. Since VC tends to be larger than FVC [27], we might have systematically overestimated the FEV₁/VC ratio. Furthermore, men were over-represented, reflecting the high mean age of the sample. Since the proportion of women with COPD is increasing, this may make our results poorly generalizable to future cohorts of elderly COPD patients.

In conclusion, we showed that in elderly people with COPD, the GLI equation for predicting FEV₁ provides similar estimates compared to an equation developed in a subset without respiratory diseases of the population in which they are applied, and higher values compared to the ERS equation, especially in women. However, this does not translate in different GOLD class allocations of patients. Finally, the GLI equation does not improve the stratification of the risk of mortality in elderly people with COPD with regard to the ERS or NHANES equations.

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