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CASE REPORT

Effect of Switching from ECSC to GLI Spirometric Reference Values on Gold Classification of Severity of Airflow Obstruction

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ABSTRACT

Introduction: GOLD recommends to classify COPD severity of airflow obstruction according to the post bronchodilator FEV1 expressed as a percentage of the predicted value. GOLD also recommends to use the clinical classification based on dyspnea severity and exacerbation risk. However, in some countries like Belgium, the reimbursement of some COPD medicines is based on the GOLD spirometric classification. The replacement of the European Community of Steel and Coal (ECSC/ERS-93) reference values by the Global Lung Function Initiative (GLI-2012) is pending. This prompted us to identify patients susceptible to a change in airway obstruction severity classification with GLI- 2012.

Results: We analyzed retrospectively 9692 tests (3134 females) of smokers/ex-smokers with a FEV1/FVC post bronchodilation < 0.7. Age range: 40 to 95 years, height between 140 to 200 cm. Due to the non-linearity of GLI-2012 equations, the difference between the GLI-2012 and ECSC/ERS-93 equations for the predicted FEV1 ranged between 0.29 and 0.62 L in females and -0.05 and 0.69 in males. This leads for example to 43.6% changes from GOLD stage 1 to 2 in females. We developed a graphical tool for visualize the individual changes in GOLD spirometric stage.

Conclusion: The change from the ECSC/ERS-93 to the new GLI-2012 spirometric references will upgrade GOLD airflow obstruction grading in several patients, especially in females with mild disease. Prospective studies are needed to evaluate the impact of these changes on the treatment of COPD patients in a real live setting. We also propose using contour plots as a new gold standard to express differences between predicted values. Plotting all the possible differences amongst predicted variables allows a rapid identification of subjects who are more susceptible to exhibit significant changes in their predicted values when adopting a new reference set.

INTRODUCTION

Chronic obstructive lung disease (COPD) is a worldwide prevalent disease, mainly diagnosed in adult smokers or ex-smokers aged over 40 years. According to the GOLD recommendations [1], the diagnosis of COPD is based on the presence of airflow limitation, defined by a post-bronchodilator FEV1/FVC ratio below 0.7. Until 2016, stratification of airflow limitation into 4 stages of severity was done by expressing post-bronchodilator FEV1 as a percentage of the predicted value: stage 1, FEV1>80%, stage 2: FEV1 between 50 and 79%, stage 3: FEV1 between 30-49% and stage 4, FEV1<30%. Since the GOLD 2017 update, the spirometry is no longer used to classify COPD patients, the current staging system being based on symptoms (dyspnea or quality of life) and risk of exacerbation. Nevertheless, Belgium, , like some other countries, still use the old spirometric classification for the reimbursement of inhaled long-acting bronchodilators, based on the ECSC/ERS 1993 reference values for spirometry (ECSC/ERS-93).

Recently, a new set of reference values was proposed by the European Respiratory Society and the Global Lung Function Initiative: the Global Lung Function 2012, or GLI-2012 [2]. With the new GLI- 2012 equations, the lower limit of normality of FEV1 and FVC remains largely unaltered, but the predicted FEV1 and FVC are higher than those of the ECSC/ERS-93 [3]. Therefore, changes in the GOLD airflow obstruction grading may be expected in some COPD patients, which may impact on clinical decision making. For instance, in Belgium, reimbursement of inhaled long-acting bronchodilators in some patients currently classified by GOLD airflow obstruction severity as stage 1, would now become possible, due to an upgrade to the old GOLD stage 2. In this paper, the different GOLD stages will refer to grades of severity of airflow obstruction, not to the global COPD assessment.

The potential effect of the new spirometric equations on COPD staging has already been assessed in a general practice in The Netherlands [4]. These authors found that switching to the GLI-2012 reclassified 6-14% of COPD patients in a population of 3,370 adults. However, their conclusions of the ECSC/ERS 93 equations consisting of the multiplication of the FEV1 and FVC predicted values by a fixed factor of 1.08. This may eventually lead to an underestimation of the number of patients shifting from one GOLD stage to another.

In the present study, we investigated to which extent switching from the original ECSC/ERS-93 to the new GLI-2012 equation affected classification of airflow obstruction of COPD patients according to the GOLD. Moreover, we aimed to assess which groups of patients were more susceptible for a reclassification and more specifically, whether reclassification induced by the GLI-equations was dependent on gender, height and age. The last aim of this study was to propose a new graphical method to express the difference between two sets of reference values.

MATERIALS AND METHODS

The spirometric tests analyzed in the present study were obtained from unselected routine spirometry records performed in two tertiary care hospitals (Cliniques Universitaires Saint-Luc (Brussels) and CHU Dinant-Godinne (Godinne unit, Yvoir)) (N=33763 and 19657, respectively). Lung function tests were acquired in both in- and outpatients and performed between 1/1/2007 and 31/12/2013. Data obtained retrospectively were anonymized. Only smokers and ex-smokers between 40 and 95 years with a post-bronchodilator FEV1/FVC ratio < 0.70 were included. Non Caucasian subjects were excluded. All tests had to comply with the quality criteria of the ERS/ATS 2005 task force [5]. The following parameters were analyzed: age, sex, height, weight, smoking status (smoker, non-smoker or ex-smoker). Although other spirometric variables of (PEF, FEF, FEV6, etc.) were available we only retained those useful for the present study: post-bronchodilator FEV1, FVC, and FEV1/FVC.

The study was approved by the Ethics Committee of our Institution (B403201318648). Data analysis

The selection of the tests and removal of duplicates was done using Microsoft Excel 2010, the statistical analysis using the IMB SPSS software 24 and the contour plots using Matlab R2013b.

Demographic data were expressed as means±SD. Predicted values for FEV1 and FVC were calculated using both the prediction equations of the ECSC/ERS-93 and the GLI-2012.

The ECSC/ERS-93 equations are linear, valid only for Caucasians between 20 and 70 years of age FEV1 (in liters) is dependent on sex, age and height (4) according to the following formula:

For males: FEV1= 0.0430. Height - 0.0290.Age - 2.490 for females: FEV1= 0.0395. Height - 0.025.Age - 2.600

The GLI-2012 equations are non-linear. They are valid for 4 ethnic groups, are function of sex (range 3-95 yrs.), age, height and ethnicity.

For Caucasians, FEV1 (in liters) is predicted according to: M = exp(a0 + a1•ln(Height) + a2•ln(Age) + Mspline)

with the exact age in years, months and days, and height in cm. The coefficients a(n) are different for males and females. Mspline is an age-varying coefficient, given by lookup tables [2].

As often done for the ECSC/ERS-93 equations, reference values for subjects older than 70 years were obtained by extrapolation. Patients were subsequently classified as GOLD 1, 2, 3 and 4 (1) using both equations according to the following limits:

Stage 1, FEV1>80%,
Stage 2: FEV1 between 50 and 79%
Stage 3: FEV1 between 30-49%
Stage 4, FEV1<30%.

Patients who shifted from one GOLD stage to another were manually identified and the characteristics (age, height) of those who did and not shift were systematically assessed.

In a preliminary study we observed that the disparities between predicted FEV1 values derived from the ECSC/ERS-93 and the GLI-2012 equations were not randomly distributed among patients. We therefore tried to develop a mathematical model in order to identify variables or combinations of variables that could predict the magnitude of the changes and identify the phenotype of patients who were more likely to change in terms of predicted FEV1 and shift from one GOLD COPD class to another.

RESULTS

We analyzed 53817 tests which were acceptable according to the ATS/ERS recommendations [5]. After applying the inclusion criteria and removing duplicates, we retained 9692 tests (Figure 1).

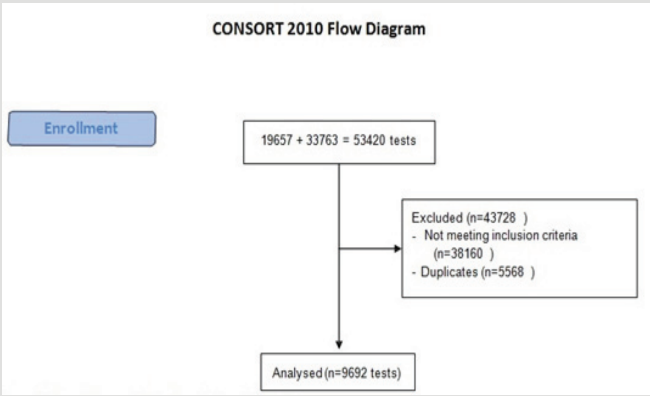

Figure 1: Consort diagram showing the selection of the tests.

The characteristics of the patients as well as the distribution of these characteristics are shown in Table 1, Figure 2A and 2B.

Table 1: Baseline characteristics of the included COPD patients.

	Males	Females	Total
Number of subjects (%)	6558 (67.7%)	3134 (32.3%)	9692
Age, yr	66.3 ± 11.3	64.3 ± 11.9	65.7 ± 11.5
BMI, kg/m²	26.8 ± 6.6	25.5 ± 6.4	26.4 ± 6.5
Height, cm	172.1 ± 7.2	160.1 ± 6.8	168.2 ± 9.0
Ex-smokers (%)	61.7	52.4	58.9
FEV1 post BD, L	1.86 ± 0.75	1.32 ± 0.55	1.68 ± 0.73
FVC post BD, L	**3.24 ± 1.01**	**2.25 ± 0.74**	**2.92 ± 1.04**
FEV1/FVC post BD, %	56.91 ± 11.33	58.28 ± 11.10	57.35 ± 11.28
FEV1 post BD, % ECSC/ERS93	61.74 ± 20.82	62.33 ± 21.58	61.93 ± 21.07
FEV1 post BD, % GLI-2012	58.67 ± 19.79	56.71 ± 19.51	58.03 ± 19.72

38.5 and 32.2 % of the male and female patients were older than 70 years. As expected, the % predicted FEV as highed using the eduation (p<6.666LJ student's paid t-test).

The distribution of the patients among the different GOLD stages using the two sets of equations is presented in table 1. Of the 2006 male and female patients classified as stage 1 using the ECSC/ERS- 93 equations, 682 (34%) were reclassified as stage 2 when using the GLI-2012. The percentage of shifters was 10.8 and 6.8 for stages 2 to 3 and stages 3 to 4, respectively. Significantly more female

(43.6, 15.1 and 9.2%,) than male subjects (43.6, 15.1 and 9.2%,) shifted from stage GOLD 1 to 2, from GOLD stage 2 to 3 and from GOLD stage 3 to 4, respectively (P<0.001). Changes in the opposite direction (i.e. from stage 2 to 1) were not observed.

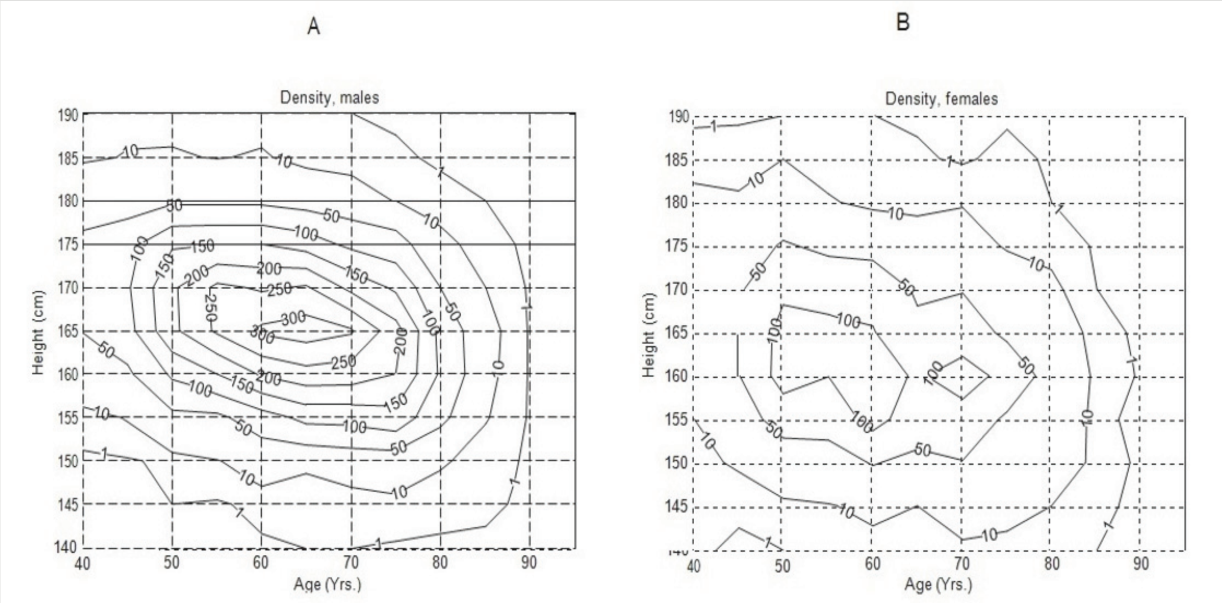

Figure 2: Density distribution of the subjects. A: males B: females

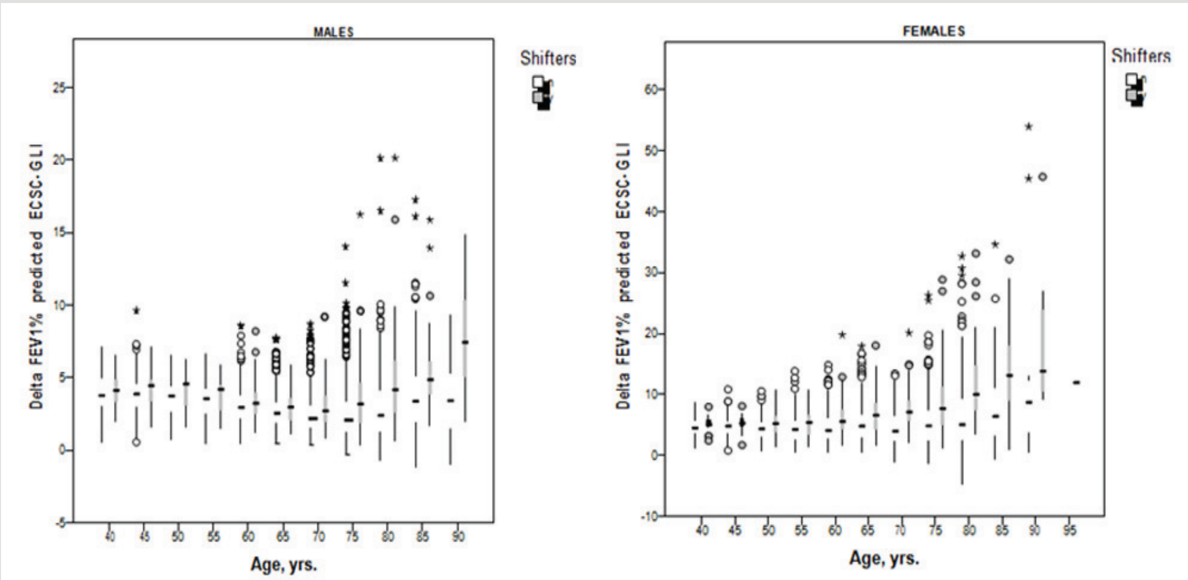

Figure 3: Box whisker plots of ECSC–GLI differences by age (in years) of FEV1 expressed in percentage of predicted values. Upper panel: males, lower panel: females. O = outliers; * = extremes. Non-shifters: white boxes, shifters: grey boxes.

Figure 3 represents the distribution of the difference in % predicted FEV1 between the ECSC/ERS-93 and the GLI-2012 equations for males and females according to age and sex. Differences tended to increase by age. A clear overlap was present between shifters and non-shifters, with the presence of outliers in both groups.

The difference between absolute predicted values of FEV1 derived from ECSC/ERS-93 and GLI-2012 is generally higher for females than males as shown on two contour plots (Figure 4).

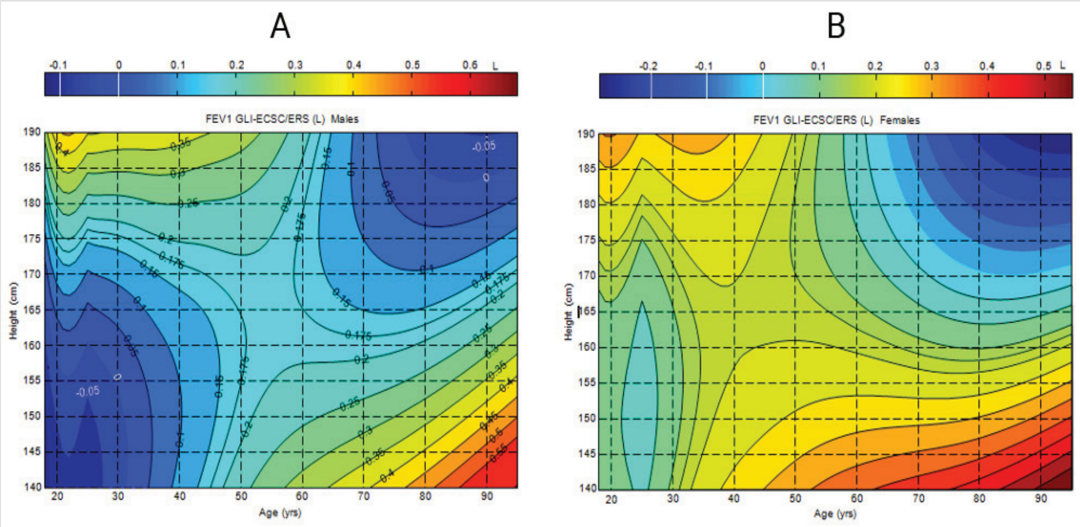

Figure 4: Difference between the predicted values of FEV1 (in litre) according to GLI and ECSC equations in males (A) and females (B). The color bars represent the magnitude of the differences.

These contour plots also show that the magnitude of the differences between predicted values is not only affected by sex, but also by age and height. For example, the difference is only 175 mL in a 50- year old female subject with a length of 170 cm, but reaches 300 mL in an 80-year old female with a length of 180 cm.

Since it is reasonable to expect that patients with a predicted FEV1 according to the ECSC/ERS-93 close to 80%, 50%, or 30% (the three fixed cut-off values used to classify COPD patients in four GOLD stages) are more susceptible to shift from a higher to a lower GOLD stage, it may be of interest to identify these patients. Figure 5

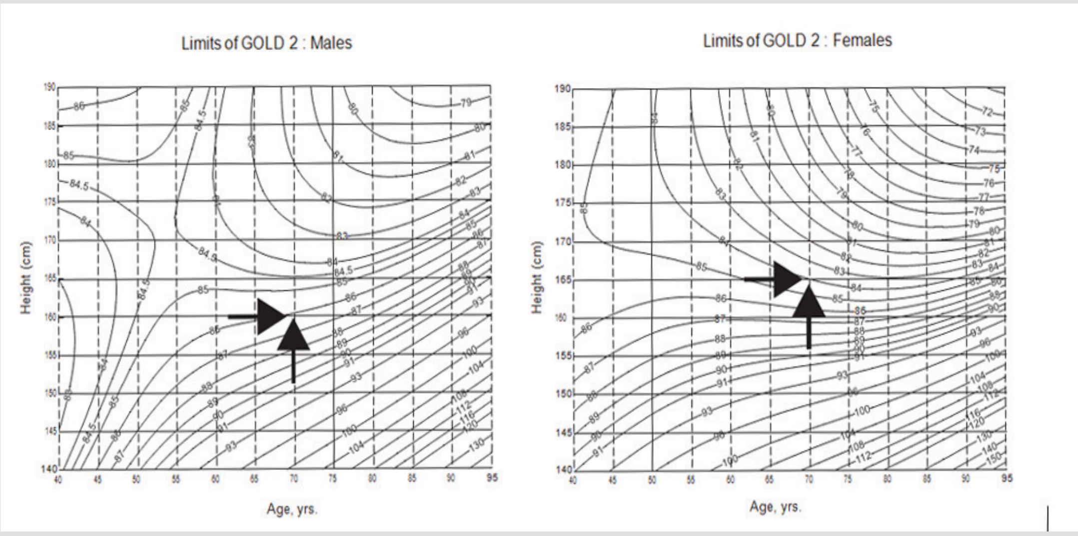

Figure 5: Limits of the GOLD 2 stage according to GLI-2012. The lines represent the % predicted FEV1 (ECSC/ERS-93) corresponding to 80% of predicted FEV1 with GLI-2012. Using the age, height and actual %FEV1 (ECSC/ERS-93) allows to identify the patients, in whom a change from GOLD stage 1 to stage 2 will occur. For further explanations: see text.

predicts the changes from GOLD stage 1 to 2, by attributing the corresponding percentage FEV1 according to the ECSC/ERS-93 reference values to patients between 40 and 95 years and 140 and 190 cm who exhibit an FEV1 of 80% predicted according to GLI-2012. Each line matches a given predicted FEV1 (ECSC/ERS 93) with several possible conditions that correspond with 80% of the predicted FEV1 according to the GLI-2012 reference equation. For example, a 70-year old woman, with a height of 165 cm will be reclassified as GOLD 2 according to GLI-2012 once her %FEV1 has fallen below 84% predicted, according ECSC/ERS 93 (see arrows on Figure 5). Likewise, a man aged 70 years with a height of 160 cm will also shift from GOLD stage 1 to 2 according to GLI-2012, once his FEV1 drops below 86% predicted according to ECSC/ERS 93.

DISCUSSION

The present study shows that, in a population of subjects assessed in two tertiary care hospitals, the introduction of the new GLI-2012 reference equations for spirometry upgrades airflow obstruction severity in a significant number of COPD patients. It also demonstrates that these changes do not occur at random, and are more likely to be seen in the elderly, in females and in patients in whom the FEV1 expressed as a predicted value using the ESCS/ERS-93 equations is just above one of the three cut-off point used to define the different GOLD stages of severity of airflow obstruction for COPD.

As expected, we obtained higher rates of reclassification of GOLD stages than Sluga et al [4], because we used the uncorrected ECSC/ERS93 equations, as recommended in Belgium and in most European countries. Proportionally, changes in GOLD stages were more frequent in females. This can be attributed to the difference in predicted FEV1 between the two sets of reference values, which is larger in women as previously demonstrated by Quanjer et al. [6] and confirmed by Figure 4.

We are the first authors to express changes in reference values for FEV1 between two sets of equations using contour plots. Such plots easily visualize the patients prone to expect larger or smaller changes in predicted FEV1 values. They also convincingly demonstrate that such changes are neither uniform nor at random. These changes can be attributed to the non-linearity of the GLI-2012 equations, which contrast with the linearity of the ECCS/ERS-93 equations. Our contour plots also highlight the plateau of the predicted FEV1 between 18 and 25 yrs. according to the ECCS/ERS-93 equations. Indeed, between age 18 and 25, the age of 25 is used to compute the FEV1 predicted values according to this equation, whereas age varies continuously between 18 and 25 when using the GLI-2012 equations.

From a practical point of view, the contour plot presented in figure 5, helps to predict the changes from GOLD stage 1 to 2 from changes in predicted values. In females, nearly all subjects smaller than 165 cm with a %FEV1 (ECSC/ERS-93) between 80% and 86% will switch to stage 2 of GOLD using the new predicted values.

Changes from COPD GOLD stage 2 to 1 or from GOLD stage 3 to 2 were not observed, although they could theoretically occur. Indeed, figure 4 shows that the use of the GLI-2012 reference values may lead to a lower predicted FEV1 compared to the ECCS/ERS-93 reference values (upper right corner of the figure). However, it is very unlikely that this may occur in clinical practice, since a substantial decrease in predicted FEV1 is only expected to happen in older (above 80 years) and very tall (above 180 cm) women who, by chance, exhibit a predicted FEV1 value just below 80, 50 or 30% of predicted FEV1. Figure 2 shows that very few subjects had such characteristics in our population.

The present study has several limitations. First, we have limited access to the clinical data of the patients, due to the retrospective nature of the study, based on the records of our pulmonary function laboratories. Second, the spirometers used in the two centers were of different brands, although they are all certified and only used by highly-trained PFT technologists. Third, it is difficult to extrapolate our results, generated in two tertiary academic hospitals, to other clinical settings, such as primary care medicine or an outpatient COPD clinic of a regional hospital. This may undoubtedly have resulted in a selection bias. Our observation that shifts more frequently occurred from GOLD stage 1 class to GOLD stage 2 than from GOLD stage 2 to 3 or GOLD stage 3 to 4, make our findings particularly relevant for the primary care physician. At least, in most countries, the GOLD recommendations take no more into account consideration the results of spirometry for patient classification into the four groups ABCD. However, some countries like Belgium do not follow the new GOLD guidelines and still require a spirometric classification to reimburse long-acting bronchodilators. Another implication of the change in spirometric predicted values is the interpretation of some clinical trials on COPD. As an example, the UPLIFT study, one of the most cited clinical trial on COPD medication, used the ECSC/ERS-93 reference values for patients selection (FEV1<70%) [7]. It could be of interest to investigate whether the conclusions of UPLIFT might have been different if the GLI-2012, had been used.

Increasing attention is currently paid to the implications of the switch from the frequently used ECSC/ERS-93, Wang or Knudson reference equations to the GLI-2012 equations on clinical decision making. Stanojevic et al. recently reported that the Wang and Knudson reference values may either mask or falsely indicate a clinical deterioration or improvement in cystic fibrosis patients [8]. In two other study populations, the use of the GLI-2012 equation resulted in a slight increase in subjects with a restrictive pulmonary syndrome [6,9]. The present study does not allow assessing the effect of GOLD reclassification secondary to changes in predicted values on COPD management and on the health-related costs. Since the new GOLD recommendations propose that COPD management should essentially be guided by symptoms (dyspnea) and frequency of exacerbations and not by GOLD spirometric stage, the impact on treatment of the GLI-2012 is probably small, unless reimbursement criteria of some treatment options in COPD rely on it.

The GLI-2012 FEV1 values are generally higher than the ECSC/ERS-93 reference values. This means that a patient with COPD GOLD stage 1 will reach stage 2 at an earlier age once the GLI-2012 reference values will have been implemented. This is, however, not an issue in countries where the NHANES III reference equations are in use, since differences between the GLI-2012 and NHANES reference values are very small [7].

CONCLUSION

The change from the ECSC/ERS 93 to the new GLI-2012 spirometric references will induce an upgrade in airflow obstruction severity in a significant number of patients, especially in females. In countries using the classification based on airflow obstruction severity, this would lead to an increased number of patients eligible to receive long-acting bronchodilators. The medical and economic impacts of these changes for the treatment of COPD patients should be further evaluated. We also propose using contour plots to represent the potential differences in predicted values in future publications. Plotting all the possible differences between predicted variables may help to identify groups of subjects susceptible to have significant changes in their predicted values when adopting a new reference set.

Table 2: GOLD classification of severity of airflow obstruction of COPD patients according to the ECSC/ERS93 and GLI-2012 reference equations all patients.

GOLD STAGE	Total	GLI-2012			
	N (%)	1 N (%)	2 N (%)	3 N (%)	4 N (%)
ECSC/ERS-93					
Total N (%)	9692 (100)	1324 (13.7)	4936 (50.9)	2594 (26.8)	838 (8.6)
1 N (%)	2006 (20,7)	1324 (66.0)	682 (34.0)	0	0
2 N (%)	4769 (49,2)	0	4254 (89.2)	515 (10.8)	0
3 N (%)	2230 (23)	0	0	2079 (93.2)	151 (6.8)
4 N (%)	687 (7,1)	0	0	0	687 (100)

Males

GOLD STAGE	Total N (%)	GLI-2012			
		1 N (%)	2 N (%)	3 N (%)	4 N (%)
ECSC/ERS-93					
Total N (%)	6558 (100)	957 (14.6)	3340 (50.9)	1723 (26.3)	538 (8.2)
1 N (%)	1355 (20.7)	957 (70.6)	398 (29.4)	0	0
2 N (%)	3224 (49.2)	0	2942 (91.3)	282 (8.7)	0
3 N (%)	1527 (23.3)	0	0	1441 (94.4)	86 (5.6)
4 N (%)	452 (6.9)	0	0	0	452 (100)

Females

GOLD STAGE	Total N (%)	GLI-2012			
		1 N (%)	2 N (%)	3 N (%)	4 N (%)
ECSC/ERS-93					
Total N (%)	3134 (100)	367 (11.7)	1596 (50.9)	871 (27.8)	300 (9.6)
1 N (%)	651 (20,8)	367 (56.4)	284 (43.6)	0	0
2 N (%)	1545 (49,3)	0	1312 (84.9)	233 (15.1)	0
3 N (%)	703 (22,4)	0	0	638 (90.8)	65 (9.2)
4 N (%)	235 (7,5)	0	0	0	235 (100)

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