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GLI-12 Reference Values versus Fixed 0.7 Ratio for the Detection of Airflow Obstruction in the Presence of Lung Hyperinflation

Lora Wahab[a] Christian G. Cornelissen[a] Wolfram Windisch[b] Michael Dreher[a]

[a]Department of Pneumology and Intensive Care Medicine, University Hospital RWTH Aachen, Aachen, Germany; [b]Cologne Merheim Hospital, Department of Pneumology, Kliniken der Stadt Köln, gGmbH, Witten/Herdecke University, Witten, Germany

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Obstruction · Prediction equations · Hyperinflation · Reference values · Global Lung Initiative 2012

Abstract
Introduction: Airflow obstruction (AO) is evidenced by reduced forced expiratory volume in 1 s/forced vital capacity (FEV1/FVC) with the threshold for diagnosis often being set at <0.7. However, currently the ATS/ERS standards for interpretation of lung function tests recommend the lower limit of normal (LLN), calculated by reference equations of the Global Lung Initiative from 2012 (GLI-12), as a threshold for AO diagnosis. The present study aims to investigate phenotypes, with focus on hyperinflation, which influence AO prevalence defined by FEV1/FVC < LLN when compared to the fixed 0.7 threshold. ***Methods:*** Data from 3,875 lung function tests (56.4% men, aged 18–95) including 3,824 body plethysmography recordings performed from July 2021 to June 2022 were analysed. The difference between both classifiers was quantified, before and after stratification by sex, age, and hyperinflation. ***Results:*** AO diagnosis was significantly less frequent with the LLN threshold (18.2%) compared to the fixed threshold (28.0%) ($p < 0.001$) with discordance rate of 10.5%. In the presence of mild or moderate hyperinflation, there was substantial agreement (Cohen's kappa: 0.616, 0.718) between the classifiers compared to near perfect agreement in the presence of severe hyperinflation (Cohen's kappa: 0.896). In addition, subgroup analysis after stratification for sex, age, and hyperinflation showed significant differences between both classifiers. ***Conclusion:*** The importance of using the LLN threshold instead of the fixed 0.7 threshold for the diagnosis of AO is highlighted. When using the fixed threshold AO, misdiagnosis was more common in the presence of mild to moderate hyperinflation.

Introduction

Airflow obstruction (AO) as assessed by spirometry is the cornerstone of the diagnosis of obstructive pulmonary disease [1]. It is determined by a decrease of the forced expiratory volume in 1 s/forced vital capacity (FEV1/FVC). The fixed threshold value of <0.7 is currently still used in COPD reports/guidelines such as the Global Initiative for Chronic Obstructive Lung Disease (GOLD) [1] report and ATS/ERS guideline on COPD [2] without any supporting evidence, while acknowledging that it does not account for the age-dependent risk of over- and underdiagnosis [1, 3], a fact already observed back in the

karger@karger.com
www.karger.com/bmh

Karger
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Correspondence to:
Lora Wahab, lwahab@ukaachen.de

19th century by John Hutchinson, the inventor of spirometry [4]. The use of the lower 5th percentile as the lower limit of normal (LLN) for FEV1/FVC attends to this, where the FEV1/FVC mean as well as +/− 1.64 standard deviation offset (z-score) is calculated from a reference equation using age, height, sex, and ethnicity as predictor variables [5].

Previously used third National Health and Nutrition Examination Survey (NHANES III) equations [6] in the USA as well as the European Community for Steel and Coal (ECSC 1993) equations [7], mostly used in Europe, were derived from data sets that accounted only for a small variety of ethnicities and age span. Additionally, the ECSC 1993 equations for women were not derived from a data set representative for a female population but estimated as 80% of the male equations [8]. Those problems were discussed back in 2008 at the European Respiratory Society (ERS) Annual Congress in Berlin, Germany, resulting in the establishment of the Global Lung Initiative (GLI) Network and publication of new reference equations in 2012 [8, 9]. Currently, the proposed reference equations of the GLI from 2012 (GLI-12) [9] are being taken up in the USA and Europe. Compared to the NHANES III and ECSC 1993 equations, the GLI-12 equations are derived from a larger population (97,759 records, 55.3% females) of healthy non-smokers covering a wide variety of ethnicities and samples of persons aged 3–95 years [9]. In addition, an ethnic independence of the FEV1/FVC index was observed [8].

Addressing the recommendations of the American Thoracic Society (ATS) and ERS [8], the current acting guideline for standardisation of spirometry in Germany recommends the use of the GLI-12 reference equations for the evaluation of presence of AO since 2015 [10]. There is an abundance of articles available examining the applicability and influence of the new reference equations in different ethnic groups [11–14]. However, currently, the influence of the new spirometry equations on the diagnosis of AO in the context of the severity of pathological changes of static lung volumes needs more studies and research. Therefore, we aimed to investigate the influence of the implementation of the GLI-12 reference equations for the evaluation of spirometry with regard to over- and underdiagnosis of AO compared to the previously widely used fixed ratio, FEV1/FVC <0.7. In addition, we aim to identify phenotypes associated with differences in the prevalence of AO diagnosis when using the LLN threshold calculated by the GLI-12 reference equations versus the fixed 0.7 threshold.

Materials and Methods

Study Population

This retrospective study was approved by the Ethics Committee of the Medical Faculty of the RWTH Aachen University (approval reference EK 22-382). We analysed data from routine spirometry and body plethysmography recordings performed at the Department of Pneumology and Intensive Care Medicine of the University Hospital RWTH Aachen, Germany from July 2021 to June 2022. The lung function tests were performed by trained nursing staff according to applicable guidelines [15, 16] on a Master Screen Body by Jaeger® spirometry and body plethysmograph.

Data from 5,286 lung function tests were used. All recordings with missing data for FEV1/FVC, recorded age over 95 years or under 18 years, recorded weight under 20 kg or recorded height under 100 cm were excluded. In case of repeated lung function, assessments performed in a single patient within the study's time interval only the first recording was chosen for further analysis, while subsequent recordings were ignored. As the non-European population in Germany accounts for only 4.2% of the German population (reference year 2021) [17], Caucasian ethnicity was assumed for all recordings.

Lung Function Measurements, Equations, and Definitions

FEV1 and FVC were measured by a spirometer and the FEV1/FVC index was calculated. TLC and RV were measured with body plethysmography and the coefficient RV/TLC calculated. LLN (1.645 negative standard deviation offset, z-score <−1.645) was calculated using the GLI-12 reference equations. ECSC 1993 reference equations [7] were used for the calculation of the reference values of the static lung volume measurements, as there is no severity evaluation scale for hyperinflation indices based on the new GLI Network equations for interpretation of static lung volumes [18].

AO was defined as FEV1/FVC <0.7, and also as FEV1/FVC < LNN calculated by GLI-12 reference equations. The assigned labels AO and no AO using the LLN threshold were evaluated as ground truth (truth value), as the use of the LLN threshold is currently recommended by the German spirometry guideline [10] as well as by the ERS/ATS standards for interpretation of pulmonary function tests [19]. Disagreements between both definitions were classified as overdiagnosis (FEV1/FVC <0.7 and FEV1/FVC > LLN [GLI-12]) or underdiagnosis (FEV1/FVC >0.7 and FEV1/FVC < LLN [GLI-12]). Hyperinflation was defined as RV/TLC > upper limit of normal (ULN, 1.645 positive standard deviation offset, z-score >+1.645) and RV > ULN, as currently recommended by ERS/ATS standards for interpretation of pulmonary function tests [19]. Severity of hyperinflation was divided in 3 groups: low hyperinflation <140%, moderate 140–170%, and severe >170% elevation of the RV/TLC measure predicted percent value as recommended in the German recommendations for interpretation of body plethysmography [20].

Statistics

All statistical analyses were performed using the statsmodels [21] library version 0.12.2 and SciPy [22] library version 1.7.1 with the programming language Python 3.8 [23]. Jupyter Notebook Version 6.4.5 [24] was used for data exploration and visualisation.

A Shapiro-Wilk test of normality was performed. Median and interquartile range (IQR, presented as 25% percentile [Q1] to 75% percentile [Q3]) were calculated and reported for all not normally distributed data, otherwise mean and standard deviation were

Table 1. Demographic characteristics (*N* = 3,875, 56.39% men) and observed spirometry and body plethysmography median values and z-scores

	Median	IQR Q1–Q3	Median men (*n* = 2,185)	IQR men Q1–Q3	Median women (*n* = 1,690)	IQR women Q1–Q3
Age, years	63	53 to 73	64	55 to 73	62	51 to 74
Height, cm	172	165 to 179	178	172 to 182	165	160 to 169
Weight, kg	80	68 to 93	85	75 to 95	71	61 to 85
FEV1/FVC	0.76	0.69 to 0.81	0.75	0.68 to 0.81	0.77	0.70 to 0.82
FEV1/FVC GLI-12 z-score	−0.34	−1.24 to 0.40	−0.3	−1.24 to 0.45	−0.37	−1.25 to 0.34
FEV1 GLI-12 z-score	−1.59	−2.57 to −0.68	−1.6	−2.55 to −0.66	−1.57	−2.58 to −0.70
FVC GLI-12 z-score	−1.42	−2.34 to −0.65	−1.47	−2.38 to −0.65	−1.36	−2.26 to −0.65
TLC ECSC z-score	0.57	−0.66 to 1.72	0.13	−1.12 to 1.33	1.07	0.04 to 2.13
RV ECSC z-score	2.24	0.98 to 3.86	1.93	0.65 to 3.56	2.62	1.54 to 4.28
RV/TLC ECSC z-score	1.74	0.80 to 2.97	1.45	0.47 to 2.71	2.03	1.18 to 3.30

IQR, interquartile range.

calculated and reported. Discordance rate (DR) and concordance rate between both classifiers were calculated and difference of spread of sex, age, TLC, RV, and RV/TLC z-score indices between the concordant group (CG) and the discordant group (DG) was examined and reported using Mann-Whitney U test for continuous and χ^2 test for categorical variables. A contingency table, depicting the frequency distribution using the LLN threshold calculated by GLI-12 reference equations and the fixed threshold (FEV1/FVC <0.7) as classifiers for AO, was generated. Prevalence of AO using each classifier was reported. A McNamar's test statistic and *p* values for equality of the two classifiers were calculated. Subgroup analysis was performed after data stratification for sex, age, and presence of hyperinflation. Bonferroni-Holm method was used to control the family-wise error rate. Significance level was set at $\alpha = 0.05$ for all performed tests.

Considering the large sample size, we used Cohen's kappa measure to quantify the magnitude of the observed agreement between classifiers after stratification for sex, age, and hyperinflation. Values <0 were rated as poor, 0.01–0.20 as slight, 0.21–0.40 as fair, 0.41–0.60 as moderate, 0.61–0.81 as substantial, and 0.81–1.00 as almost perfect agreement, as suggested by Landis and Koch [25].

Furthermore, we accounted for the large sample size by calculating calibrated statistic scores and calibrated *p* values (pC) for the whole data set and all subgroups with sample size >300 after stratification for sex, age, presence of hyperinflation and restriction. A sample size of 50 (Fc,50), 100 (Fc,100), and 300 (Fc,300) was used to calculate the calibrated statistic score as demonstrated by Park et al. Fc,50, Fc,100, and Fc,300 score >3.84 (+ + +) showed strong significance, while Fc,50, Fc,100, and Fc,300 score <3.84 (− − −) showed strong insignificance. Fc,50 and/or Fc,100 <3.84 and Fc,300 >3.84 (− + + or − − +) were considered of weak significance, as suggested by Park et al. [26].

Results

In total 3,875 (56.4% men) spirometry recordings and 3,824 (56.5% men) body plethysmography recordings from patients aged 18–95 years were selected for final analysis. The median age was 63 (IQR: 53–73) years and the median height 172 (IQR: 165–179) cm, shown in Table 1. Most recordings were from patients aged 41–60 (32.8%) and 61–80 (46.8%) years, while only 10.8% were from patients aged >80 years and 11.5% from patients aged 18–40 years.

Overall, a median FEV1/FVC of 0.76 (IQR: 0.69–0.81) was observed from all spirometry recordings, further median (IQR) spirometry values are shown in Table 1. AO was observed in 707 (18.2%, LLN threshold calculated by GLI-12) versus 1,085 (28.0%, fixed threshold of 0.7) recordings. The overall calculated median FEV1/FVC z-score was −0.34 (IQR: −1.24 to 0.40), as shown in Table 1.

Overdiagnosis of AO was observed when applying the fixed 0.7 threshold definition in 12.4% of the records, while underdiagnosis was observed in only 2.1%, as shown in Figure 1. Additionally, only recordings of patients <40 years old showed to account for the small proportion of AO underdiagnosis, while AO overdiagnosis was observed exclusively in recordings of patients aged >40 years old, as shown in Figure 1. DR for diagnosis of AO was 10.5% (408 recordings). Age, sex, and hyperinflation but not TLC measurements' spread between the DG and CG showed significant disparity ($p < 0.001$) for all variables of interest between both groups, with significantly higher median z-scores in the DG for RV (DG: 2.98 [IQR: 1.45–4.72] versus CG: 2.18 [IQR: 0.93–3.75] and for RV/TLC (DG: 2.22 [IQR: 1.22–3.29] versus CG: 1.70 [IQR: 0.76–2.92]), as shown in Table 2. The proportion of recordings detecting severe hyperinflation was lower in the DG by RV% TLC: DG 3.9% versus CG 8.4%, while there was a comparable proportion of

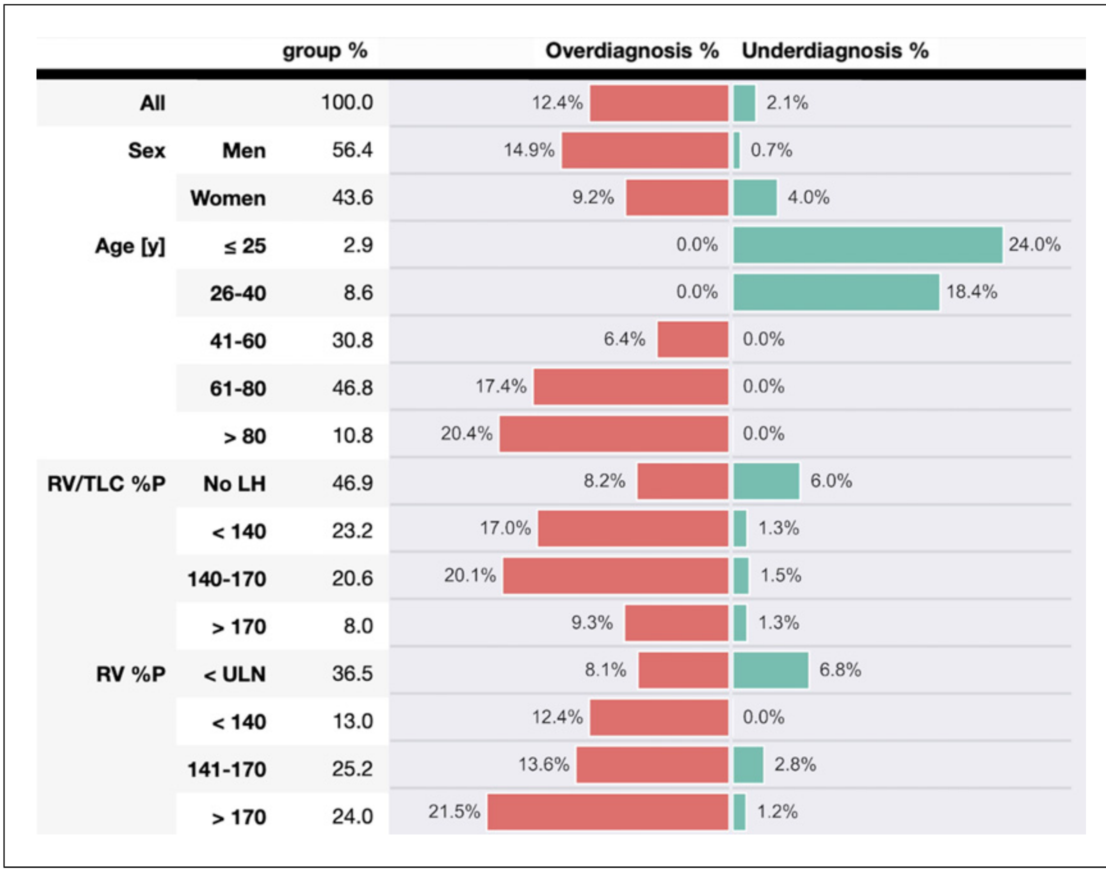

Fig. 1. Rate of underdiagnosis and overdiagnosis using the fixed threshold definition (FEV1/FVC <0.7) as a classifier of AO versus FEV1/FVC LLN threshold calculated by GLI-12 reference equations. No LH, no lung hyperinflation.

recordings with severe hyperinflation by RV (DG: 27.4% vs. CG: 23.3%). On the other hand, the proportion of patients with no lung hyperinflation by RV was 37.6% (CG) versus 27.7% (DG) and by RV/TLC was 48.2% (CG) versus 35.5% (DG). Patients with mild or moderate hyperinflation by RV and RV/TLC accounted for most of the patients in the DG (RV [DG: 42.9% vs. CG: 37.5%]; RV/TLC [DG: 58.8% vs. CG: 42.1%]).

Equality between the two AO classifiers was tested by McNemar test. A significant difference (*p* value <0.001 with strong significance after calibration, + + +) was found in the detection of AO when using FEV1/FVC LLN threshold versus the fixed threshold definition (FEV1/FVC <0.7) despite the calculated Cohen's kappa value for agreement between both classifiers showing substantial agreement (Cohen's kappa: 0.708). This was also observed after stratification of the data for men (*p* value <0.001, pC: + + +, Cohen's kappa: 0.674) and women (*p* value <0.001, pC: + + +, Cohen's kappa: 0.756).

Additionally, significant results for the difference in AO diagnosis between both classifiers were observed for all further subgroup analysis. However, *p* value calibration showed weak significance (pC: – – +) for ages 26–40, 41–60 (pC: – + +) as well as RV/TLC %predicted >170% (pC: – – +) with Cohen's kappa score of 0.883, 0.856, and 0.896, respectively, indicating almost perfect classifier agreement. These results indicate that the use of either threshold leads to a lower chance of misclassification in patients aged in the range 26–60 years as well as in patients with severe hyperinflation.

Cohen's kappa values showed only moderate classifier agreement in patients with no hyperinflation (RV%TLC Cohen's kappa: 0.563, RV Cohen's kappa: 0.554) and the classifier agreement increased with higher levels of lung inflation. This higher rate of misdiagnosis of AO in patients with no, mild, or moderate hyperinflation is shown in Figure 2. Further statistics and subgroup analysis can be found in Table 3 and Figure 2.

Table 2. Discordance and concordance group spread of sex, age, and hyperinflation indices

	DR = 10.5%		CR = 89.5%		*p* value
	median	IQR, Q1–Q3	median	IQR, Q1–Q3	
Sex (male)	65.7%		55.3%		<0.001
Age, years	71	63 to 79	62	52 to 72	<0.001
RV ECSC z-score	2.98	1.45 to 4.72	2.18	0.93 to 3.75	<0.001
RV/TLC ECSC z-score	2.22	1.22 to 3.29	1.70	0.76 to 2.92	<0.001
TLC ECSC z-score	0.46	−0.67 to 1.83	0.57	−0.66 to 1.71	0.463

Percent recordings of male patients proportion reported for each group. DR, discordance rate; CR, concordance rate; IQR, interquartile range.

Discussion

We present a large-scale retrospective study comparing the use of the FEV1/FVC LLN as a threshold value, calculated using GLI-12 reference equations, against the fixed threshold <0.7 for the diagnosis of AO with respect to static lung volumes measurements, usually performed when evaluating lung function status by body plethysmography. This study confirms previous findings that the use of the fixed threshold of 0.7 for the diagnosis of AO leads to differences in the prevalence of AO when compared to using the LNN threshold [11–14]. We have now shown that for patients with mild or moderate hyperinflation the disparity between both AO definitions is higher than in patients with severe hyperinflation.

Misdiagnosis of AO in the Presence of Mild or Moderate Hyperinflation

In this study, a significant difference in the prevalence of AO was seen in 12.4% of subjects when using the fixed 0.7 threshold as a classifier. Overall, the prevalence of AO was found to be 18.2% (by LLN criterion) versus 28.0% (by fixed threshold criterion), a result that is similar to that observed in other cohorts [27]. In the present analysis, the LLN threshold was set to a z-score <−1.645, the lower 5th percentile, as recommended by ERS/ATS [19]. However, it is argued that a threshold of <−1.96 could be more suitable for subjects with no lung disease history [28]. This would reduce the false-positive rate but would yield an even lower AO detection rate and much higher discordance between both classifiers. The diagnosis of AO should not be made solely based on spirometry findings but include other clinical features of the patient [28]. On the other hand if applied to diagnosis of hyperinflation, a z-score threshold of >+1.96 ULN should be critically assessed and debated, as changes in hyperinflation indices are shown to associate with the severity of COPD, the progression of dyspnoea and exacerbations [29, 30].

As static lung volume measurements provide further insight into pathophysiology of lung diseases, we demonstrated that the rate of misdiagnosis of AO in the presence of hyperinflation is not robust. The application of the fixed 0.7 threshold for a diagnosis of AO leads to higher over- and underdiagnosis rates in patients with mild or moderate hyperinflation. Of note, AO diagnosis using the GLI-12 LLN threshold has previously been shown to associate with significant higher values for TLC [31], as hyperinflation tends to occur more often in patients with moderate to severe chronic obstructive pulmonary disease (COPD) [32] as well as patients at risk for COPD diagnosis [33]. This can be attributed to a discordant decrease of FEV1, VC versus an increase of the hyperinflation markers, while a reduction in RV following acute bronchodilator is shown to lead to an improvement of AO markers [34]. Additionally, presence of hyperinflation has been shown to associate with cardiovascular abnormalities and events as it leads to impaired left ventricular filling and reduction of left ventricular mass [35] and could lead to chronic chest pressure alterations, known to be important not only in the context of diagnosis of AO [36]. The interpretation of the spirometry results in the context of static lung volume findings provides evidence that a fixed threshold for diagnosis of AO may be unsuitable in the presence of mild to moderate hyperinflation. While static lung volume measurements are not essential for a diagnosis of AO, physicians should consider, where possible, reporting spirometry findings with reference to static lung volume data, as it pertains not only to pathophysiological processes in the respiratory system [36]. On the other hand, it is also argued that the use of either threshold (<0.7 or LLN) for the diagnosis of AO should be interpreted in the context of presence of other lung function abnormalities, such as decrease of FEV1 or hyperinflation, both associated with a risk for adverse events in the presence of AO [27, 33].

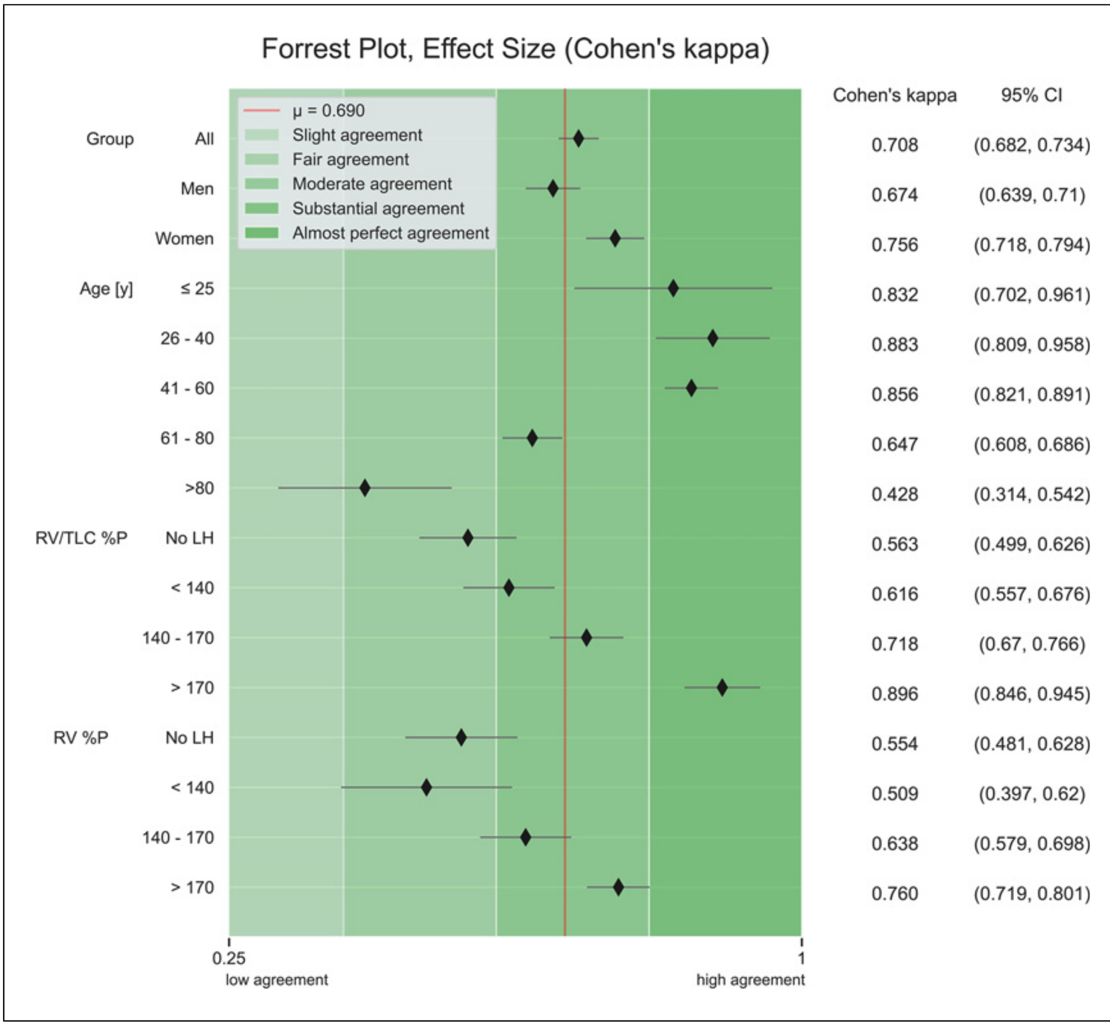

Fig. 2. Forrest plots for Cohen's kappa (Effect Size) showing the agreement between using the fixed threshold definition (FEV1/FVC <0.7) as a classifier of AO versus the FEV1/FVC LLN threshold calculated by GLI-12 reference equations before and after stratification for sex, age, and hyperinflation. The figure shows that the phenotypes of patients with no, mild, or moderate hyperinflation had a lower prevalence of misdiagnosis using the LLN GLI-12 threshold versus the fixed 0.7 threshold. On the other hand, the differences between both classifiers were much smaller in those with severe hyperinflation. Red vertical line: mean Cohen's kappa of 0.690 (substantial agreement). No LH, no lung hyperinflation.

Age Dependant Misdiagnosis Using the Fixed 0.7 Threshold versus LLN Calculated by GLI-12 Reference Equations

The data additionally reflect the physiological age-related decline in the FEV1/FVC ratio with significantly higher overdiagnosis rate of 17.4% and 20.4% in the groups of the 61–80 and over 80 years old patients' recordings, respectively, when using the fixed 0.7 threshold value. In our data, the rate of misdiagnosis (6.4%) showed to be lowest for patient's recordings aged 41–60, accounting for almost 1/3 of all recordings. The drawbacks of the fixed 0.7 threshold, when applied to all age groups have been previously acknowledged [1, 5]. These results suggest that using the FEV1/FVC LLN calculated by GLI-12 reference equations is more suitable for the evaluation of spirometry recordings of patients either side of age 41–60, even though it may be more cumbersome to apply than the fixed threshold.

Strengths and Drawbacks

A major strength of this study is the use of a large sample of recordings performed with the same body plethysmograph and spirometry device. While most subgroups are large, recordings of patients <40, >80 years

Table 3. Equality of FEV1/FVC LLN threshold calculated by GLI-12 reference equations versus the fixed threshold definition (FEV1/FVC <0.7) as a classifier of AO

	Group		McNamar *p* value	Fc,50	Fc,100	Fc,300	*p* cal
	N	%					
All	3,875	100.0	<0.001	4.519	9.038	27.113	+ + +
Sex							
Men	2,185	56.4	<0.001	5.861	11.722	35.167	+ + +
Women	1,690	43.6	<0.001	2.844	5.687	17.062	+ + +
Age							
≤25 years	114	2.9	0.014	n.a.	n.a.	n.a.	n.a.
26–40 years	333	8.6	<0.01	1.351	2.703	8.108	− − +
41–60 years	1,195	30.8	<0.001	2.552	5.105	15.314	− + +
61–80 years	1,815	46.8	<0.001	7.025	14.05	42.149	+ + +
>80 years	418	10.8	<0.001	9.211	18.421	55.263	+ + +
RV/TLC %P							
No LH	1,819	46.9	<0.001	3.28	6.561	19.683	− + +
<140	899	23.2	<0.001	6.737	13.473	40.42	+ + +
140–170	798	20.6	<0.001	5.926	11.852	35.557	+ + +
>170	308	8.0	<0.01	1.461	2.922	8.766	− − +
RV %P							
No LH	1,414	36.5	<0.001	3.192	6.384	19.153	− + +
<140	503	13.0	<0.001	5.765	11.531	34.592	+ + +
140–170	977	25.2	<0.001	5.197	10.394	31.181	+ + +
>170	930	24.0	<0.001	5.048	10.095	30.285	+ + +

n.a., not applicable; No LH, no lung hyperinflation; *p* cal, *p* value calibrated.

and with a severe restrictive pattern were underrepresented. Additionally, the recordings represent the current non-healthy population treated at a tertiary care centre without providing a diagnosis label (asthma, COPD, smoker, non-smoker, etc.). Furthermore, Caucasian ethnicity was assumed for all recordings for the calculation of all predicted reference values. However, the relative ethnic independence of the GLI-12 predicted FEV1/FVC index has already been shown [8]. Although the GLI Network provides equations for the calculation of reference valued for static lung volumes [18], we used the ECSC equations for the calculation of all static lung variables z-scores and predicted values because the only available severity scale for grading hyperinflation is based on indices calculated using the ECSC reference equation, a drawback to be considered as a subject for future studies.

Conclusions

In conclusion, our study has highlighted the significant difference in the detection of AO when using FEV1/FVC LLN calculated by GLI-12 reference equations in comparison to the fixed 0.7 threshold in a large population. We have also demonstrated the unsuitability of the fixed 0.7 threshold in the presence of mild to moderate hyperinflation and the need to refer to hyperinflation markers for a comprehensive lung function analysis.

Statement of Ethics

The study fulfilled the Declaration of Helsinki. This study protocol was reviewed and approved by the Ethics Committee of the medical faculty of the Rheinish-Westphalian Technical University (RWTH) in Aachen (approval reference EK 22-382). The need for informed consent was waived by the Ethics Committee of the Medical Faculty of the Rheinish-Westphalian Technical University (RWTH) in Aachen. No vulnerable participant was included in the study.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All authors had full access to the data and approved the final version of the manuscript. Concept and design of the study: L.W., C.G.C., and M.D.; data acquisition and writing and drafting of the manuscript: L.W.; data analysis and interpretation and revision of the manuscript: L.W., C.G.C., M.D., and W.W.

Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available upon provision of a data sharing agreement with the university hospital RWTH Aachen.

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