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ORIGINAL RESEARCH

Influences of Two FEV_1 Reference Equations (GLI-2012 and GIRH-2017) on Airflow Limitation Classification Among COPD Patients

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Objective: To explore the clinical effects of different forced expiratory volume in 1s (FEV_1) reference equations on chronic obstructive pulmonary disease (COPD) airflow limitation (AFL) classification.

Methods: We conducted a COPD screening program for residents over 40 years old from 2019 to 2021. All residents received the COPD screening questionnaire (COPD-SQ) and spirometry. Postbronchodilator FEV_1/FVC (forced vital capacity) <0.7 was used as the diagnostic criterion of COPD and two reference equations of FEV_1 predicted values were used for AFL severity classification: the European Respiratory Society Global Lung Function Initiative reference equation in 2012 (GLI-2012) and the Guangzhou Institute of Respiratory Health reference equation in 2017 (GIRH-2017). Clinical characteristics of patients in GOLD (Global Initiative for Chronic Obstructive Pulmonary Disease) 1–4 grades classified by the two reference equations were compared.

Results: Among 3524 participants, 659 subjects obtained a COPD-SQ score of 16 or more and 743 participants were found to have AFL. The COPD-SQ showed high sensitivity (59%) and specificity (91%) in primary COPD screening. Great differences in COPD severity classification were found when applying the two equations ($p < 0.001$). Compared with GIRH-2017, patients with AFL classified by GLI-2012 equations were significantly severer. The relationship between symptom scores, acute exacerbation (AE) history distributions and COPD severities classified by the two equations showed a consistent trend of positive but weak correlation. Group A, B, C and D existed in all GOLD 1 to 3 COPD patients, but in GOLD 4, only Groups B and D existed. However, no clear significant differences were found in symptoms, AE risk assessments, risk factors exposure and even the combined ABCD grouping under the two equations.

Conclusion: There were significant differences in COPD AFL severity classification with GLI-2012 and GIRH-2017 FEV_1 reference equations. But these severity estimation differences did not affect symptoms, AE risk assessments and ABCD grouping of patients at all GOLD grades.

Keywords: COPD, airflow limitation, FEV_1%pred, symptoms assessment, acute exacerbation

Background

Spirometry is still the recommended routine diagnostic procedure of choice for Chronic Obstructive Pulmonary Disease (COPD), which is characterized by airflow limitation (AFL).[1] In China, the Forced Expiratory Volume In 1s (FEV_1) reference equation of the European Coal and Steel Community in 1993 (ECSC-1993) has been widely used for the classification of AFL due to the lack of authoritative domestic reference values.[2] However, confusion regarding the accuracy of severity assessment, correlation with symptoms, acute exacerbations and impact on prognosis remains a major hurdle to improving health care for patients with COPD.

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A study found that Chinese people are discrepant from Western countries in physique due to ethnic and regional differences, in which normal lung function reference value estimation will be directly affected.[3] In the last 20 years (2002–2022), Chinese scholars have been devoted to exploring reference spirometric values in the normal Chinese population.[4–6] In 2002, Zheng and Zhong's team found that compared with ECSC-1993 predictions, the values for FVC (Forced Vital Capacity) and FEV_1 were 5.3% smaller in Chinese males and 3.3% smaller in Chinese females on average, with maximal differences in South China and minimal differences in North China. Conversion factors (males by 0.95 and females by 0.93) were given for adjusting the ECSC-1993 equations to fit Chinese.[4] However, the sample size was relatively small, and the research time was relatively long ago. China as one of the research subcenters, in 2012, the European Respiratory Society Global Lung Function Initiative (GLI) created continuous prediction equations for spirometric values with adjustment of fixed ethnic conversion factors.[5] However, it seems challenging to promote globally,[7] because of the complexity of races and regions. In 2017, another new age-related FEV_1 reference equation was developed by the Guangzhou Institute of Respiratory Health (GIRH).[6] This was a unified and Chinese-suited spirometric equation established from healthy Chinese people through a large-sample and multicenter study. As we know, appropriate reference values are critical for accurately evaluating lung function impairment, thus a near-exact assessment of prognosis and surgical risk.[8,9] Especially for patients in early stages or asymptomatic.[10] These patients, to some extent, are more likely to ignore their unhealthy status, leading to inadequate self-management.[11,12] However, the use of appropriate equations for AFL severity assessment is still controversial, and there has been little comparison of these classifications.

Therefore, in this study we aimed to explore the influences of the recent two FEV_1 reference equations (GLI-2012 and GIRH-2017) on COPD severity classification and its correlation with clinical symptoms assessments and acute exacerbation histories in a cross-sectional, Chinese general population-based sample of adults.

Patients and Methods

We conducted a nonrandomized cross-sectional COPD screening program for residents over 40 years old in Hengyang City from 2019 to 2021, aiming at screening COPD patients, popularizing lung function examination and promoting standardized COPD management. Residents with respiratory symptoms or associated risks exposure were a priority for screening. The screening mainly adopted the form of free medical clinic with primary hospitals. Before our survey, all residents were invited to sign informed consent and then received a simple questionnaire screening (the COPD screening questionnaire (COPD-SQ))[13] and spirometry. The 0.7 fixed ratio recommended by Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD 0.7 fixed ratio) was used as the diagnostic criterion of COPD in the study design, and only participants with an $FEV_1/FVC < 0.7$ before a bronchodilator accepted the bronchodilation test. Participants with spirometry of $FEV_1/FVC < 0.7$ after postbronchodilator (AFL) were then invited to finish a detailed COPD specific questionnaire and included in the analysis of different FEV_1 reference equations on COPD AFL classification. Data relating to demographics, respiratory health, risk factors, exacerbations and spirometry were collected. The ABCD assessment scheme was based on the GOLD 2021 revised report.[14]

Spirometry

Spirometry was performed using a portable turbine spirometer (Sai Ke Medical Instrument Co., LTD, X1, China) for screening by our trained operators in accordance with the American Thoracic Society criteria and quality controlled using 2005 criteria.[15] Participants with $FEV_1/FVC < 0.72$ at initial screening were further confirmed by a differential pressure spirometry (Medisoft S.A., HYPAIR M provo4, Belgium). Subjects with AFL defined by the GOLD 0.7 fixed ratio underwent postbronchodilator testing 15 to 20 minutes after inhaling a dose of 400 μg of salbutamol (Ventolin; GlaxoSmithKline, Middlesex, UK) through a 500 mL spacer. Spirometry results with grades A, B, or C were considered acceptable operations.

Classification of AFL severity in COPD was performed using two FEV_1 reference equations based on postbronchodilator FEV_1% predicted value (FEV_1%pred): the GLI-2012 reference equation[5] and GIRH-2017 FEV_1 reference equation.[6] To minimize the impact of diagnostic disagreements of different criteria for COPD detection, only data of participants who were simultaneously diagnosed with COPD by $FEV_1/FVC < 0.7$ fixed ratio, GLI-2012 Lower Limit of

Normal (LLN)[5] and GIRH-2017 LLN[6] threshold were retained for analyses. AFL severity was assessed according to FEV_1%pred of GOLD: ≥80%, GOLD 1; ≥50 and <80%, GOLD 2; ≥30 and <50%, GOLD 3; and <30%, GOLD 4.[14]

COPD Exacerbations

COPD exacerbation histories during the previous year were recorded in the form of recall. Acute exacerbations (AEs) that need outpatient or inpatient treatment due to the aggravation of COPD-related symptoms beyond the variation of daily symptoms (moderate or severe exacerbation history)[14] will be calculated for analysis.

Questionnaire and Risk Factors for COPD

The COPD-SQ consisted of seven items: age, smoking pack-years, body mass index, cough, dyspnea, family history of respiratory diseases and exposure to biomass smoke from cooking, with a cut-off score of 16 for a high suggestive of COPD (≥16).[13,16] The detailed COPD specific questionnaire interview was performed using a standardized questionnaire revised from the international BOLD (Burden of Obstructive Lung Diseases) study,[17] including possible risk factors for COPD, such as family history of respiratory diseases, smoking status, occupational exposure, biomass fuel exposure and related medical history. Having a family history of respiratory diseases was identified by blood-related family members experiencing pulmonary diseases such as chronic bronchitis, asthma, emphysema, COPD, lung cancer, bronchiectasia and other heredity diseases that may affect the lung. A subject was referred to as a smoker if he or she had smoked more than five packs per year in his or her life.[18] Exposure to high concentrations of all types of dust for more than 1 year without any protective measure was defined as occupational exposure.[18] Lifetime smoking status was classified as never or ever by comparison of self-reported smoking status over all available examinations. Body mass index (BMI) scores were defined as weight in kilograms divided by height in meters squared. Other questionnaire components, including acute exacerbations in the previous year, COPD Assessment Test[19] (CAT) and COPD Clinical Questionnaire[20] (CCQ), the modified British Medical Research Council (mMRC) Questionnaire,[21] comorbidities, drug use, history of allergies, etc. will also be collected. This study complies with the Declaration of Helsinki and has been approved by the Medical Ethics Committee of the University of South China.

Risk Aversion Measures During COVID-19 Pandemic

There was a global epidemic of the Coronavirus Disease in 2019 (COVID-19) during the conduction of our study. The study was carried out in strict compliance with the COVID-19 prevention and control documents of the National Centers for Disease Control. Screening was suspended during the COVID-19 control period, only when there were no local nucleic acid positive cases and the domestic epidemic control was relatively stable. Each screening was reported to the local health department. Trip code and health code of every resident were checked before investigation, and both codes must be green (which indicates safe in China). All residents should follow basic infection control measures, including social distancing, hand washing, and wearing a mask or face covering. Subjects with symptoms of COVID-19 such as fever, sore throat, or a history of travel to medium-high risk areas will be denied screening and reported to local health authorities in a timely manner.

Statistical Analyses

One-way ANOVA and Bonferroni method were used to analyze the differences of continuous variables in each group of COPD-SQ scores. Chi-square test was used for comparison of categorical variables (percentages of patients in four severity stages, gender, smoking, ABCD assessment scheme) and differences of continuous variables, such as age, CAT scores, CCQ scores, mMRC grades and AE histories were compared using *t*-test. Then, a McNemar method was performed for comparison between groups with the two FEV_1 reference equations. Relationships between continuous variables such as mMRC grades, CAT scores, CCQ sores, AE histories and FEV_1%pred were analyzed using Spearman correlation analysis. All analyses were performed using IBM SPSS V.19.0, and $P < 0.05$ was considered statistically significant.

Results

A total of 3524 participants finished COPD-SQ and 3203 participants accepted spirometry test, among whom 659 subjects obtained a self-screening questionnaire score of 16 or more. 743 participants were found to have AFL with postbronchodilator FEV_1/FVC <0.7, among whom 38 were eliminated for unacceptable spirometry, 108 were excluded due to incomplete questionnaires (38) or diagnosed with non-AFL by GLI-2012 LLN and GIRH-2017 LLN thresholds (70), leading to a total of 597 subjects included in our analyses for different FEV_1 reference equations on COPD AFL classification (Figure 1).

The frequency of AFL was 21.08% (743/3524) among participants aged over 40 years old in our study with criterion of the GOLD 0.7 fixed ratio. Using the COPD-SQ to screen for COPD, the sensitivity and specificity were, respectively, 59%, 91% (Table 1). In population with COPD-SQ scores ≥16, the normal group showed obviously lower proportion of males ($p < 0.001$) and lower smoking index scores ($p < 0.001$), than the COPD group.

Of the 597 COPD patients included in the analysis, the mean age was 64.26±8.3 years, females constituted 13.9% of the cohort. There were significant differences in the proportion of patients in different severity grades when the two reference equations were used ($p < 0.001$, Table 2). According to the GLI-2012 FEV_1 reference equation, 206 COPD patients were in GOLD 1, 244 were in GOLD 2, 114 were in GOLD 3, and 33 were in GOLD 4 (Table 2). Patients in GOLD 1 accounted for the largest proportion (46.9%). While the number of patients in GOLD 1–4 was 280, 202, 90, and 25, respectively, when the GIRH-2017 reference equation was used (Table 2). Patients in GOLD 2 accounted for the

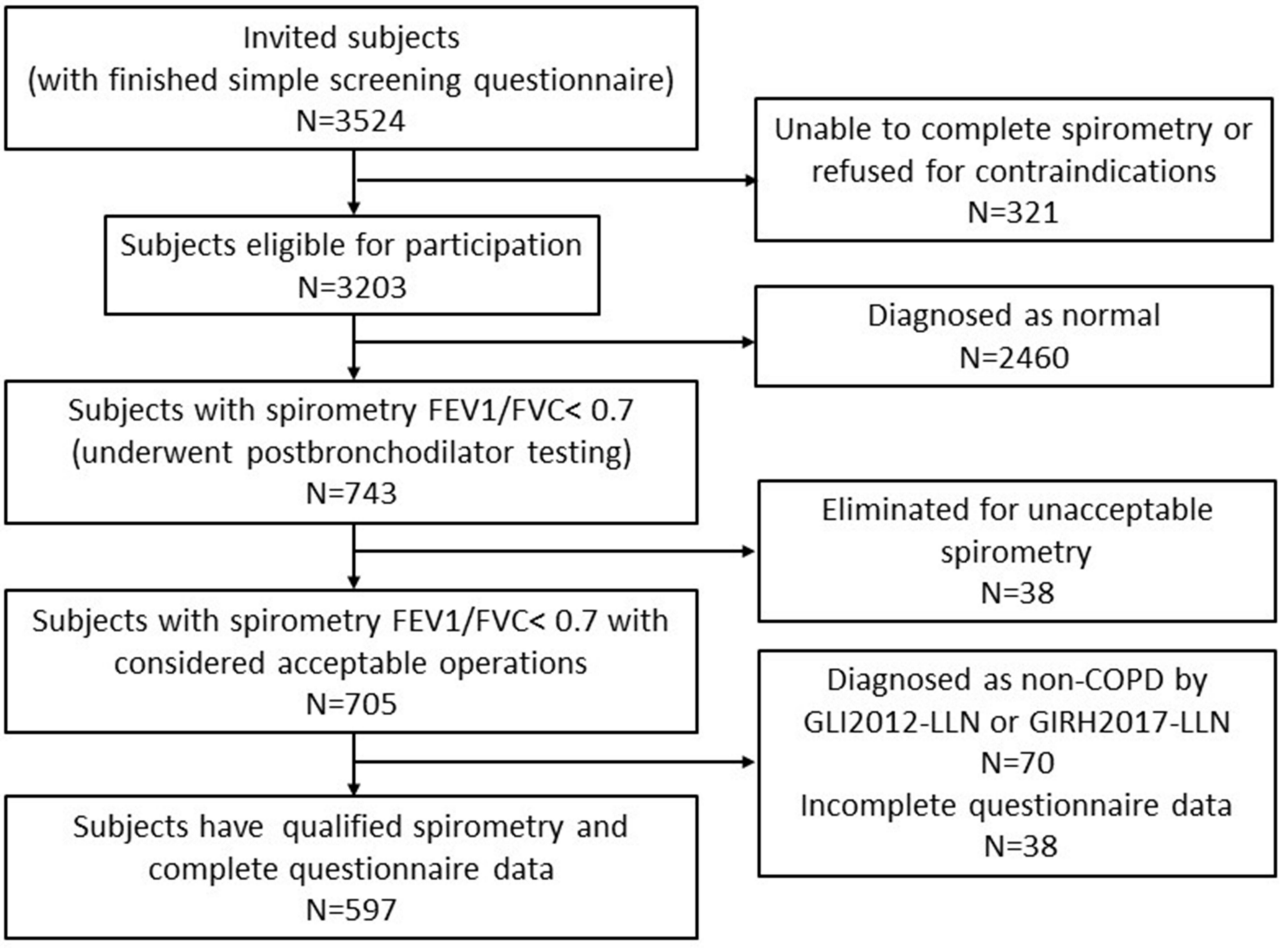

Figure 1 Subjects included for analysis.

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; GLI, Global Lung Function Initiative; GIRH, Guangzhou Institute of Respiratory Health; LLN, Lower Limit of Normal.

Table 1 Consistency of AFL and COPD-SQ Score Groups and Clinical Characteristics of Each Group

COPD-SQ Score Group	$FEV_1/FVC<0.7$ N=743		$FEV_1/FVC\geq0.7$ N=2460		*P* value*
	≥16	<16	≥16	<16	
N(%)	438 (59.0)	305 (41.0)	221 (9.0)	2239 (91.0)	
COPD-SQ scores(SD)[#]	18.78 (2.5)	10.69 (3.3)	17.98 (2.2)	8.74 (3.6)	<0.001
Age-year(SD)	67.45 (6.98)	58.5 (8.0)	69.15 (8.4)	54.91 (9.7)	<0.001
Male-N(%)[§]	411 (93.6)	264 (86.5)	140 (63.3)	1211 (54.1)	<0.001
BMI scores(SD)	4.45 (1.8)	2.76 (1.7)	4.58 (1.9)	2.84 (1.7)	<0.001
Smocking index scores(SD)[£]	1.79 (0.6)	1.41 (0.8)	0.87 (1.0)	0.59 (0.9)	<0.001
Cough scores(SD)	2.15 (1.4)	0.68 (1.3)	1.95 (1.4)	0.68 (1.3)	<0.001
Dyspnea scores(SD)	1.58 (1.2)	0.63 (1.0)	1.21 (1.0)	0.62 (0.9)	<0.001
Biofuel exposure scores(SD)	0.39 (0.5)	0.29 (0.5)	0.42 (0.5)	0.19 (0.4)	<0.001
Family history scores(SD)	0.64 (0.9)	0.38 (0.8)	0.73 (1.0)	0.25 (0.7)	<0.001

Notes: *P represents intra-group differences among the 4 groups; [#]The scores of each variable is expressed in the form of mean value and standard deviation, one-way ANOVA and Bonferroni method were used to analyze the differences of continuous variables in each group; [§]p value of the comparison between the normal group and the COPD group in subjects with COPD-SQ scores≥16 was <0.001; [£]p value of the comparison between the normal group and the COPD group in subjects with COPD-SQ scores≥16 was <0.001.

Abbreviations: AFL, airflow limitation; COPD-SQ, COPD screening questionnaire; BMI, body mass index; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; SD, standard deviation.

largest proportion (40.9%), and GOLD 2–4 patients were more than that of GIRH-2017. The proportion of males and smoking patients in each GOLD grade was very high. However, in general, no significant differences were found in sex, age distribution and smoking exposure under the two FEV_1 equations (Table 2).

Further paired analysis found that there were significant differences in COPD severity classification using the two reference equations (p = 0.001, Table 3), and the differences were found at every GOLD grade. In particular, compared with GIRH-2017, part of patients in GOLD1-3 with GLI-2012 were assigned to a higher severity grade of AFL (Table 3).

Figure 2 shows the distribution of symptoms and exacerbation risk assessments of AFL severity under GIRH-2017 and GLI-2012 FEV_1 predicted reference equations. COPD severity was positively correlated with CAT scores, mMRC grading, CCQ scores, and average AEs in the previous year regardless of which equation was chosen. However, there were no statistically significant differences in symptoms and AE risk assessments for each GOLD grade (Figure 2). Correlations between FEV_1%pred and CAT scores, mMRC grades, CCQ scores, and average AEs with GLI-2012 and GIRH-2017 FEV_1 reference equations are shown in Table 4. The correlations between CAT scores, mMRC grades and FEV_1%pred were slightly higher than that of CCQ scores and AEs, but all of them showed weak correlations. The "r" of CAT scores and FEV_1 %pred with the two FEV_1 reference equations showed no statistical significance (95% confidence interval (95% CI) was crossed). The same results were observed in "r" of mMRC grades, CCQ scores, AEs and FEV_1%pred (Table 4).

Figure 3 shows the ABCD assessment scheme in every GOLD grade with GIRH-2017 and GLI-2012 FEV_1 predicted reference equations. Group A, B, C and D existed in all GOLD 1 to 3 COPD patients, but in GOLD 4, only Groups B and D existed. Overall, Group C was least represented, even among patients in GOLD 3. At each GOLD severity grade, there was no significant difference in ABCD assessment grouping under the two equations (P = 0.578 for GOLD 1; P = 0.578 for GOLD 2; P = 0.942 for GOLD 3; and P = 0.695 for GOLD 4).

Discussion

In China, the prevalence of COPD was estimated to be 100 million,[22] among which approximately 97.8% cases remain undiagnosed. Confusion regarding how to diagnose airflow obstruction, proper selection of references of spirometry parameters, the major physiological feature of COPD, remains a major hurdle to improving care for patients with COPD. In this study, we used two methods (spirometry and simple questionnaire) for COPD screening and two reference

Table 2 Severity Classification and Characteristics of Patients with GLI-2012 and GIRH-2017 FEV_1 Predicted Value Reference Equations

GOLD Grade	GLI-2012	GIRH-2017	*P* value[#]
GOLD 1			P<0.001[$]
N(%)	206 (34.5)	280 (46.9)	-
Sex (male, %)	167 (81.1)	229 (81.8)	0.336
Age (year, SD)	63.7 (8.6)	62.9 (8.5)	0.721
Smoking* (Yes, %)	148 (71.8)	201 (71.8)	0.564
GOLD 2			
N(%)	244 (40.9)	202 (33.8)	-
Sex (male, %)	206 (84.4)	173 (85.6)	0.15
Age (year, SD)	64.6 (8.1)	65.2 (7.7)	0.683
Smoking* (Yes, %)	174 (71.3)	143 (70.8)	0.602
GOLD 3			
N(%)	114 (19.1)	90 (15.1)	-
Sex (male, %)	109 (95.6)	87 (96.7)	0.44
Age (year, SD)	65.0 (8.1)	66.3 (8.4)	0.206
Smoking* (Yes, %)	85 (74.6)	68 (75.60)	0.888
GOLD 4			
N(%)	33 (5.5)	25 (4.2)	-
Sex (male, %)	32 (97.0)	25 (100.0)	0.652
Age (year, SD)	62.9 (8.2)	63.8 (7.5)	0.674
Smoking* (Yes, %)	29 (87.9)	24 (96.0)	0.655
Total	597	597	-

Notes: [#]Data were collected from 597 patients who were diagnosed with COPD by GOLD 0.7 fixed ratio and both the GLI-2012 and GIRH-2017 LLN diagnosis thresholds. Differences in age were compared using *t*-test, and the chi-square test was used for comparison of categorical variables (percentage of patients in four severity stages, sex and smoking). [$]P value represents the difference of chi-square test in percentage of patients in four severity stages with the two reference formulas. *Smoking includes current smoking and ex-smoking.

Abbreviations: COPD, chronic obstructive pulmonary disease; SD, standard deviation; GOLD, Global initiative for chronic obstructive pulmonary disease; GLI, Global Lung Function Initiative; GIRH, Guangzhou Institute of Respiratory Health; LLN, lower limit of normal.

equations of FEV_1 predicted value for COPD AFL severity classification. We found high sensitivity and specificity of COPD-SQ in primary screening for COPD and significant differences in severity classification between equations of GIRH-2017 and GLI-2012. While few effects were detected on symptoms estimation, risk factor exposure, and AEs among patients in different stages with different FEV_1 prediction equations.

Interpretation of the severity of lung function impairment is dependent on having appropriate reference values. Though other different classifications have been proposed for AFL severity assessment, such as $FEV_{1Quotient}$[23] (absolute value of FEV_1 divided by the sex-specific first percentile), $FEV_1/Height^2$ [24] (FEV_1 divided by the squared height), $FEV_1/Height^3$ [23] (FEV_1 divided by the cubed height), $FEV_{1z\text{-}score}$[25] ((measured minus predicted) divided by the residual standard deviation of the predicted value). FEV_1%pred is the most widely used parameter recommended by GOLD. For many years, criteria for diagnosis and equations for AFL severity estimation from Western countries were introduced due to the lack of lung function data from large, multicenter epidemiological surveys among the normal Chinese population. As a canonical reference equation, ECSC-1993 has been widely used in China. Data from normal Hong Kong participants were involved in the establishment of this equation.[26] which may not well represent the normal lung function status in China for her vast geographical area. Moreover, ethnic and regional differences will make great differences in chest size, muscle development and strength, which have an important impact on lung function. The large epidemiological survey in 2002 confirmed that the FEV_1 and FVC of normal Chinese individuals are smaller than those

Table 3 Severity Distribution and Differences of 597 COPD Patients Classified by GIRH-2017 and GLI-2012 FEV_1 Predicted Value Reference Equations

FEV_1 Reference Equation		GLI-2012#(N)					GLI-2012(N)			
		GOLD1	GOLD2	GOLD3	GOLD4		Yes	No	Total	P-value
GIRH-2017	GOLD1	201	79	0	0	Yes	201	79	280	<0.001
						No	5	312	317	
						Total	206	391	597	
	GOLD2	5	163	34	0	Yes	163	39	202	<0.001
						No	81	314	395	
						Total	244	353	597	
	GOLD3	0	2	80	8	Yes	80	10	90	0.001
						No	34	473	507	
						Total	114	483	597	
	GOLD4	0	0	0	25	Yes	25	0	25	0.039
						No	8	564	572	
						Total	33	564	597	

Notes: #Data were collected from 597 patients who were diagnosed with COPD by GOLD 0.7 fixed ratio and both the GLI-2012 and GIRH-2017 LLN diagnosis thresholds. McNemar method was performed for comparison analysis of the two FEV_1 reference equations, and the overall statistical difference between the two standards was P<0.001.
Abbreviations: COPD, chronic obstructive pulmonary disease; GOLD, global initiative for chronic obstructive pulmonary disease; GLI, Global Lung Function Initiative; GIRH, Guangzhou Institute of Respiratory Health; LLN, lower limit of normal.

of Caucasians, with FEV_1 approximately 5.3% smaller on average for males and 3.3% smaller for females. Conversion factors were given for adjusting the ECSC-1993 equation to fit Chinese (with males by 0.95 and females by 0.93).[4] Similarly, those living in Southeast Asia, sub-Saharan Africa, East Asia, the Middle East and South America had FEV values that were on average 31%, 21%, 13%, 11%, and 6% lower than those of individuals living in North America or Europe, respectively, independent of age, height, sex, and smoking status.[27] Unless relevant predicted values are used, the severity of AFL will be overestimated.

In recent ten years, the advocation of diagnostic criteria for COPD by LLNs has attracted much attention from scientists, and more than one LLNs and normal reference value equations have been successively reestablished by countries and organizations.[5,6,28] As a key guide, the GLI has published spirometric prediction equations for the 3–95 age range in 2012, including appropriate age-dependent LLN, and tries to make it available for global application. Estimates of normal lung function in North Asia are mainly from countries such as South Korea.[5] A study from North Africa found that the recent multiethnic global lung initiative 2012 (GLI-2012) reference values did not reflect contemporary adult North African spirometry,[7] limiting the global application of GLI-2012. Therefore, in 2017, the GIRH-2017 standard was established through a large sample multicenter epidemiological investigation in China. This provides a reference for the selection of normal values in the Chinese population. In our study, we found that the percentage of COPD patients in GOLD 1 according to the GIRH-2017 equation was significantly higher than that according to the GLI-2012 equation, while the proportion of patients in GOLD 2–4 was less. The difference was statistically significant. Compared with GIRH-2017, patients with AFL classified by GLI-2012 equations were significantly severer, with patients in GOLD 2 accounted for the largest proportion (40.9%). Suggesting an underestimation of lung function in normal Chinese population. In view of the GIRH-2017 equation was established through large-scale epidemiological investigation in China which may show good representation of normal values for Chinese adults regardless of large racial differences, and especially, it makes reference values available in populations with an age range of 3–80 years. For another, the gradual decrease in the proportion of patients from mild to very severe AFL also seems to be more consistent with the progression of decline in human lung function. Therefore, it is worth recommending as a reference for spirometry suitable for Chinese.

Further analysis of the differences in risk factors exposure under the two equations showed that severity differences caused by different equations did not bring discrepancies in age, sex or smoking exposure. Males make

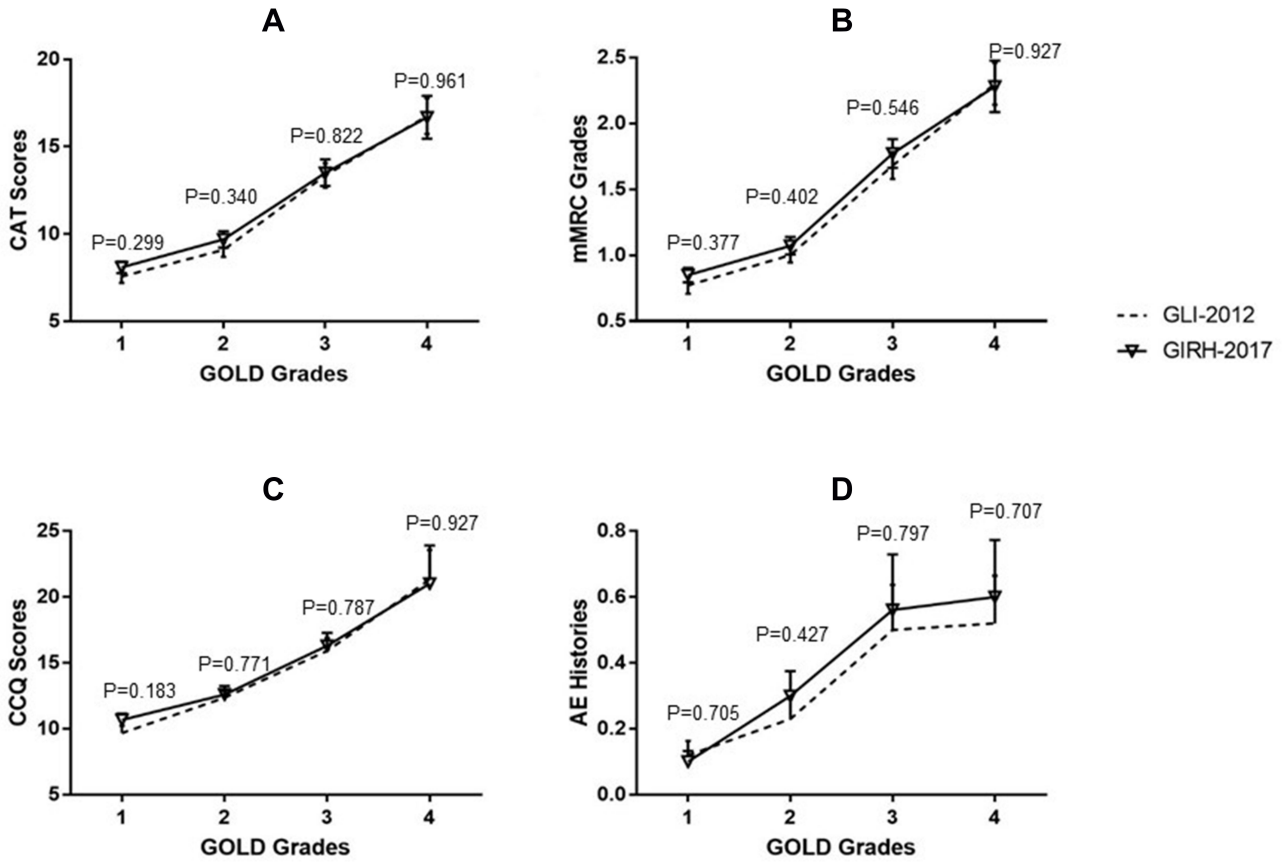

Figure 2 Distribution of symptoms and exacerbation risk assessments of AFL severity under GIRH-2017 and GLI-2012 FEV_1 predicted reference equations. Subfigures (**A**–**D**) represent the assessments of CAT scores (**A**), mMRC grades (**B**), CCQ scores (**C**), AE histories in the last year (**D**) of GOLD grades under the two FEV_1 predicted reference equations respectively. Data were collected from 597 patients who were diagnosed with COPD by GOLD 0.7 fixed ratio and both the GLI-2012 and GIRH-2017 LLN diagnosis thresholds. Data were shown as the mean with standard error. *t*-test was used for statistical analysis.

Abbreviations: AE, acute exacerbation; AFL, airflow limitation; CAT, COPD Assessment Test; CCQ, COPD Clinical Questionnaire; COPD, Chronic Obstructive Pulmonary Disease; FEV_1, forced expiratory volume in one second; GOLD, Global initiative for chronic obstructive pulmonary disease; GLI, Global Lung Function Initiative; GIRH, Guangzhou Institute of Respiratory Health; LLN, Lower Limit of Normal; mMRC, the modified British Medical Research Council.

up the vast majority of COPD patients, and most of them have a high smoking index.[14] Small changes in sex percentage and smoking status may not be adequately enough to result in significant differences. More work in this area is needed for differential discovery, especially studies with larger sample scales. It is widely known that smoking is the only independent risk factor for the occurrence of COPD.[29] While more common in males many years ago, COPD now affects males and females almost equally.[30] Although controversial, some studies have suggested that females are more susceptible to the effects of tobacco smoke than males, leading to more severe disease for the equivalent quantity of cigarettes consumed.[31,32] This notion has been validated in animal studies and human pathology specimens.[33] Many of the female patients tended to be elderly women with a history of organ-specific autoimmune disease and peripheral blood lymphopenia.[34] This indicates the great significance of improving the early diagnosis and prevention of female COPD patients, and probably reflects the changing patterns of tobacco smoking and male sex. Consistent with the GOLD2021 report,[14] we found consistent positive but weak correlations between symptom scores, AE history distributions and COPD severities classified by the two equations. However, there were no statistically significant differences with these regardless of which equation was chosen. For this reason, a comprehensive assessment may be more clinically significant to achieve the goals of GOLD global initiative. In 2017, GOLD reports revised the strategy to separate airflow restriction from the ABCD assessment to better guide therapy based only on symptoms and acute exacerbations in the previous year.[35] But interestingly, at each GOLD severity grade, there was still no significant difference in ABCD assessment grouping under the two equations in our

Table 4 Correlations Between FEV_1%pred and CAT Scores, mMRC Grades, CCQ Scores, and Average AEs with GLI-2012 and GIRH-2017 FEV_1 Reference Equations

Variables	FEV_1%pred	
	GLI-2012	GIRH-2017
CAT scores		
P	P<0.001	P<0.001
r†(95% CI)	−0.386 (−0.462,-0.316)	−0.315 (−0.387,-0.242)
mMRC grades		
P	P<0.001	P<0.001
r(95% CI)	−0.399 (−0.469,-0.322)	−0.342 (−0.418,-0.262)
CCQ scores		
P	P<0.001	P<0.001
r(95% CI)	−0.296 (−0.373,-0.217)	−0.245 (−0.319,-0.166)
AE histories in the previous year		
P	P<0.001	P<0.001
r(95% CI)	−0.227 (−0.305,-0.154)	−0.274 (−0.342,-0.206)

Notes: †r stands for correlation coefficient using Spearman correlation analysis. Data were collected from 597 patients who were diagnosed with COPD by GOLD 0.7 fixed ratio and both the GLI-2012 and GIRH-2017 LLN diagnosis thresholds.

Abbreviations: AEs, acute exacerbations; CAT, COPD assessment test; CCQ, COPD Clinical Questionnaire; COPD, chronic obstructive pulmonary disease; FEV_1%pred, FEV_1% predicted value; GOLD, Global initiative for chronic obstructive pulmonary disease; GLI, Global Lung Function Initiative; GIRH, Guangzhou Institute of Respiratory Health; LLN, Lower Limit of Normal; mMRC, the modified British Medical Research Council; 95% CI, 95% confidence interval.

results. From this point of view, the ABCD assessment grouping measure better avoids the impact on treatment caused by the use of different FEV_1 predicted value reference formulas. Such as the choice of appropriate inhalers. It is worth noting that, we found Group A, B, C and D existed in all GOLD 1 to 3 COPD patients, but in GOLD 4, only Groups B and D existed. This suggests that symptom assessments vary widely in mild to severe COPD, when AFL demonstrating very severe, patients will generally have obvious symptoms. Overall, Group C was least represented, even among patients in GOLD 3. In some cases, patients may endorse minimal symptoms despite demonstrating severe AFL. Adapting to the limitations induced by COPD, these patients may reduce their level of physical activity in a way that may result in an underestimation of the symptom load. In these cases, exercise tests like the 6-minute walking distance may reveal that the patients are severely constrained and do need more intense treatment than the initial evaluation would have suggested.[14] The $FEV_{1Quotient}$ was the only classification that differentiated the patients according to the GOLD "C/D" reported by Anane with a cut-off of 2.5 through 55 COPD patients.[36] This classification has been demonstrated it outperformed the other classifications in predicting the risk of severity adverse event (SAE), hospitalization, as well as physical and mental decline.[37–39] However, future work using large and ethnically diverse populations to refine and validate the cut-off values were still needed to enhance the prediction of outcomes.

Even so, AFL severity still plays an important role in the assessment of COPD prognosis. Over time, physical activity substantially decreases across all severity stages of COPD, and this decline is paralleled by a worsening of lung function and health status.[40] Nevertheless, studies have confirmed that physical activity was the strongest predictor of all-cause mortality in patients with COPD.[41] Poor physical activity level is consistently associated with frequent exacerbations.[42] Therefore, more accurate predictive references seem to more accurately predict the risk of future adverse events in patients. For example, the GIRH-2017 reference equation. Of course, more high-quality clinical studies are still needed to confirm the value of this reference equation.

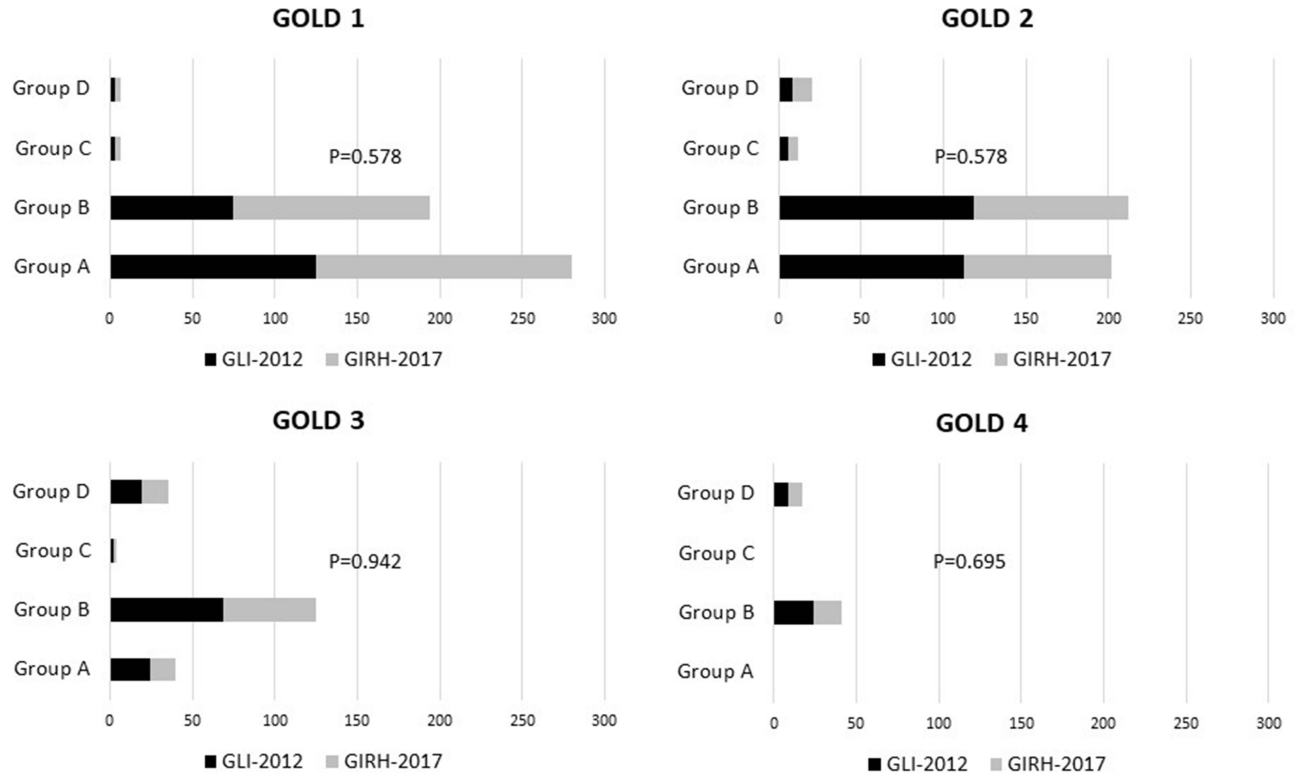

Figure 3 ABCD assessment scheme in every GOLD grade with GIRH-2017 and GLI-2012 FEV_1 predicted reference equations. Data were collected from 597 patients who were diagnosed with COPD by GOLD 0.7 fixed ratio and both the GLI-2012 and GIRH-2017 LLN diagnosis thresholds. Chi-square test was used for comparison of ABCD groups distribution with the two reference equations.

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in one second; GOLD, Global initiative for chronic obstructive pulmonary disease; GLI, Global Lung Function Initiative; GIRH, Guangzhou Institute of Respiratory Health; LLN, Lower Limit of Normal.

Overall, our study findings have some important public health implications. First, we compared two commonly used FEV_1 prediction reference formulas; for the first time, significant impacts were found on COPD severity classification. To some extent, this provides important recommendations for the selection of domestic FEV_1 reference equations. Second, little impact was found on symptom and AE history assessments and even on the combined ABCD assessment scheme, when using different reference equations. This further confirmed the scientificity and practicability of ABCD assessment tool for COPD therapy. Third, the subjects we chose were patients in the stable stage whose symptom and lung function assessments would be relatively accurate and representative. Of course, other classifications could be the direction of future researches to find a better way for airflow limitation severity estimation. But in general, equations or parameters that established from large sample of normal Chinese population through a well-designed screening program may be the most suitable.

There are also some limitations existed in our study. First, the COPD sample size is relatively insufficient. Subjects in our study were selected from the community screening to ensure that more stable patients in different stages can be screened. However, the high proportion of males and smokers in this screening sample resulted in a higher overall COPD screening rates than in other large random sample studies.[10,22] However, different regions and screening methods may also affect COPD prevalence. In particular, the global outbreak of COVID-19 has severely affected our screening efforts. In addition, we did not use a strict random sampling method, and sex and age composition bias may exist. Asymptomatic patients are the majority, leading to some differences that might have not been discovered.

Conclusion

In conclusion, the results of our study show that there are significant differences in COPD severity classification when applying GLI-2012 and GIRH-2017 FEV_1 predicted reference equations. However, these severity estimation differences

did not affect the evaluation of symptoms, AE histories and even the combined ABCD assessment scheme of patients at all GOLD grades. This further confirmed the scientificity and practicability of the ABCD assessment tool for COPD therapy recommended by GOLD guidelines. As a unified spirometric equation established from large-sample healthy Chinese population, the GIRH-2017 reference equation is worth recommending as a normal reference for spirometry suitable for Chinese.

Abbreviations

AEs, acute exacerbations; AFL, airflow limitation; BOLD, Burden of Obstructive Lung Diseases; BMI, body mass index; COPD-SQ, COPD screening questionnaire; CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; CCQ, COPD Clinical Questionnaire; China-2002, the China revised reference equation in 2002; COVID-19, coronavirus disease in 2019; 95% CI, 95% confidence interval; ECSC, European Coal and Steel Community; ERS, European Respiratory Society; FEV1, Forced expiratory volume in 1 s; FVC, forced vital capacity; GOLD, Global initiative for chronic obstructive pulmonary disease; GLI, Global Lung Function Initiative; GIRH, Guangzhou Institute of Respiratory Health; LLN, Lower Limit of Normal; SD, Standard deviation; mMRC, the modified British Medical Research Council.

Clinical Trial Registration

Registrar: Liu Sha

Website: http://www.chictr.org.cn

Clinical trial registration Number: ChiCTR1900026502.

Data Sharing Statement

Please contact author for data requests.

Ethics Approval and Consent to Participate

All the participants were made fully aware of the purpose of study, and all participants gave informed consent. The Medical Ethics Committee, University of South China approved the study.

Consent for Publication

All participants have signed consent for publishing their personal data for scientific research. DFW and YW contributed equally to the article.

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Disclosure

All authors declare that there is no conflict of interest in the publication.

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