



# Prevalence and characteristics of chronic obstructive pulmonary disease in China with a diagnostic criterion of FEV<sub>1</sub>/FVC less than the lower limit of normal—a reanalysis of Chinese epidemiological survey of COPD (CESCOPD) study

Sha Liu<sup>1#</sup>, Yumin Zhou<sup>2#</sup>, Weifeng Zou<sup>3</sup>, Xiaowu Tan<sup>1</sup>, Pixin Ran<sup>2</sup>

<sup>1</sup>The Second Hospital, University of South China, Hengyang, China; <sup>2</sup>The State Key Laboratory of Respiratory Disease, National Clinical Research Center for Respiratory Diseases, Guangzhou Institute of Respiratory Health, the First Affiliated Hospital, Guangzhou Medical University, Guangzhou, China; <sup>3</sup>Guangzhou Chest Hospital, Guangzhou, China

**Contributions:** (I) Conception and design: P Ran, S Liu; (II) Administrative support: Y Zhou, X Tan, P Ran; (III) Provision of study materials or patients: S Liu, Y Zhou, W Zou, X Tan; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: S Liu, Y Zhou, P Ran; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

<sup>#</sup>These authors contributed equally to this work.

**Correspondence to:** Pixin Ran. The State Key Laboratory of Respiratory Disease, National Clinical Research Center for Respiratory Diseases, Guangzhou Institute of Respiratory Health, the First Affiliated Hospital, Guangzhou Medical University, Guangzhou, China. Email: pxran@gzhmu.edu.cn.

**Background:** To reappraise the prevalence and characteristics of chronic obstructive pulmonary disease (COPD) in China with a criterion of FEV<sub>1</sub>/FVC < the lower limit of normal (LLN).

**Methods:** We assessed the incidence and characteristics of airflow limitation using data from the Chinese Epidemiological Survey of COPD study—a multicenter, randomized trial, with an age-dependent LLN reference equation [established by the Guangzhou Institute of Respiratory Health (GIRH)]. Questionnaire and spirometry data were collected for all eligible subjects. COPD prevalence, risk factors, severity distribution, as well as comparisons of characteristics between the LLN and 0.7 were analyzed.

**Results:** COPD prevalence was 9.0% among participants aged 40–80 years in China with the criterion of LLN. Greater prevalence was observed in female sex, rural areas and never smokers than with the GOLD 0.7 fixed ratio. Age distribution showed a higher incidence of COPD in people under 60 years but lower in participants over 60 years of age. With the LLN FEV<sub>1</sub> reference equation, patients in stage I were decreased (15.8% vs. 24.6%, P<0.001), while the proportion of patients in stage III and IV were increased when compared with the China 2002 revised equation (27.7% vs. 21.1%, for stage III, P<0.001; 8.7% vs. 5.6% for stage IV, P=0.001). Only 30.8% of patients with COPD had ever been “diagnosed” with COPD and 60.6% of the patients had respiratory symptoms, both lower than that under the GOLD 0.7 fixed-ratio criterion (35.5%, P=0.004; 64.8% for symptoms, P=0.014).

**Conclusions:** With the GIRH-LLN criterion, COPD prevalence was slightly higher, and a large number of women, rural patients and nonsmokers with young age and little symptoms were diagnosed when compared with GOLD 0.7 fixed ratio. These subjects may, therefore, deserve further attention and may warrant regular follow-up.

**Trial Registration:** Registration number: ChiCTR-ECS-13004110.

**Keywords:** Chronic obstructive pulmonary disease (COPD); prevalence; lower limit of normal (LLN); GOLD 0.7 fixed ratio; lung function

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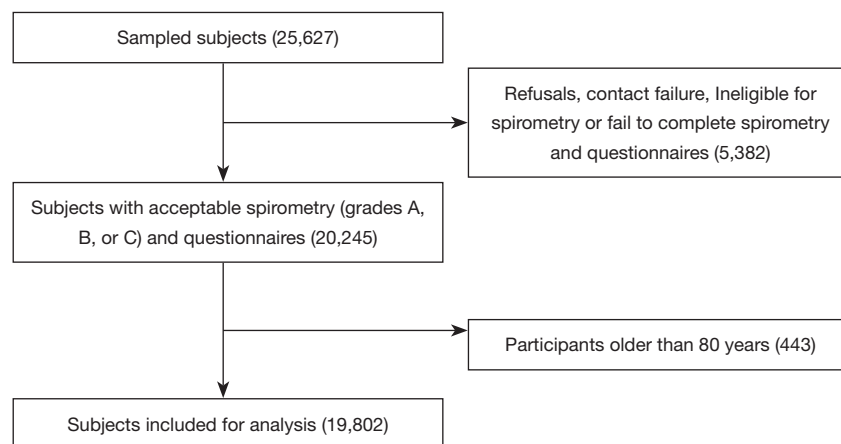
## Introduction

Spirometry is still the recommended routine diagnostic procedure of choice for chronic obstructive pulmonary disease (COPD), which is characterized by air flow limitation (1,2). In the past ten years, the incidence of COPD among Chinese individuals over 40 years old has increased from 8.2% in 2002 (3) to 13.7% in 2012 with the criterion of  $FEV_1/FVC < 0.7$  (4). However, numerous studies have demonstrated that regular changes in  $FEV_1/FVC$  are seen with aging, which challenges the traditional fixed ratio of 0.7 (5,6). Thus, many scientists believe that the threshold of the lower limit of normal (LLN) of  $FEV_1/FVC$  should be used to diagnose COPD (7,8). The age-related LLN of  $FEV_1/FVC$  has been shown to reduce the increases in COPD prevalence seen among the older healthy population when using the fixed-ratio criterion ( $FEV_1/FVC < 0.7$ ) and increased the diagnosis among younger patients (9-12). It seems challengeable to promote reference equations globally although the European Respiratory Society (ERS) Global Lung Function Initiative (GLI) have created continuous prediction equations and LLNs for spirometric values with adjustment of fixed ethnic conversion factors (13,14). Possible reasons might be the limited sample size and insufficient representative sample clusters. In 2017, a new age-related LLN reference equation was developed by the Guangzhou Institute of Respiratory Health (GIRH). For the first time, a unified and Chinese-suited LLN reference equation from Chinese healthy people was published through a large-sample and multicenter study (15). Further research has reported that this individual-dependent GIRH-LLN equation appears to perform better at detecting airflow limitations and reduces the risk of underdiagnosis for young adults and overdiagnosis for the elderly (12). Therefore, it is of great necessity to investigate the exact prevalence of COPD in China using this LLN reference equation. We present the following article in accordance with the STROBE reporting checklist (available at <http://dx.doi.org/10.21037/jtd-21-95>).

## Methods

We retrieved data from participants in the Chinese Epidemiological Survey of COPD (CESCOPD) study for COPD prevalence estimation in residents aged 40 to 80 years with the criterion of the GIRH-LLN. The CESCOPD study was a multicenter, randomized trial with the objective to obtain the COPD prevalence in China

through a large-population, spirometry-based, cross-sectional survey of COPD from September 2002 through September 2004. Residents invited in our study were given individual interviews by our trained interviewers using a standardized questionnaire revised from the international BOLD study. All interviewers and spirometry operators had been well trained and accredited before the survey. Questionnaire data were coded and entered into the standardized Excel database (Microsoft, Redmond, WA) by two persons independently, with computer programs checking for out-of-range values and logic mistakes. Participants' characteristics and prevalence of COPD with the GOLD 0.7 criterion have been published previously (3). Spirometry was conducted using portable spirometers (Micro Medical Ltd, Chatham, Kent, UK), along with the procedure recommended by the American Thoracic Society (ATS) (16). Subjects with airflow limitations defined by the GOLD 0.7 fixed ratio underwent postbronchodilator testing 15 to 20 minutes after inhaling a dose of 200  $\mu$ g of salbutamol (Ventolin; GlaxoSmithKline, Middlesex, UK) through a 500 ml spacer. Before data collection, each spirometer was calibrated daily with a volume variation of less than 3% by a 3-L syringe. Spirometry results were sent every 2 weeks to Guangzhou for quality control. The results were double-checked by the principal investigator and fed back to each field worker. Subjects with unacceptable measurement were invited to receive a make-up test within 30 days. Spirometry results with grades A, B, or C were considered as acceptable operations. Spirometry and questionnaire-based interview were conducted at a convenient and accessible site or at home. Those residents temporarily out of reach were given a home interview on a later occasion. Interviewers for questionnaire were staff (doctors, nurses) and volunteers from local medical institutions, while spirometry was completed only by doctors and nurses. All interviewers and spirometry operators had been well trained and accredited before the survey. The GOLD 0.7 fixed ratio was used as the diagnostic criterion in the study design, and only participants with an  $FEV_1/FVC < 0.7$  before a bronchodilator (including a small number of participants with  $FEV_1/FVC$  around 71% to 70%) accepted the bronchodilation test. For a small group of patients who were underdiagnosed by the GOLD 0.7 fixed ratio (but lack of bronchodilation test), spirometry data collected before bronchodilation were used. Classification of airflow limitation severity in COPD was based on post-bronchodilator  $FEV_1\%$ pred according to the China revised 2002 reference equation [by applying conversion factors



**Figure 1** Subjects included for analysis.

from the European Coal and Steel Community 1993 (ECSC93) FEV<sub>1</sub> reference equation with males by 0.95 and females by 0.93] (17) and GIRH-LLN FEV<sub>1</sub> reference equation.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University approved the study (approved No. 2013-37). All the participants were made fully aware of the purpose of study, and all participants gave informed consent.

### Statistical analysis

Multivariate logistic regression models were performed to analyze the odds ratios (ORs) and 95% confidence intervals (CIs) for COPD in relation to potential risk factors. Variables including geographic area, sex, age groups, body mass index (BMI), smoking status, occupational exposure to dusts/gases/fumes, exposure to biomass fuel for cooking or heating, ventilation in the kitchen, family history of respiratory disease, pulmonary problems in childhood, and education were forced into the multivariate logistic regression model. Factors with no statistical difference were removed from the final model. Before multivariate regression, univariate logistic regressions were performed for screening for statistically significant factors. Details of the definition of risk factors are given in the published literature (3). Categorical variables such as COPD stage differences and comparison of the distributions of clinical outcomes between the GIRH-LLN criterion and GOLD 0.7 fixed ratio were analyzed using chi-squared tests. A

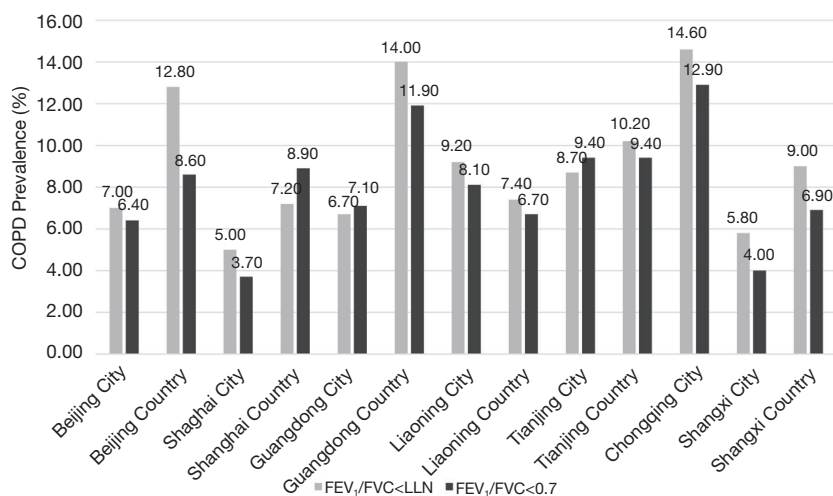
P value <0.05 was considered statistically significant. All analyses were performed using IBM SPSS 19.0.

### Results

Among 20,245 participants who completed acceptable spirometry (grades A, B, or C) and questionnaires in the survey, 19,802 people aged 40 to 80 years were included in our reanalysis. A total of 443 participants older than 80 years were removed for lack of the expected reference value of FEV<sub>1</sub>/FVC (*Figure 1*).

### COPD prevalence

The COPD prevalence was 9.0% (1,784/19,802) among participants aged 40–80 years in China with the GIRH-LLN criterion, which was slightly higher than the GOLD 0.7 fixed ratio (8.0%). The COPD prevalence from different regions are shown in *Figure 2*. Shanghai had the lowest prevalence of 5.0%, while Chongqing had the highest prevalence of 14.6%. With the GIRH-LLN criterion, the COPD prevalence was higher in most regions than that of GOLD 0.7 fixed ratio, except for the rural areas of Shanghai, Guangzhou and Tianjin that showed lower prevalence. On the whole, the COPD prevalence was significantly higher in rural (10.0%) areas compared with urban areas (8.2%) (*Table 1*). More remarkably, the COPD prevalence in rural areas increased by 1.4 percentage points (from 8.6% to 10%), while in urban areas, it only increased by 0.8 percentage points (from 7.4% to 8.2%) when compared with the GOLD 0.7 fixed ratio. Great prevalence disparities were also observed in sex distribution.



**Figure 2** COPD prevalence among participants aged 40–80 years in China with the GIRH-LLN criterion and GOLD 0.7 fixed ratio in different regions. GIRH, Guangzhou Institute of Respiratory Health; LLN, lower limit of normal of FEV<sub>1</sub>/FVC.

The COPD prevalence in females was 6.5%, which was 1.6 percentage points higher than diagnosed by the GOLD 0.7 fixed ratio, but only 0.2 percentage points higher when compared with males (*Table 1*).

### Risk factors

Multivariate logistic regression analyses showed that, consistent with the GOLD 0.7 fixed ratio, smoking, pulmonary problems in childhood, family history of respiratory diseases, male sex, low education level, aging, lower BMI, and occupational exposure (dusts/gases/fumes) are associated with COPD when the GIRH-LLN criterion was used. The adjusted ORs (95% CIs) of these potential risk factors are shown in *Table 1*. Significantly, COPD prevalence was higher in participants never smoked (6.6% for LLN *vs.* 5.0% for GOLD), and poor ventilation in the kitchen seems to be harmful to COPD (OR 1.13, 95% CI: 1.00–1.28). Age distribution showed a higher prevalence in people under 60 years of age but lower in participants over 60 years of age compared to the GOLD 0.7 fixed-ratio standard (*Table 1*).

### Symptoms and severity distribution

Under the GIRH-LLN reference equation for the FEV<sub>1</sub> expected value, the percentage of COPD in stages I (mild), II (moderate), III (severe), and IV (very severe)

were 15.8%, 47.8%, 27.7%, and 8.7%, respectively. The COPD percentage in stage I classified by the GIRH-LLN reference equation was obviously lower than that classified by the China revised ECSC1993 equation (15.8% *vs.* 24.6%,  $P < 0.001$ ), while patients in stages III and IV were relatively higher than that classified by the China revised ECSC1993 equation (27.7% *vs.* 21.1%,  $P < 0.001$  for stage III; 8.7% *vs.* 5.6%,  $P = 0.001$  for stage IV, *Table 2*). This kind of similar phenomenon can also be found in COPD patients diagnosed by FEV<sub>1</sub>/FVC less than 70%, but the GIRH-LLN FEV<sub>1</sub> reference equation was used ( $P < 0.001$ , for stage I;  $P < 0.001$ , for stage III;  $P = 0.001$ , for stage IV) (*Table 3*).

The prevalence of respiratory symptoms, such as cough, sputum, wheezing, and dyspnea in patients with COPD was 40.1%, 35.8%, 27.1%, and 46.6%, respectively (*Table 4*). A total of 60.6% of COPD patients had at least one of the above respiratory symptoms, which was slightly lower than that of the GOLD 0.7 fixed-ratio criterion (64.8%,  $P = 0.014$ ), reflecting that a higher proportion of patients with COPD were asymptomatic (39.4%). Patients with respiratory symptoms gradually increased with the aggravation of airflow limitation. Notably, with GIRH-LLN FEV<sub>1</sub> reference equation, only 30.8% of patients with COPD had ever been “diagnosed” with emphysema, asthma, bronchitis, or COPD, which was lower than that of the GOLD 0.7 fixed-ratio with China 2002 revised equation (35.5%,  $P = 0.004$ ), especially in stage I–II (9.9% *vs.* 18.5% for stage I, and 20.8% *vs.* 30.5% for stage II, *Table 4*).

**Table 1** Characteristics of subjects in the Chinese Epidemiological Survey of COPD study in residents aged 40 to 80 years with the GIRH-LLN criterion and GOLD 0.7 fixed ratio

Variable	FEV <sub>1</sub> /FVC < LLN*				FEV <sub>1</sub> /FVC < 0.7*			
	N (n)	COPD (n)	COPD prevalence (%)	Adjusted OR	N (n)	COPD (n)	COPD prevalence (%)	Adjusted OR
Region								
Urban	10,500	856	8.20%	1.00 (reference)	10,500	779	7.40%	1.00 (reference)
Rural	9,302	928	10.00%	1.22 (1.07–1.39) <sup>†</sup>	9,302	803	8.60%	1.28 (1.11–1.47)
Sex								
Male	8,477	1,044	12.30%	1.67 (1.45–1.92)	8,477	1,022	12.10%	1.88 (1.61–2.19)
Female	11,325	740	6.50%	1.00 (reference)	11,325	560	4.90%	1.00 (reference)
Age (years)								
40–	6,742	392	5.80%	1.00 (reference)	6,742	153	2.30%	1.00 (reference)
50–	5,517	369	6.70%	1.05 (0.90–1.22)	5,517	278	5.00%	2.02 (1.64–2.48)
60–	4,518	489	10.80%	1.66 (1.43–1.93)	4,518	530	11.70%	4.99 (4.10–6.06)
70–	3,025	534	17.70%	2.71 (2.29–3.20)	3,025	621	20.50%	9.38 (7.61–11.55)
Smoking status								
Never	12,181	802	6.60%	1.00 (reference)	12,181	608	5.00%	1.00 (reference)
Current	5,834	675	11.60%	1.03 (0.86–1.24)	5,834	649	11.10%	1.23 (1.01–1.50)
Former	1,787	307	17.20%	1.50 (1.23–1.83)	1,787	325	18.20%	1.69 (1.37–2.08)
Occupational exposure								
Yes	3,972	411	10.30%	NS	3,972	372	9.40%	1.20 (1.03–1.40)
No	15,830	1,373	8.70%	1.00 (reference)	15,830	1,210	7.60%	1.00 (reference)
Family history								
Yes	4,431	595	13.40%	2.04 (1.82–2.27)	4,431	519	11.70%	2.16 (1.92–2.44)
No	15,371	1,189	7.70%	1.00 (reference)	15,371	1,063	6.90%	1.00 (reference)
Childhood lung infection								
Yes	4,737	479	10.10%	1.17 (1.02–1.33)	4,737	433	9.10%	1.23 (1.06–1.42)
No	15,065	1,305	8.70%	1.00 (reference)	15,065	1,149	7.60%	1.00 (reference)
Education status								
Never	3,616	497	13.70%	2.40 (1.84–3.13)	3,616	460	12.70%	1.97 (1.49–2.61)
Primary school	4,981	512	10.30%	1.55 (1.21–2.00)	4,981	493	9.90%	1.36 (1.05–1.77)
Junior high school	5,775	416	7.20%	1.35 (1.06–1.72)	5,775	354	6.10%	1.32 (1.02–1.70)
Senior high school	3,907	266	6.80%	1.36 (1.06–1.75)	3,907	183	4.70%	1.14 (0.87–1.50)
Graduate and above	1,523	93	6.10%	1.00 (reference)	1,523	92	6.00%	1.00 (reference)

**Table 1** (continued)

Table 1 (continued)

Variable	FEV <sub>1</sub> /FVC < LLN*				FEV <sub>1</sub> /FVC < 0.7*			
	N (n)	COPD (n)	COPD prevalence (%)	Adjusted OR	N (n)	COPD (n)	COPD prevalence (%)	Adjusted OR
BMI (kg/m <sup>2</sup> ) <sup>#</sup>								
<18.5	740	140	18.90%	2.87 (2.21–3.73)	740	150	20.30%	3.75 (2.84–4.96)
18.5–23.9	9,681	998	10.30%	1.59 (1.32–1.91)	9,681	892	9.20%	1.74 (1.41–2.14)
24.0–27.9	7,062	495	7.00%	1.12 (0.92–1.36)	7,062	418	5.90%	1.17 (0.94–1.46)
≥28.0	2,319	151	6.50%	1.00 (reference)	2,319	122	5.30%	1.00 (reference)
Kitchen ventilation equipment								
Yes	11,274	883	7.80%	1.00 (reference)	11,274	815	7.20%	NS
No	8,528	901	10.60%	1.13 (1.00–1.28)	8,528	767	9.00%	1.00 (reference)
Biofuel exposure								
Yes	9,403	972	10.30%	1.12 (0.99–1.28)	9,403	857	9.10%	1.16 (1.02–1.33)
No	10,399	812	7.80%	1.00 (reference)	10,399	725	7.00%	1.00 (reference)

\*, postbronchodilator FEV<sub>1</sub>/FVC < lower limit of normal established by the Guangzhou Institute of Respiratory Health and FEV<sub>1</sub>/FVC < 70% were used to define COPD; †, data are shown as odds ratio in percentage with 95% confidence intervals in parentheses; #, the classification boundary value of BMI adopted the normal reference range of BMI in China, 18.5–23.9. Calculations of odd ratios (ORs) and 95% CI values for COPD in relation to potential risk factors were performed with multivariate logistic regression models. The variables of geographic area, sex, age groups, body mass index (BMI), smoking status, occupational exposure to dusts/gases/fumes, exposure to biomass fuel for cooking or heating, ventilation in the kitchen, respiratory disease in family, pulmonary problems in childhood, and education were all forced into the multivariate logistic regression model and factors with no statistical difference were removed from the final model. NS, no statistical significance; BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; OR, odds ratio; LLN, lower limit of normal of FEV<sub>1</sub>/FVC.

Table 2 Air flow limitation severity and sex distribution of COPD patients with two diagnostic criterion and FEV<sub>1</sub> reference equations

Level	Diagnostic criterion (FEV <sub>1</sub> /FVC < LLN)*			Diagnostic criterion (FEV <sub>1</sub> /FVC < 0.7) <sup>§</sup>			P		
	Male, n (%)	Female, n (%)	Total, n (%)	Male, n (%)	Female, n (%)	Total, n (%)	Male	Female	Total
I	137 (13.1%)	145 (19.6%)	282 (15.8%)	225 (22.8%)	148 (28.0%)	373 (24.6%)	<0.001	0.102	<0.001
II	522 (50.0%)	330 (44.6%)	852 (47.8%)	490 (49.5%)	250 (47.3%)	740 (48.7%)	0.061	0.127	0.570
III	290 (27.8%)	204 (27.6%)	494 (27.7%)	212 (21.4%)	108 (20.4%)	320 (21.1%)	0.068	<0.001	<0.001
IV	95 (9.1%)	61 (8.2%)	156 (8.7%)	62 (6.3%)	23 (4.3%)	85 (5.6%)	0.095	0.001	0.001
Total	1,044 (100.0%)	740 (100.0%)	1,784 (100.0%)	989 (100.0%)	529 (100.0%)	1,518 (100.0%)	<0.001	<0.001	<0.001

\*, postbronchodilator FEV<sub>1</sub>/FVC < lower limit of normal established by the Guangzhou Institute of Respiratory Health (GIRH) was used to define COPD, and the GIRH FEV<sub>1</sub> reference equation was used for air flow limitation classification; §, postbronchodilator FEV<sub>1</sub>/FVC < 70% was used to define COPD, and the China 2002 revised ECSC93 FEV<sub>1</sub> reference equation was used for air flow limitation classification; 64 COPD patients over 78 years of age were not graded, because there is no predicted value of FEV<sub>1</sub> for adults over 78 years of age. Comparison of the distributions of COPD stages and sex between the GIRH-LLN criterion and GOLD 0.7 fixed ratio were analyzed using chi-squared tests. COPD, chronic obstructive pulmonary disease.

**Table 3** Air flow limitation severity and sex distribution of COPD patients diagnosed by GOLD 0.7 fixed ratio with two FEV<sub>1</sub> reference equations

Level	Diagnostic criterion (FEV <sub>1</sub> /FVC <0.7) <sup>#</sup>			Diagnostic criterion (FEV <sub>1</sub> /FVC <0.7) <sup>§</sup>			P		
	Male, n (%)	Female, n (%)	Total, n (%)	Male, n (%)	Female, n (%)	Total, n (%)	Male	Female	Total
I	136 (13.3)	74 (13.2)	210 (13.3)	225 (22.8)	148 (28.0)	373 (24.6)	<0.001	<0.001	<0.001
II	510 (49.9)	243 (43.4)	753 (47.6)	490 (49.5)	250 (47.3)	740 (48.7)	0.980	0.399	0.820
III	288 (28.2)	190 (33.9)	478 (30.2)	212 (21.4)	108 (20.4)	320 (21.1)	0.001	<0.001	<0.001
IV	88 (8.6)	53 (9.5)	141 (8.9)	62 (6.3)	23 (4.3)	85 (5.6)	0.055	<0.001	0.001
Total	1,022 (100)	560 (100)	1,582 (100)	989 (100.0)	529 (100.0)	1,518 (100.0)	0.749	0.749	–

<sup>#</sup>, the GIRH FEV<sub>1</sub> reference equation was used for air flow limitation classification; <sup>§</sup>, the China 2002 revised ECSC93 FEV<sub>1</sub> reference equation was used for air flow limitation classification; 64 COPD patients over 78 years of age were not graded, because there is no predicted value of FEV<sub>1</sub> for adults over 78 years of age. Comparison of the distributions of COPD stages and sex between the GIRH-LLN criterion and GOLD 0.7 fixed ratio were analyzed using chi-squared tests. COPD, chronic obstructive pulmonary disease.

## Discussion

As a noninvasive and readily available test, spirometry is the most reproducible and objective diagnostic measurement of airflow limitation. The COPD prevalence varied among different criteria, such as the fixed-ratio and GIRH-LLN. In our study, a higher total morbidity but younger incidence, more female patients, and increased severe patient proportion were detected with the GIRH-LLN criterion than with the GOLD 0.7 fixed ratio.

With the GIRH-LLN criterion, the COPD prevalence was 1.0% higher than that of the GOLD 0.7 fixed ratio (8.0%) among participants aged 40–80 years in China, especially the higher prevalence in women. This was consistent with another large study conducted in China, which GLI2012 LLN was used (18). Of which, airflow obstruction prevalence defined as FEV<sub>1</sub>/FVC <0.7 was 4.0% in females and 5.1% in males, and 5.9%, 5.2% respectively when FEV<sub>1</sub>/FVC < LLN was used (spirometry data of pre-bronchodilator was used). COPD prevalence was 1.9 percentage points higher than the GOLD 0.7 fixed ratio for females, but only 0.1 percentage points higher with males. A recent study reported that the overall prevalence of spirometry-defined COPD was 8.6% (95% CI: 7.5–9.9), accounting for 99.9 (95% CI: 76.3–135.7) million people with COPD in China. In people aged 40 years or older, the COPD prevalence was increased to 13.7% (12.1–15.5) (4). COPD patients would be even higher if the GIRH-LLN criterion was used because of China's large population base. In particular, it is of great significance in improving early diagnosis and prevention in patients underdiagnosed by GOLD, because of their impaired ventilation and faster

lung function decline (12).

Significantly, those newly diagnosed patients by LLN were not found to have higher smoking rates, but were predominantly rural and females, with high rates of biofuel explosion and poor kitchen conditions (Table 1). Biofuels are still the most important source of fuel in Chinese vast rural areas, especially over the past 20 years. As the primary undertakers of kitchen work, women are the main demographic who come into contact with biofuels. Biofuel smoke exposure has been found to be associated with COPD in rural and urban women (19). Moreover, these exposed residents always tend to have poor kitchen ventilation (20), as shown in our past studies. In addition, some other insights from the study of patients with COPD without a major causal factor are likely to provide insights into factors that contribute to endogenous immunological mechanisms. Many of them tended to be elderly women with a history of organ specific autoimmune disease and peripheral blood lymphopenia (21). More common in men many years ago, COPD now affects men and women almost equally (22). In Norway, the prevalence declined in men but not in women from 1995–1997 and 2006–2008 (23).

There are differences in COPD severity classification between these two criteria. The COPD percentage in stage I classified by the GIRH-LLN reference equation was obviously lower, while patients in stages III and IV were relatively higher than that classified by the ECSC1993 equation. What we have proved is that the GOLD criterion has caused a portion of the patients to be misdiagnosed as having COPD (12). These patients tend to be of a relatively high age, with lung function above the predicted value of 80%. Actually, lung function in these patients is a part

**Table 4** Symptoms distribution of COPD patients in different stages with the diagnostic criteria of LLN and fixed ratio among residents aged 40 to 80 years

Symptoms	Diagnostic criterion (FEV <sub>1</sub> /FVC < LLN)				Diagnostic criterion (FEV <sub>1</sub> /FVC < 0.7)				P*		
	I (n=282)	II (n=852)	III (n=494)	IV (n=156)	Total (n=1,784)	I (n=373)	II (n=740)	III (n=320)		IV (n=85)	Total (n=1,518)
Cough <sup>†</sup>	74 (26.2%)	284 (33.3%)	265 (53.6%)	93 (59.6%)	716 (40.1%)	120 (32.2%)	301 (40.7%)	197 (61.6%)	46 (54.1%)	664 (43.7%)	0.036
Sputum	69 (24.5%)	256 (30.0%)	232 (47.0%)	82 (52.6%)	639 (35.8%)	95 (25.5%)	293 (39.6%)	174 (54.4%)	41 (48.2%)	603 (39.7%)	0.021
Wheezing	36 (12.8%)	158 (18.5%)	200 (40.5%)	89 (57.1%)	483 (27.1%)	58 (15.5%)	187 (25.3%)	149 (46.6%)	44 (51.8%)	438 (28.9%)	0.256
Dyspnea	85 (30.1%)	326 (38.3%)	302 (61.1%)	119 (76.3%)	832 (46.6%)	129 (34.6%)	353 (47.7%)	212 (66.3%)	63 (74.1%)	757 (49.9)	0.064
One of above	130 (46.1%)	459 (53.9%)	363 (73.5%)	129 (82.7%)	1,081 (60.6%)	180 (48.3%)	479 (64.7%)	253 (79.1%)	71 (83.5%)	983 (64.8%)	0.014
Chronic cough with phlegm	38 (13.5%)	184 (21.6%)	186 (37.7%)	72 (46.2%)	480 (26.9%)	64 (17.2%)	213 (28.8%)	143 (44.7%)	34 (40.0%)	454 (29.9%)	0.056
Lifetime diagnosis of COPD <sup>‡</sup>	28 (9.9%)	177 (20.8%)	235 (47.6%)	110 (70.5%)	550 (30.8%)	69 (18.5%)	226 (30.5%)	182 (56.9%)	62 (72.9%)	539 (35.5%)	0.004

<sup>†</sup>, the duration of all symptoms was at least 3 months per year in the previous 2 years; <sup>‡</sup>, including COPD, bronchitis, emphysema, and asthma; \*, differences in total positive manifestations for each symptom; Chi-squared tests were used for analysis.

of the normal evolution of the population (24-26), which may result in the lower stage I incidence, when they were excluded by the GIRH-LLN criterion. In contrast, the increased female patients, especially rural women patients, were the major contributors to the increased prevalence of COPD with the GIRH-LLN criterion, and many of them had a FEV<sub>1</sub>%pred less than 80%. These subjects accounted for the higher proportion of patients with COPD stage II and above to a certain extent. Meanwhile, in the CESCOPD, we have used the adjusted ECSC93 FEV<sub>1</sub> predicted value by applying conversion factors (males by 0.95 and females by 0.93) for the assessment of COPD severity (China revised 2002 reference equation), and it was established by collecting lung function data (4,773 subjects) in 1996–2002. While the new GIRH-LLN FEV<sub>1</sub> reference equation was established ten years later with a larger sample size, stricter random sampling and better quality spirometry would be much individualized. Moreover, in the past 20 years, the overall nutritional status of people in China has been significantly improved, and they are physically stronger and taller than before (27,28), which may have narrowed the gap of lung function with the Europeans. All these things may lead to some bias in the estimation of the FEV<sub>1</sub> predicted value with the China revised 2002 reference equation. Nevertheless, because there is no predicted value of FEV<sub>1</sub> for adults over 78 years of age, 64 COPD patients could not be further identified by the ECSC93 criterion, as did the China revised 2002 reference equation.

The higher proportion of asymptomatic COPD patients and lower diagnosis with GIRH-LLN criterion, suggesting that less attention may be paid to their bodies. For symptoms are the main motivator for hospital visits and recommendation for spirometry by GOLD. Studies have shown that subjects in stages I and II followed a trajectory of rapidly declining FEV<sub>1</sub> (29). Meanwhile, these subjects had poorer exercise tolerance than healthy controls upon exertion, and a significant proportion of them had dynamic hyperinflation (30) though few of them presented chronic symptoms. These subjects may, therefore, deserve further attention and may warrant regular follow-up.

Overall, our study findings have important public health implications. First, we have almost accurately evaluated the prevalence of COPD under the criterion of GIRH-LLN from a national wide, randomized, cross-sectional and multi-center survey. Increased prevalences were detected in rural areas and female residents. Indicating sufficient attention should be taken by the government, and possible etiology and related mechanisms should be



actively explored. And then, for the first time, we found significant differences between different FEV<sub>1</sub> reference equations on COPD severity classification. Results showed that airflow limitation severity determining will be even worse when GIRH FEV<sub>1</sub> reference equation was used. The GIRH-LLN we have chosen was established through a large-sample, multicenter and all Chinese originated study. Further research has evidenced its advantages on detecting airflow limitations to reduce the risk of underdiagnosis for young adults and overdiagnosis for the elderly. It seems more Chinese-suitable and convincing to be recommended nationwide. Moreover, the CESCOPD study was a rare large-sample multicenter epidemiological investigation with strict random sampling and data quality control in China. It is of great representative for assessing COPD prevalence among people over 40 years of age.

There also exists some limitations in our study. One hundred and fifty-eight patients underdiagnosed by the GOLD 0.7 fixed ratio used spirometry data collected before bronchodilation, which may lead to a slightly higher prevalence of COPD. Consistent with the findings (3.1%) of Johannessen and colleagues (31), our published article reported 3.3% of the population had a low ratio of FEV<sub>1</sub>/FVC (<70%) before bronchodilation and a normal ratio (FEV<sub>1</sub>/FVC ≥70%) after bronchodilation in the present study (3). However, there was no statistically significant difference in diagnostic property when using pre- or postbronchodilator FEV<sub>1</sub>/FVC among people with respiratory symptoms in the studies by Mohamed and Kato (32,33). On the other hand, it is difficult to define patients newly diagnosed by LLN as COPD precisely (34), for a few of them may possibly have small lungs (35). The same is true for GOLD. Another situation, they do have respiratory impairment. Whether these populations are pre-COPD or early-stage COPD is controversial. Our previous study has demonstrated that the underdiagnosed participants (by GOLD) showed more symptoms, impaired ventilation and faster lung function decline through a two-year longitudinal follow-up research compared with normal participants (12), prefer to support a think of early stage of COPD. Certainly, longer-term follow-up of these populations may be more helpful to assess their health status.

## Conclusions

In conclusion, the COPD prevalence with the GIRH-LLN criterion was slightly higher than with the GOLD 0.7 fixed-ratio criterion, especially in women and rural participants.

These residents always showed little symptoms and low diagnosis, suggesting serious attention should be paid to them.

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## Footnote

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## References

- Vogelmeier CF, Criner GJ, Martinez FJ, et al. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report. GOLD Executive Summary. *Am J Respir Crit Care Med* 2017;195:557-82.
- Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease (2021 reports). Available online: <https://goldcopd.org/2021-gold-reports/>
- Zhong N, Wang C, Yao W, et al. Prevalence of chronic obstructive pulmonary disease in China: a large, population-based survey. *Am J Respir Crit Care Med* 2007;176:753-60.
- Wang C, Xu J, Yang L, et al. Prevalence and risk factors of chronic obstructive pulmonary disease in China (the China Pulmonary Health CPH study): a national cross-sectional study. *Lancet* 2018;391:1706-17.
- Culver BH. How should the lower limit of the normal range be defined? *Respir Care* 2012;57:136-45, 143-5.
- Stanojevic S, Wade A, Stocks J, et al. Reference ranges for spirometry across all ages: a new approach. *Am J Respir Crit Care Med* 2008;177:253-60.
- Cerveri I, Corsico AG, Accordini S, et al. Underestimation of airflow obstruction among young adults using FEV1/FVC <70% as a fixed cut-off: a longitudinal evaluation of clinical and functional outcomes. *Thorax* 2008;63:1040-5.
- Vaz Fragoso CA, Concato J, McAvay G, et al. The ratio of FEV1 to FVC as a basis for establishing chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2010;181:446-51.
- Vollmer WM, Gislason T, Burney P, et al. Comparison of spirometry criteria for the diagnosis of COPD: results from the BOLD study. *Eur Respir J* 2009;34:588-97.
- Luoto JA, Elmstahl S, Wollmer P, et al. Incidence of airflow limitation in subjects 65-100 years of age. *Eur Respir J* 2016;47:461-72.
- Güder G, Brenner S, Angermann CE, et al. GOLD or lower limit of normal definition? A comparison with expert-based diagnosis of chronic obstructive pulmonary disease in a prospective cohort-study. *Respir Res* 2012;13:13.
- Liu S, Zhou Y, Liu S, et al. Clinical impact of the lower limit of normal of FEV1/FVC on detecting chronic obstructive pulmonary disease: A follow-up study based on cross-sectional data. *Respir Med* 2018;139:27-33.
- Ben Saad H, El AM, Hadj MK, et al. The recent multi-ethnic global lung initiative 2012 (GLI2012) reference values don't reflect contemporary adult's North African spirometry. *Respir Med* 2013;107:2000-8.
- Quanjer PH, Stanojevic S, Cole TJ, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. *Eur Respir J* 2012;40:1324-43.
- Jian W, Gao Y, Hao C, et al. Reference values for spirometry in Chinese aged 4-80 years. *J Thorac Dis* 2017;9:4538-49.
- Standardization of Spirometry, 1994 Update. American Thoracic Society. *Am J Respir Crit Care Med* 1995;152:1107-36.
- Zheng J, Zhong N. Normative values of pulmonary function testing in Chinese adults. *Chin Med J (Engl)* 2002;115:50-4.
- Smith M, Li L, Augustyn M, et al. Prevalence and correlates of airflow obstruction in ~317 000 never-smokers in China. *Eur Respir J* 2014;44:66-77.
- Sana A, Somda S, Meda N, et al. Chronic obstructive pulmonary disease associated with biomass fuel use in women: a systematic review and meta-analysis. *BMJ Open Respir Res* 2018;5:e000246.
- Zhou Y, Wang C, Yao W, et al. COPD in Chinese nonsmokers. *Eur Respir J* 2009;33:509-18.
- Pavord ID, Yousaf N, Birring SS. Chronic obstructive pulmonary disease in non-smokers. *Lancet* 2009;374:1964, 1965-66.
- World Health Organisation. Chronic obstructive pulmonary disease (COPD). 2016. Available online: <http://www.who.int/mediacentre/factsheets/fs315/en/> (accessed 15 Jun 2017)
- Bhatta L, Leivseth L, Mai XM, et al. Prevalence and trend of COPD from 1995-1997 to 2006-2008: The HUNT study, Norway. *Respir Med* 2018;138:50-6.
- Akkermans RP, Biermans M, Robberts B, et al. COPD prognosis in relation to diagnostic criteria for airflow obstruction in smokers. *Eur Respir J* 2014;43:54-63.
- Akkermans RP, Berrevoets MA, Smeele IJ, et al. Lung function decline in relation to diagnostic criteria for airflow obstruction in respiratory symptomatic subjects.. *BMC Pulm Med* 2012;12:12.
- Sator L, Horner A, Studnicka M, et al. Overdiagnosis of

- COPD in Subjects With Unobstructed Spirometry: A BOLD Analysis. *Chest* 2019;156:277-88.
27. Yang XG, Li YP, Ma GS, et al. Study on weight and height of the Chinese people and the differences between 1992 and 2002. *Zhonghua Liu Xing Bing Xue Za Zhi* 2005;26:489-93.
  28. Song Y, Hu PJ, Zhang B, et al. Secular trends of height among Chinese students aged 17 in 18 ethnic minorities from 1985 to 2010. *Beijing Da Xue Xue Bao Yi Xue Ban* 2015;47:414-9.
  29. Lange P, Celli B, Agusti A, et al. Lung-Function Trajectories Leading to Chronic Obstructive Pulmonary Disease. *N Engl J Med* 2015;373:111-22.
  30. Soumagne T, Laveneziana P, Veil-Picard M, et al. Asymptomatic subjects with airway obstruction have significant impairment at exercise. *Thorax* 2016;71:804-11.
  31. Watz H, Tetzlaff K, Magnussen H, et al. Spirometric changes during exacerbations of COPD: a post hoc analysis of the WISDOM trial. *Respir Res* 2018;19:251.
  32. Mohamed Hoesein FA, Zanen P, Sachs AP, et al. Spirometric thresholds for diagnosing COPD: 0.70 or LLN, pre- or post-dilator values? *COPD* 2012;9:338-43.
  33. Kato B, Gulsvik A, Vollmer W, et al. Can spirometric norms be set using pre- or post- bronchodilator test results in older people? *Respir Res* 2012;13:102.
  34. Schermer TR, Robberts B, Crockett AJ, et al. Should the diagnosis of COPD be based on a single spirometry test? *NPJ Prim Care Respir Med* 2016;26:16059.
  35. Postma DS, Bush A, van den Berge M. Risk factors and early origins of chronic obstructive pulmonary disease. *Lancet* 2015;385:899-909.

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