

Assessment of Preserved Ratio Impaired Spirometry (PRISm) Based on Different Definitions in the Early COPD Cohort

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Background: Preserved ratio impaired spirometry (PRISm), which identifies a population at high risk for COPD, has drawn increasing attention. However, definitions for PRISm vary across studies, and researches comparing these definitions are limited.

Objective: We aim to assess the agreement, the clinical features, and the prevalence of PRISm defined by restrictive spirometric pattern (RSP) method [that is forced vital capacity (FVC) method] versus forced expiratory volume in the first second (FEV₁) method and by fixed values versus the lower limit of normal (LLN).

Methods: All 1862 participants from the E-COPD study underwent questionnaire investigation, spirometry, biphasic CT, and impulse oscillometry. Participants were categorized into control and two targeted groups (RSP fixed and PRISm fixed excluding RSP fixed) based on FVC and FEV₁ fixed definitions. Similar categorizations were conducted for RSP LLN versus PRISm LLN and PRISm fixed versus PRISm LLN. We assessed the agreement, the clinical features, and the prevalence of PRISm among these various definitions, repeating all analyses using Global Lung function Initiative (GLI) equation.

Results: Significant overlap with merely moderate agreement (Kappa coefficient = 0.706, P value <0.001) existed between RSP fixed and PRISm fixed definitions. Participants identified as PRISm by both definitions exhibited lower lung function, higher airway reactance, and increased airway resistance compared to the control group. Similar findings were observed in RSP LLN versus PRISm LLN and PRISm fixed versus PRISm LLN. Our sensitivity analysis verified the consistency of these results. Furthermore, the prevalence of PRISm varied from 2.0% to 12.5% depending on the definitions and predicted equations, with the Chinese equation, LLN definition in Chinese equation and fixed definition in GLI equation yielding higher prevalence rates.

Conclusion: Our findings highlight concerns about the comparability of studies and the interchangeability of various definitions and reference equations for PRISm.

Keywords: PRISm, definitions, clinical features, prevalence, reference equations

Background

Preserved ratio impaired spirometry (PRISm), characterized by proportionate impairments in forced vital capacity (FVC) and forced expiratory volume in the first second (FEV₁) while maintaining a normal FEV₁/FVC ratio, is associated with higher body mass index (BMI),^{1,2} cumulative smoke exposure,^{1,2} increased respiratory symptoms,²⁻⁴ decreased exercise capacity,^{5,6} and higher levels of quantitative emphysema,² airway wall thickness,⁷ and systemic inflammation.⁸

Additionally, individuals with PRISm faced increased risks of morbidity,^{1,3,8} progression to COPD,¹ and all-cause mortality.¹⁻⁴ Thus, recognizing PRISm is crucial, as it identifies an at-risk population denoted as pre-COPD, making its definition a primary concern.

Definitions for PRISm varied greatly across studies. Many define preserved ratio low lung function as the absence of airflow obstruction with reduced FVC using the restrictive spirometric pattern (RSP) method or FEV₁ using the PRISm method. For example, the RSP definition is commonly used in NHANES,^{5,9} ARIC,¹⁰ and ELSA studies.¹¹ Meanwhile, the PRISm definition appears in the BOLD,¹² COPDgene,^{2,13} Rotterdam,¹⁴ and UK biobank studies.¹ This abnormal spirometric phenotype is also referred to as preserved ratio impaired spirometry.¹⁵ The RSP and PRISm definitions can be further categorized into fixed methods (FVC or FEV₁<80% predicted; FEV₁/FVC ratio ≥ 0.7), based on fixed cutoff, and the lower limit of normal (LLN) methods (FVC or FEV₁<LLN; FEV₁/FVC ratio \geq LLN).

Since Wan et al proposed the scientific definition of PRISm in 2014, most studies have directly adopted this approach, characterized by a preserved FEV₁/FVC ratio and impaired FEV₁. However, the interchangeable application of fixed methods (denoted as PRISm fixed method in this study) and LLN method (denoted as PRISm LLN method in this study) persists across studies.^{11-14,16,17} What differences among these various definitions including RSP & PRISm method and PRISm fixed and PRISm LLN methods for PRISm, and whether these methods can apply interchangeably across different studies are unclear. And there is a paucity of data on the agreement level among these definitions, as well as the prevalence and the clinical features of PRISm participants identified by these different definitions. To address this knowledge gap, we conducted a cross-sectional study aimed 1) to assess the level of agreement, the clinical features and the prevalence of PRISm defined by RSP and PRISm methods; and 2) to assess these aspects for PRISm defined by PRISm fixed and PRISm LLN methods.

Materials and Methods

Study Population

This study was a cross-sectional analysis for the baseline of the Early Chronic Obstructive Pulmonary Disease (ECOPD) study, a prospective observational cohort conducted in Guangzhou, Shaoguan, and Heyuan in Guangdong Province, China. Baseline enrollment began in July 2019 and ended in August 2021, with detailed study protocol published previously.¹⁸ Briefly, we screened participants through a large COPD community screening programme for individuals aged 40–80 years (n=5887). We randomly invited a quarter of participants (n=1261/4647) with non-obstructive spirometry (post-bronchodilator FEV₁/FVC ≥ 0.70) and all patients (n=939) with obstructive spirometry (post-bronchodilator FEV₁/FVC<0.70) to participate in the ECOPD study and completed computed tomography (CT) and impulse oscillometry (IOS) tests. Our analysis focused on participants with valid and complete data regarding questionnaires, spirometry, CT and IOS. The ECOPD study has been approved by the Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University (No. 2018-53), and all participants provided written informed consent.

Questionnaire

We utilized a standard respiratory epidemiological questionnaire from our previous studies,^{19,20} administered by trained investigators. It collected information on demographics, COPD-related risk factors (including smoking and occupation exposure), chronic respiratory symptoms, respiratory comorbidities, and acute respiratory events during the preceding year. Chronic respiratory symptoms such as cough, phlegm, and wheezing were assessed by asking if these symptoms were present outside of cold episodes. Known annual household income was categorized into three groups (low: <10,000 RMB; medium: 10,000–100,000 RMB; high: >100,000 RMB). Other definitions regarding smoking status, smoking index, occupation exposure, and respiratory comorbidities have been described in detail elsewhere.¹⁸

Spirometry

Spirometry was performed using a portable spirometer (CareFusion, Yorba Linda, CA, USA) in accordance with the operational methods and quality control standards recommended by the American Thoracic Society and Europe Respiratory Society.^{21,22} All participants underwent post-bronchodilator spirometry after inhaling 400 μ g of salbutamol

for 20 minutes. We recorded pre- and post-bronchodilator FVC and FEV₁ from at least three acceptable and two repeatable measurement curves. Pre- and post-bronchodilator maximal mid-expiratory flow (MMEF), forced expiratory flow at 50% (FEF50), and forced expiratory flow at 75% (FEF75) were recorded from the curve corresponding to the maximum FEV₁ + FVC. Given that all the participants are Chinese, the predictive equations used in our main analyses were based on Chinese reference equations as developed by Jian et al.²³ We also conducted sensitivity analyses using Global lung function initiative (GLI) reference equations,²⁴ specifically the predicted values for South East Asian group, as all participants were from Guangdong Province.

Impulse Oscillometry

IOS is a non-invasive pulmonary function assessment tool that measures airway resistance and reactance by analyzing the respiratory system's response to superimposed sound wave oscillations during tidal breathing. IOS (Masterscreen IOS, Hochberg, Germany) was performed by well-trained operator in accordance with European Respiratory Society guidelines.²⁵ IOS is an effort-independent test conducted prior to premedication and spirometry to avoid the influence of medication and excessive force. We recorded the parameters including resistance at 5 Hz (R5), resistance at 20 Hz (R20), the difference between R5 and R20 (R5–R20), reactance at 5 Hz (X5), reactance area (AX), and resonant frequency (Fres) to assess the reactance and resistance of PRISm defined by various methods.

Imaging

Biphasic CT was performed on a multidetector-row CT scanner (Siemens Definition AS Plus 128-slicers and United-imaging uCT 760 128-slicers) at full inspiration and at maximum expiration. Further operational details, CT protocol, and quality control have been illustrated previously.¹⁸ We used Chest Imaging Platform (<https://www.chestimagingplatform.org>) on the semi-automated 3D Slicer 4.11 software (<https://www.slicer.org>) for quantitative image assessment. Emphysema was quantified by the percentage of low attenuation units below –950 hU at full inspiration (LAA_{–950}), and gas trapping was measured by the percentage of low-attenuation units below –856 hU at full expiration (LAA_{–856}).²⁶ We also recorded the ratio of residual volume to total lung capacity (RV/TLC) to assess air trapping.

Definition Groups

Lung function parameters used in different definitions for PRISm were derived from post-bronchodilator spirometry. The RSP and PRISm methods are defined by fixed cutoff measurements (FVC or FEV₁ < 80% predicted; FEV₁/FVC ≥ 0.7) or the LLNs, corresponding to approximately the fifth percentile (Z-score < –1.645). Therefore, the RSP method is distinguished as RSP fixed (FVC < 80% predicted and FEV₁/FVC ≥ 0.7) and RSP LLN (FVC & FEV₁/FVC ≥ LLN). Similarly, the PRISm method comprises PRISm fixed (FEV₁ < 80% predicted and FEV₁/FVC ≥ 0.7) and PRISm LLN (FEV₁ < LLN & FEV₁/FVC ≥ LLN). To validate our first study objective, we compared the RSP fixed method with the PRISm fixed method, followed by a comparison of RSP LLN with PRISm LLN. Additionally, we compared the PRISm fixed and PRISm LLN methods to assess the second study objective. The study groups in main analyses based on Chinese predictive equations were defined as follows:

- 1) a. Control: FEV₁/FVC ≥ 0.70 and FVC ≥ 80% predicted and FEV₁ ≥ 80% predicted;
 b. RSP fixed: FEV₁/FVC ≥ 0.70 and FVC < 80% predicted;
 c. PRISm fixed excluding RSP fixed: FEV₁/FVC ≥ 0.70 and FEV₁ < 80% predicted and FVC ≥ 80% predicted.
- 2) a. Control: FEV₁/FVC ≥ LLN & FVC ≥ LLN & FEV₁ ≥ LLN;
 b. RSP LLN: FEV₁/FVC ≥ LLN & FVC < LLN;
 c. PRISm LLN excluding RSP LLN: FEV₁/FVC ≥ LLN & FEV₁ < LLN & FVC ≥ LLN.
- 3) a. Control: FEV₁/FVC ≥ 0.70 and FEV₁ ≥ 80% predicted and FEV₁/FVC ≥ LLN & FEV₁ ≥ LLN;
 b. PRISm fixed: FEV₁/FVC ≥ 0.70 and FEV₁ < 80% predicted;
 c. PRISm LLN excluding PRISm fixed: FEV₁/FVC ≥ LLN & FEV₁ < LLN excluding FEV₁/FVC ≥ 0.70 and FEV₁ < 80% predicted.

We considered all the control groups as reference groups. For the sensitivity analyses, we replaced Chinese predictive equations with GLI equations while maintaining the same definitions for study groups as in the main analyses.

Statistical Analysis

Continuous variables were presented as mean±standard deviation, and ordinal/categorical variables were expressed as numbers and percentages. The Kappa coefficient assessed the agreement between the two definitions. Continuous variables with a normal distribution were compared by one-way ANOVA among three groups, while the Kruskal–Wallis test was applied for variables following a skewed distribution. Categorical variables were compared using Chi-square tests or Fisher’s exact test as appropriate. Multiple comparisons were adjusted by using the Bonferroni method. We used multivariate regression analysis to compare the imaging features, airway resistance and reactance of PRISm among three groups, including covariates such as age, sex, BMI, smoking status and smoking index. Sensitivity analyses employed the same methods as the main analyses. A two-sided P value <0.05 was considered statistically significant. Statistical analysis was performed using SPSS v25.0.

Results

Of the 2200 participants recruited for the ECOPD study, 76 were excluded due to ineligible CT or lung function data, 69 had comorbidities affecting lung function, and 193 had incomplete IOS tests. Ultimately, 1862 participants were included in the final analysis (Figure S1). Post-bronchodilator FVC correlated moderately with post-bronchodilator FEV₁ ($R^2=0.603$, P value <0.001) (Figure 1).

Agreement and Clinical Features for PRISm — RSP Fixed Versus PRISm Fixed

Only 58.0% of PRISm participants were co-identified by RSP and PRISm methods based on fixed cutoffs. Specifically, 56 of 226 (24.8%) were identified by PRISm fixed method, and 39 of 226 (17.2%) by RSP fixed method (Figure 2). A significant overlap with moderate agreement was noted between RSP and PRISm (Kappa coefficient = 0.706, P value <0.001), indicating that RSP and PRISm definitions are not completely equivalent.

Among the 1029 participants in the RSP fixed and PRISm fixed methods, 803 were in the control group, 170 in the RSP fixed group, and 56 in the PRISm fixed excluding RSP fixed group. The mean age was higher in the RSP fixed group than in the control group (60.0 ± 8.0 years vs 58.0 ± 7.8 years, P value <0.05), with no difference relative to the

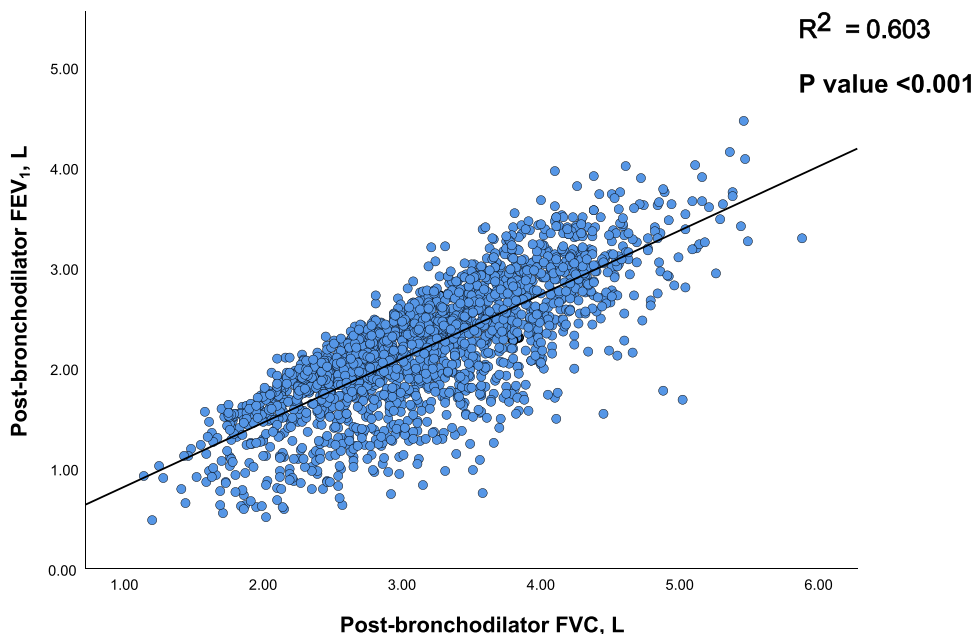


Figure 1 Scatter correlation plot for post-bronchodilator FVC and FEV₁.

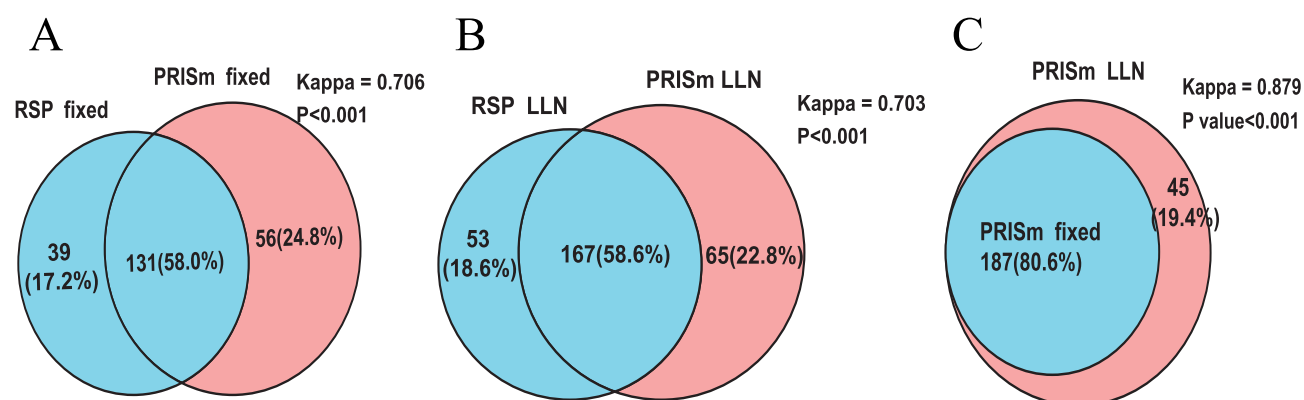


Figure 2 Venn diagram indicating the number and overlap of participants identified with various definitions of Chinese reference equations, including Kappa value and p value. (A) RSP fixed versus PRISm fixed; (B) RSP LLN versus PRISm LLN; (C) PRISm LLN versus PRISm fixed.

PRISm fixed excluding RSP fixed group. The RSP fixed group had a lower proportion of male compared to the other two groups (50.0% vs 60.6%, P value <0.05; 50.0% vs 73.2%, P value <0.05). Other demographics and clinical characteristics were similar among the three groups (Table 1). In spirometric tests, both the RSP fixed and PRISm fixed excluding RSP fixed groups had lower lung function levels than control group. Regardless of pre- or post-bronchodilator lung function, FVC %predicted was lower in the RSP fixed group compared to the PRISm fixed excluding RSP fixed group (75.1±8.0% vs 85.6±6.1%, P value <0.05), while the direction of differences for mid-to-end expiratory flow rates were opposite between them (Table 2).

Table 1 Characteristics of PRISm Based on Fixed Definition of Chinese Reference Equations Grouping by RSP and PRISm Methods

Characteristics	Control (n=803)	RSP Fixed (n=170)	PRISm Fixed Excluding RSP Fixed (n=56)
Age, yrs	58.0±7.8	60.0±8.0*	59.5±8.1
Male sex, %	487 (60.6)	85 (50.0)*	41 (73.2) [†]
BMI, kg/m ²	23.3±3.1	23.3±3.4	23.3±3.4
Educational level, %			
Primary school or less	381 (47.4)	92 (54.1)	29 (51.8)
Middle or high school	392 (48.8)	72 (42.4)	24 (42.9)
College or higher	30 (3.7)	6 (3.5)	3 (5.4)
Annual household income, %			
Low	134 (16.7)	25 (14.7)	14 (25.0)
Medium	587 (73.1)	128 (75.3)	35 (62.5)
High	66 (8.2)	15 (8.8)	6 (10.7)
Unknown	16 (2.0)	2 (1.2)	1 (1.8)
Smoking status, %			
Never smoker	416 (51.8)	99 (58.2)	25 (44.6)
Former smoker	102 (12.7)	23 (13.5)	8 (14.3)
Current smoker	285 (35.5)	48 (28.2)	23 (41.1)
Smoking index, pack-years	19.3±28.6	18.7 ±30.6	24.7±30.0
Smokers living at home, %	331 (41.2)	76 (44.7)	25 (44.6)
Parental history of respiratory diseases, %	67 (8.3)	17 (10.0)	7 (12.5)
Occupation exposure>6 months, %	127 (15.8)	28 (16.5)	13 (23.2)
History of respiratory comorbidities, %	419 (52.2)	98 (57.6)	25 (44.6)
History of prior year acute respiratory events, %	43 (5.4)	14 (8.2)	7 (12.5)

(Continued)

Table 1 (Continued).

Characteristics	Control (n=803)	RSP Fixed (n=170)	PRISm Fixed Excluding RSP Fixed (n=56)
Respiratory symptoms without colds, %			
Cough	130 (16.2)	32 (18.8)	16 (28.6)
Sputum	191 (23.8)	40 (23.5)	17 (30.4)
Wheeze	39 (4.9)	16 (9.4)	4 (7.1)
mMRC dyspnea score	0.23±0.50	0.32±0.58	0.21±0.46
CAT score	3.80±8.46	3.62±8.55	3.00±4.42

Notes: Data are expressed as Mean ± SD or n (%) as appropriate. *P<0.05 compared with the control group; †P<0.05 compared with the RSP fixed group. All p values were adjusted for multiple comparisons using Bonferroni correction method.

Abbreviations: RSP, restrictive spirometric pattern; PRISm, preserved ratio impaired spirometry; BMI, body mass index; yrs, years; mMRC, modified Medical Research Council; CAT, COPD Assessment Test.

Table 2 Lung Function Levels of PRISm Based on Fixed Definition of Chinese Reference Equations Grouping by RSP and PRISm Methods

Spirometry Parameters	Control (n=803)	RSP Fixed (n=170)	PRISm Fixed Excluding RSP Fixed (n=56)
Pre-bronchodilator			
FVC, %predicted	99.4±11.3	75.1±8.0*	85.6±6.1*,†
FEV ₁ , %predicted	94.0±10.8	73.3±9.0*	75.4±5.5*
MMEF, %predicted	79.1±28.5	65.9±27.9*	48.2±13.9*,†
FEF50, %predicted	82.0±27.3	67.9±25.5*	50.3±13.2*,†
FEF75, %predicted	84.4±40.1	74.2±42.6*	48.8±16.1*,†
Post-bronchodilator			
FVC, %predicted	99.3±10.5	74.2±5.7*	85.5±2.7*,†
FEV ₁ , %predicted	97.4±10.0	75.2±7.7*	78.3±2.1*
MMEF, %predicted	92.1±29.3	76.3±31.6*	56.0±11.3*,†
FEF50, %predicted	93.9±27.3	76.8±27.3*	58.6±10.8*,†
FEF75, %predicted	84.4±40.1	74.2±42.6*	48.8±16.1*,†

Notes: Reference equation was based on Chinese reference equation from Jian et al. *P<0.05 compared with the control group; †P<0.05 compared with the RSP fixed group. All p values were adjusted for multiple comparisons using Bonferroni correction method.

Abbreviations: RSP, restrictive spirometric pattern; PRISm, preserved ratio impaired spirometry; % predicted, percentage of predicted; FVC, forced vital capacity; FEV₁, forced expiratory volume in the first second; MMEF, maximal mid-expiratory flow; FEF50, forced expiratory flow at 50 of forced vital capacity; FEF75, forced expiratory flow at 75 of forced vital capacity.

In imaging features, after adjusting for age, sex, BMI, smoking status and smoking index, only RV/TLC was higher in the RSP fixed group compared to the control group; there was no difference when compared to the PRISm fixed excluding RSP fixed group. Airway reactance and resistance were more pronounced in both two targeted groups compared to the control group. Besides, R20, R5-R20, and AX were higher in the PRISm fixed excluding RSP fixed group than in the RSP fixed group, while other parameters were balanced (Figure 3).

Agreement and Clinical Features for PRISm — RSP LLN Versus PRISm LLN

When LLN value replaced fixed cutoff value, the agreement level (Figure 2), demographics, characteristics, lung function, imaging features, airway reactance, and airway resistance were consistent with findings from RSP fixed and PRISm fixed groups. Notably, never smokers (57.3% vs 38.5%, P value <0.05) and respiratory comorbidities (57.7% vs 40.0%, P value <0.05) were more common in the RSP LLN group compared to the PRISm LLN excluding RSP LLN group, but there were no differences relative to the control group (Tables S1, S2 and Figure S2).

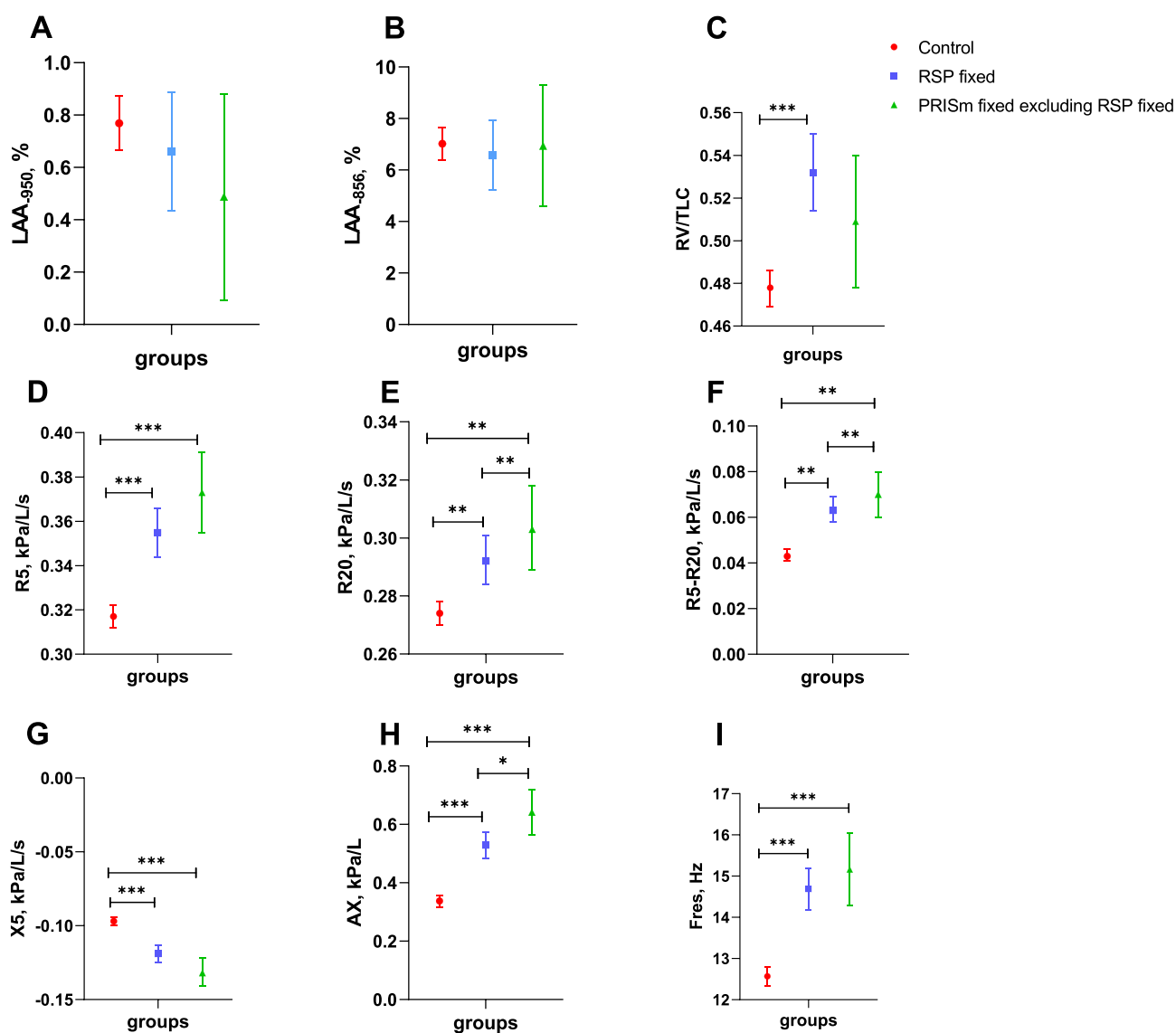


Figure 3 Imaging features and airway resistance and reactivity of PRISm based on fixed definition of Chinese reference equations grouping by RSP and PRISm methods. **Note:** The dot and the bar indicate mean and 95% confidence interval adjusted for age, sex, BMI, smoke status, and smoking index, respectively. *indicates P value <0.05; **indicates P value <0.01; ***indicates P value <0.001. Bonferroni correction method was used for multiple comparisons. (A–C) correspond to the imaging features LAA₋₉₅₀, LAA₋₈₅₆, and RV/TLC, respectively. (D–I) correspond to the airway resistance and reactivity features R5, R20, R5-R20, X5, AX, and Fres, respectively. **Abbreviations:** RSP, restrictive spirometric pattern; PRISm, preserved ratio impaired spirometry; LAA₋₉₅₀, low-attenuation area of the lung with attenuation values below -950 hounsfield units on full-inspiration CT; LAA₋₈₅₆, low-attenuation area of the lung with attenuation values below -856 hounsfield units on full-expiration CT; RV/TLC, the ratio of residual volume to total lung capacity; R5, resistance at 5 hz; R20, resistance at 20 hz; R5-R20, the difference from resistance at 5 hz to resistance at 20 hz; X5, reactance at 5 hz; AX, reactance area; Fres, resonant frequency; %, percent.

Agreement and Clinical Features for PRISm — PRISm Fixed Versus PRISm LLN

Among 187 PRISm participants co-identified by fixed or LLN-based cutoff values, 45 of 232 (19.4%) participants were identified only by the PRISm LLN method, yielding a Kappa coefficient of 0.879 (Figure 2). The average age was highest in the PRISm LLN excluding PRISm fixed group at 63.2 years old, followed by the PRISm fixed group at 60.0 years old, and lowest in the control group lowest at 58.2 years old (Table S3). The PRISm LLN excluding PRISm fixed group had more smoke exposure (current smoker: 53.3% vs 32.6%, P value <0.05; smoking index: 34.1±31.0 vs 20.3±30.3, P value <0.05) but a lower history of exacerbations in the prior year (4.4% vs 10.2%, p value <0.05) compared to the PRISm fixed group. Wheezing was more common in the PRISm fixed group than in the control group. Other characteristics were balanced among the three groups. Lung function levels were lower in both two targeted groups than

Table 3 The Prevalences for PRISm Identified by Different Definitions Based on Chinese and GLI Reference Equations

Reference Equations	RSP Fixed	PRISm Fixed	RSP LLN	PRISm LLN
Chinese	9.1 (170/1862)	10.0 (187/1862)	11.8 (220/1862)	12.5 (232/1862)
GLI	3.7 (72/1862)	5.0 (94/1862)	2.0 (37/1862)	2.2 (41/1862)

in the control group, with FVC %predicted in the PRISm fixed group lower than in the PRISm LLN excluding PRISm fixed group, whereas the opposite was true for post-bronchodilator MMEF and FEF50 %predicted ([Table S4](#)).

In addition, LAA₋₈₅₆ was higher in the PRISm LLN excluding PRISm fixed group than in the other two groups. RV/TLC, airway reactance, and resistance were more pronounced in both two targeted groups compared to the control group, indicating that PRISm subjects with functional airway abnormalities can be identified using both fixed and LLN value methods ([Figure S3](#)).

Results for Sensitivity Analyses

In sensitivity analyses using GLI equations, the levels of agreement were comparable to those in the main analysis comparing RSP and PRISm ([Figure S4](#)). There were no differences in characteristics among the three groups from RSP fixed versus PRISm fixed ([Table S5](#)). However, lung function ([Table S6](#)), emphysema index, airway reactance, and airway resistance ([Figure S5](#)) were worse in both targeted groups compared to the control group based on fixed values. Notably, these features did not differ between the two targeted groups, which contrasts with the main analysis findings. For RSP LLN versus PRISm LLN, respiratory symptom and higher air trapping were more common in the PRISm LLN excluding RSP LLN group compared with the other two groups ([Table S7](#) and [Figure S6](#)). Results for lung function, emphysema index, airway reactance, and airway resistance were similar to those based on the fixed method ([Table S8](#) and [Figure S6](#)).

For PRISm fixed versus PRISm LLN, a moderate agreement was observed (Kappa index = 0.503, P value < 0.001) ([Figure S4](#)), significantly lower than the main analysis (Kappa index = 0.879). The characteristics were nearly balanced among the three groups ([Table S9](#)). Lung function was worse in the two targeted two groups compared with the control group ([Table S10](#)). Except for R5-R20, AX, and Fres, other imaging and IOS features did not differ between the targeted groups after adjusting for confounders. R5-R20, AX, and Fres were higher in the PRISm LLN group than in the PRISm fixed excluding PRISm LLN group. Air trapping, airway reactance and airway resistance were also more pronounced in both two targeted groups than in the control group ([Figure S7](#)).

Prevalence of PRISm by Different Definitions and Reference Equations

PRISm prevalence varied from 9.1% to 12.5% when defined using Chinese predicted equations, but decreased significantly with GLI reference equations, varying from 2.0% to 5.0%. Furthermore, fixed definitions identified more PRISm subjects (RSP fixed: 72/1862; PRISm fixed: 94/1862) than LLN definitions (RSP LLN: 37/1862; PRISm: 41/1862), with or without statistical significance. Conversely, under Chinese reference equations, LLN definition identified more PRISm subjects (RSP LLN: 220/1862; PRISm LLN: 232/1862; RSP fixed: 170/1862; PRISm fixed: 187/1862) ([Table 3](#)).

Discussion

In this cross-sectional analysis of the ECOPD study, we found only moderate agreement between the RSP and PRISm definitions for identifying PRISm. Participants classified under both methods exhibited abnormal lung function and airway compliance compared to controls, regardless of whether fixed values or LLN values were used. Similar findings were observed when comparing PRISm fixed and PRISm LLN definitions. Furthermore, the prevalence and clinical features of PRISm varied significantly based on the definitions and reference equations employed, raising concerns about the interchangeability of these definitions. To our knowledge, this is the first study to systemically explore the agreements, prevalence, and characteristics of PRISm based on different definitions and reference equations.

Previously, preserved ratio low lung function, a restrictive spirometry pattern, has been labeled variously as “GOLD unclassified”, “non-specific”, and “preserved ratio impaired spirometry (PRISm)” by researchers.^{7,15,27} This pattern is characterized by reduced FVC or FEV₁ while maintaining a preserved FEV₁/FVC ratio. Various researches have adopted various definitions,²⁷ yet no data have systematically compared these definitions, despite the formal introduction of the PRISm concept, which utilizes FEV₁ as a restriction measure. Our results indicate that approximately 60% participants were co-classified by both definitions, while over 40% were identified independently by either RSP or PRISm methods. Notably, PRISm subjects classified by both definitions demonstrated poorer lung function, airway reactance, and airway resistance than controls. In this asymptomatic nonobstructive population, impulse oscillometric measurements revealed elevated airway resistance and frequency dependence, suggesting that spirometric abnormalities may arise from distal small airway dysfunction.²⁸ Further comparison revealed that the RSP method identified participants with lower FEV₁ or FVC %prediction, whereas the PRISm method associated with higher airway reactance and resistance measurements (R20, R5-R20, and AX). The observed functional abnormalities varied across definitions, suggesting that it remains unclear which method is superior. The arbitrary choice of definitions may lead to missed identifications or misclassifications in prior studies, potentially biasing research findings.

In addition to the previously mentioned definitions, a widely used method for PRISm classification relies on fixed cutoff or LLN values, particularly following the introduction of the term “PRISm”. Our findings indicate that PRISm subjects identified by these definitions exhibited poorer spirometry and IOS performance than controls, suggesting that both definitions effectively identified individuals with functional abnormalities consistent with PRISm. Furthermore, PRISm subjects identified by the LLN method had greater smoking exposure, while those classified by the fixed definition reported more acute respiratory events in the previous year and lower FVC %predicted. This discrepancy, explored for the first time in our study, remains unexplained. Most studies select one of these definitions for primary analysis and use the other for sensitivity checks, while a few rely solely on one for conclusive analysis. However, employing non-uniform definitions can hinder comparability across studies. PRISm, as a subtype of pre-COPD indicating a high-risk population for COPD progression, has garnered increasing attention, necessitating focused research on its identification for effective screening, management, and intervention. The choice of definition may not alter the validity of primary results, but it can affect the identified population. Thus, establishing a consensus definition for PRISm would benefit both researchers and clinicians.

Previous reviews reported PRISm prevalence ranging from 4.7% to 25.2%.²⁹ These variations are likely influenced by age, sex, race, targeted population, region, pre- and post-bronchodilator measurements, and the definitions and predictive equations used.^{17,26,29–31} Our study found PRISm prevalence between 2.0% and 12.5%, partially explaining these discrepancies. Notably, prevalence decreased significantly when GLI reference equations were applied, aligning with Backman’s findings.³⁰ The large prevalence differences may stem from GLI predicted values of FVC and FEV₁ being lower than the observed values in population samples.³² In addition, a letter demonstrated that fixed definition yield higher PRISm and RSP prevalences than LLN definition when using GLI equations,³³ we also observed more subjects classified as PRISm using fixed definition, regardless of statistical significance. This may result from overdiagnosis associated with percent predicted methods, especially in older populations.³⁴ In contrast, when using Chinese reference equations, we observed the opposite trend between fixed and LLN definitions. Jian et al found that the predicted values for FVC, FEV₁, and FEV₁/FVC were larger than the LLN values in Chinese equations, providing a reasonable explanation for our results and enhancing the interpretation of spirometry in this population. Additionally, they note that the GLI 2012 equations significantly underestimated FEV₁, FVC, and FEV₁/FVC ratio for Chinese subjects, regardless of the metric used. This highlights the need for caution when applying GLI predicted equations in Chinese populations during analysis.

Clinical features of PRISm varied significantly across reference equations. For instance, PRISm subjects identified by RSP definition exhibited lower lung function, while those identified by PRISm definition showed higher airway reactance and resistance, particularly using Chinese reference equations. This heterogeneity likely stems from the varied choice of reference equations, which reflect differences in demographic characteristics and health status within populations. These findings underscore concerns regarding the interchangeability of definitions and reference equations for PRISm in clinical and scientific research.

Currently, there is no universally accepted definition for PRISm. Although the GOLD 2024 guidelines propose an FEV₁-based definition, derived from Wan et al, without clear rationale or evidence, the choice between FVC or FEV₁, fixed values or LLN, and various reference equations for identifying PRISm remains contentious. Which definition standard of PRISm is better? Our study cannot resolve this issue, and future recommendations may even advocate for including symptom recognition alongside spirometric criteria, akin to definitions for asthma or COPD.³¹ A refined definition and diagnostic criterion for PRISm is crucial for both research and clinical practice and should be a priority for professional societies. Larger population studies with longer follow-ups are needed to further address this question.

Several limitations of this study must be acknowledged. Firstly, the sample size for some research groups was small, raising concerns about false negatives. However, significant positive results were obtained in comparisons between target and control groups, suggesting the reliability of our findings. Secondly, as a cross-sectional study, it cannot determine if outcomes (eg, lung function decline or all-cause mortality) differ among PRISm populations identified by various definitions. Thirdly, the absence of LLN values in the European Coal and Steel Community 1993 reference formula limits the ability to conduct comprehensive comparisons among multiple predictive equations.

Conclusions

In summary, this cross-sectional study revealed only moderate agreement and significant variation in PRISm prevalence across different definitions and reference equations. Additionally, all PRISm participants identified by these various definitions demonstrated potential airway functional abnormalities compared to control subjects. These findings highlight concerns about the comparability of studies using different definitions and the interchangeable application of diverse definitions and reference equations for PRISm.

Abbreviations

PRISm, preserved ratio impaired spirometry; LLN, lower limit of normal; RSP, restrictive spirometric pattern; GLI, Global lung function initiative; BMI, body mass index; mMRC, modified Medical Research Council; CAT, COPD Assessment Test; % predicted, percentage of predicted value; FVC, forced vital capacity; FEV₁, forced expiratory volume in the first second; MMEF, maximal mid-expiratory flow; FEF50, forced expiratory flow at 50 of forced vital capacity; FEF75, forced expiratory flow at 75 of forced vital capacity; LAA₋₉₅₀, low-attenuation area of the lung with attenuation values below -950 hounsfield units on full-inspiration CT; LAA₋₈₅₆, low-attenuation area of the lung with attenuation values below -856 hounsfield units on full-expiration CT; RV/TLC, the ratio of residual volume to total lung capacity; R5, resistance at 5 hz; R20, resistance at 20 hz; R5-R20, the difference from resistance at 5 hz to resistance at 20 hz; X5, reactance at 5 hz; AX, reactance area; Fres, resonant frequency.

Data Sharing Statement

The datasets used and analyzed in this study are available on reasonable request from the corresponding authors.

Ethics Approval and Consent to Participate

The ECOPD study was carried out in accordance with the guidelines and regulations of the Declaration of Helsinki. The ECOPD study was approved by the Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University (No. 2018-53). And written informed consent was obtained from all participants before taking part.

Acknowledgments

We thank all the participants for their active participation in the ECOPD study. Besides, we thank the medical staff of the First Affiliated Hospital of Guangzhou Medical University, Lianping County People's Hospital and Wengyuan County People's Hospital for their continuous support, assistance and cooperation.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was supported by the Foundation of Guangzhou National Laboratory (SRPG22-018 and SRPG22-016), the Clinical and Epidemiological Research Project of State Key Laboratory of Respiratory Disease (SKLRD-L-202402), the National Natural Science Foundation of China (81970038 and 82270043), the Grant of State Key Laboratory of Respiratory Disease (SKLRD-Z-202315), the Major Clinical Research Project of Guangzhou Medical University's Scientific Research Capability Improvement Plan (GMUCR2024-01012), and Zhongnanshan Medical Foundation of Guangdong Province (ZNSXS-20250019).

Disclosure

All the authors declare they have no real or potential competing financial or non-financial interests for this work.

References

- Higbee DH, Granell R, Davey Smith G, Dodd JW. Prevalence, risk factors, and clinical implications of preserved ratio impaired spirometry: a UK Biobank cohort analysis. *Lancet Respir Med.* 2022;10(2):149–157. doi:10.1016/S2213-2600(21)00369-6
- Wan ES, Fortis S, Regan EA, et al. Longitudinal phenotypes and mortality in preserved ratio impaired spirometry in the COPDGene Study. *Am J Respir Crit Care Med.* 2018;198(11):1397–1405. doi:10.1164/rccm.201804-0663OC
- Guerra S, Sherrill DL, Venker C, Ceccato CM, Halonen M, Martinez FD. Morbidity and mortality associated with the restrictive spirometric pattern: a longitudinal study. *Thorax.* 2010;65(6):499–504. doi:10.1136/thx.2009.126052
- Vaz Fragoso CA, Gill TM, McAvay G, Yaggi HK, Van Ness PH, Concato J. Respiratory impairment and mortality in older persons: a novel spirometric approach. *J Invest Med.* 2011;59(7):1089–1095. doi:10.2310/JIM.0b013e31822bb213
- Mannino DM, Ford ES, Redd SC. Obstructive and restrictive lung disease and functional limitation: data from the Third National Health and Nutrition Examination. *J Intern Med.* 2003;254(6):540–547. doi:10.1111/j.1365-2796.2003.01211.x
- Wan ES, Cho MH, Boutaoui N, et al. Genome-wide association analysis of body mass in chronic obstructive pulmonary disease. *Am J Respir Cell Mol Biol.* 2011;45(2):304–310. doi:10.1165/rccm.2010-0294OC
- Wan ES, Hokanson JE, Murphy JR, et al. Clinical and radiographic predictors of GOLD-unclassified smokers in the COPDGene study. *Am J Respir Crit Care Med.* 2011;184(1):57–63. doi:10.1164/rccm.201101-0021OC
- Lim SY, Rhee EJ, Sung KC. Metabolic syndrome, insulin resistance and systemic inflammation as risk factors for reduced lung function in Korean nonsmoking males. *J Korean Med Sci.* 2010;25(10):1480–1486. doi:10.3346/jkms.2010.25.10.1480
- Mannino DM, Buist AS, Petty TL, Enright PL, Redd SC. Lung function and mortality in the United States: data from the First National Health and Nutrition Examination Survey follow up study. *Thorax.* 2003;58(5):388–393. doi:10.1136/thorax.58.5.388
- Mannino DM, Doherty DE, Sonia Buist A. Global Initiative on Obstructive Lung Disease (GOLD) classification of lung disease and mortality: findings from the Atherosclerosis Risk in Communities (ARIC) study. *Respir Med.* 2006;100(1):115–122. doi:10.1016/j.rmed.2005.03.035
- He D, Sun Y, Gao M, et al. Different risks of mortality and longitudinal transition trajectories in new potential subtypes of the preserved ratio impaired spirometry: evidence from the English longitudinal study of aging. *Front Med.* 2021;8:755855. doi:10.3389/fmed.2021.755855
- Mannino DM, McBurnie MA, Tan W, et al. Restricted spirometry in the burden of lung disease study. *Int J Tuberc Lung Dis.* 2012;16(10):1405–1411.
- Wan ES, Hokanson JE, Regan EA, et al. Significant spirometric transitions and preserved ratio impaired spirometry among ever smokers. *Chest.* 2022;161(3):651–661. doi:10.1016/j.chest.2021.09.021
- Wijnant SRA, De Roos E, Kavousi M, et al. Trajectory and mortality of preserved ratio impaired spirometry: the Rotterdam Study. *Eur Respir J.* 2020;55(1):1901217. doi:10.1183/13993003.01217-2019
- Wan ES, Castaldi PJ, Cho MH, et al. Epidemiology, genetics, and subtyping of preserved ratio impaired spirometry (PRISm) in COPDGene. *Respir Res.* 2014;15(1):89. doi:10.1186/s12931-014-0089-y
- Cousins M, Hart K, Kotecha SJ, et al. Characterising airway obstructive, dysanaptic and PRISm phenotypes of prematurity-associated lung disease. *Thorax.* 2023;78(9):895–903. doi:10.1136/thorax-2022-219301
- Schwartz A, Arnold N, Skinner B, et al. Preserved ratio impaired spirometry in a spirometry database. *Respir Care.* 2021;66(1):58–65. doi:10.4187/respcare.07712
- Wu F, Zhou Y, Peng J, et al. Rationale and design of the Early Chronic Obstructive Pulmonary Disease (ECOPD) study in Guangdong, China: a prospective observational cohort study. *J Thorac Dis.* 2021;13(12):6924–6935. doi:10.21037/jtd-21-1379
- 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(8):753–760. doi:10.1164/rccm.200612-1749OC
- Zhou Y, Hu G, Wang D, et al. Community based integrated intervention for prevention and management of chronic obstructive pulmonary disease (COPD) in Guangdong, China: cluster randomised controlled trial. *BMJ.* 2010;341:c6387. doi:10.1136/bmj.c6387
- Miller MR, Crapo R, Hankinson J, et al. General considerations for lung function testing. *Eur Respir J.* 2005;26(1):153–161. doi:10.1183/09031936.05.00034505
- Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J.* 2005;26(2):319–338. doi:10.1183/09031936.05.00034805
- Jian W, Gao Y, Hao C, et al. Reference values for spirometry in Chinese aged 4–80 years. *J Thorac Dis.* 2017;9(11):4538–4549. doi:10.21037/jtd.2017.10.110

24. 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(6):1324–1343. doi:10.1183/09031936.00080312
25. Oostveen E, MacLeod D, Lorino H, et al. The forced oscillation technique in clinical practice: methodology, recommendations and future developments. *Eur Respir J*. 2003;22(6):1026–1041. doi:10.1183/09031936.03.00089403
26. Labaki WW, Martinez CH, Martinez FJ, et al. The role of chest computed tomography in the evaluation and management of the patient with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2017;196(11):1372–1379. doi:10.1164/rccm.201703-0451PP
27. Godfrey MS, Jankowich MD. The vital capacity is vital: epidemiology and clinical significance of the restrictive spirometry pattern. *Chest*. 2016;149(1):238–251. doi:10.1378/chest.15-1045
28. Friedman SM, Maslow CB, Reibman J, et al. Case-control study of lung function in World Trade Center Health Registry area residents and workers. *Am J Respir Crit Care Med*. 2011;184(5):582–589. doi:10.1164/rccm.201011-1909OC
29. Zhao NN, Zhou YM. [Progress in preserved ratio impaired spirometry]. *Zhonghua Jie He He Hu Xi Za Zhi*. 2022;45(10):1046–1050. Chinese. doi:10.3760/cma.j.cn112147-20220518-00426
30. Backman H, Eriksson B, Hedman L, et al. Restrictive spirometric pattern in the general adult population: methods of defining the condition and consequences on prevalence. *Respir Med*. 2016;120:116–123. doi:10.1016/j.rmed.2016.10.005
31. Magner KMA, Cherian M, Whitmore GA, et al. Assessment of preserved ratio impaired spirometry using pre- and post-bronchodilator spirometry in a randomly sampled symptomatic cohort. *Am J Respir Crit Care Med*. 2023;208(10):1129–1131. doi:10.1164/rccm.202305-0805LE
32. Backman H, Lindberg A, Sovijärvi A, Larsson K, Lundbäck B, Rönmark E. Evaluation of the global lung function initiative 2012 reference values for spirometry in a Swedish population sample. *BMC Pulm Med*. 2015;15:26. doi:10.1186/s12890-015-0022-2
33. Schiffers C, Mraz T, Breyer MK, Hartl S, Breyer-Kohansal R, Wouters EFM. Restrictive spirometry or PRISm: does it matter? *Am J Respir Crit Care Med*. 2023;208(8):905–907. doi:10.1164/rccm.202304-0765LE
34. Cooper BG, Stocks J, Hall GL, et al. The global lung function initiative: dispelling some myths of lung function test interpretation. *Breathe*. 2013;9(6):462–474. doi:10.1183/20734735.012113

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