Establishment and application of reference equations for FEF_{50} and FEF_{75} in the Chinese population

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Background: Reference equations for forced expiratory flow at 50% and 75% of forced vital capacity (FVC) (FEF_{50} and FEF_{75}) in the Chinese population are lacking. It is of great importance to establish equations covering most age groups and to study their applicability in clinical practice.

Methods: Using the lambda-mu-sigma (LMS) method, reference equations for FEF_{50} and FEF_{75} were constructed based on pulmonary function data from healthy subjects collected from January 2007 to June 2010 at 24 centers throughout China. Differences between the established equations and extraneous equations were compared using standardized means (Z values) and percentage errors (PE). The proportion of small airway dysfunction (SAD) defined by the present equations was calculated. The Fisher precision probability test and the Mann-Whitney test were used to analyze the magnitude of changes in small and large airway indices after bronchodilator inhalation in patients with suspected asthma and chronic obstructive pulmonary disease (COPD).

Results: Reference equations for FEF_{50} and FEF_{75} were established based on data from 7,115 healthy individuals (aged 4 to 80 years, 50.9% female, height between 95 and 190 cm). The present equations (all Z values were −0.0 and PE ranged from 2.0% to 4.2%) showed advantages over the European Community for Steel and Coal (ECSC) equations in 1993 (with Z values ranging from −0.7 to −0.2 and PE ranged from −23.4% to −4.5%). A total of 4,356 patients with suspected asthma (51.1% female; a mean age of 45.4 years) and 6,558 patients with suspected COPD (10.1% female; a mean age of 65.0 years) were included. The present equations defined 95.7% and 99.9% of SAD in these patients. After bronchodilator inhalation, greater mean improvement rates in small airway indices were observed both in patients with suspected asthma [mean ± standard deviation (SD) =48%±47%] and in patients with suspected COPD (mean ± SD =20%±30%) ($P<0.05$).

Conclusions: The reference equations for FEF_{50} and FEF_{75} established in this study should be considered for use in China. Further studies are needed to validate their value in the diagnosis of some chronic respiratory diseases.

Keywords: Reference equations; small airway indices; lambda-mu-sigma (LMS)

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Introduction

Background

Pulmonary function test (PFT) is one of the most important tests for the diagnosis and treatment of pulmonary diseases and for improving the quality of life and prognosis of patients (1-3). Small airway indices in spirometry such as forced expiratory flow at 50% of forced vital capacity (FVC) (FEF_{50}), forced expiratory flow at 75% of FVC (FEF_{75}), and maximal mid-expiratory flow (MMEF) are valuable in detecting small airway lesions in patients with asthma and chronic obstructive pulmonary disease (COPD) at an early stage (4-7).

Except for FEF_{50} and FEF_{75}, our team has already established the reference equations for the MMEF and the large airway indices in spirometry (8). According to the nationally representative China Pulmonary Health study, small airway dysfunction (SAD) was defined when two of the three small airway indices were less than 65% of the predicted values (9). Therefore, the reference equations for FEF_{50} and FEF_{75} should be established to fill the gaps in clinical practice in China.

Rationale and knowledge gap

Reference values of pulmonary function indices depend on factors such as race, sex, age and height (8). In establishing predictive values related to growth, conventional methods such as the linear regression method have several limitations, mainly because of the violation of the normal distribution with age. To avoid bias, the lambda-mu-sigma (LMS) method of the generalized additive model for location, scale, and shape (GAMLSS) was more suitable for dealing with data with skewed distribution. By providing three curves, including L-, M- and S-curves, the reference values for a given age can be determined (10). The European Respiratory Society (ERS) also used this method in 2020 to establish reference equations for lung function indices such as functional residual capacity (FRC), total lung capacity (TLC) and residual volume (RV) (11).

Previously, the establishment of reference equations for small airway indices in spirometry in China was mainly based on single-center data or the application of linear regression methods, which can lead to large biases (8). Organizations such as the Global Lung Initiative (GLI) and the European Community for Steel and Coal (ECSC) have also provided reference equations for some small airway indices, but they are incomplete (12,13). And most importantly, the equations based on foreign races may not be applicable to the Chinese population.

Highlight box

Key findings

- Using the lambda-mu-sigma method, reference equations for forced expiratory flow at 50% and 75% of forced vital capacity (FEF_{50} and FEF_{75}) were established.

What is known and what is new?

- Small airway indices in spirometry are valuable in detecting small airway lesions in some chronic respiratory diseases at an early stage. However, the reference equations for FEF_{50} and FEF_{75} should be given to fill the gaps in clinical practice.
- Equations in our study were suitable for the Chinese population and defined a large proportion of small airway dysfunction in patients with suspected asthma and suspected chronic obstructive pulmonary disease.

What is the implication, and what should change now?

- The reference equations for the small airway indices established in this study should be considered for use in China and further studies are needed to validate their value.

Objective

In brief, SAD is common in China, and its presence may worsen patients' clinical symptoms, disease control and risk of recurrence (9). To avoid the uncertainty of the reference values for the small airway indices in China, we aimed to establish the reference equations for FEF_{50} and FEF_{75} in the Chinese population and observe their application in clinical practice.

Methods

Population

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This retrospective study was approved by the ethics committee of the First Affiliated Hospital of Guangzhou Medical University (No. 2020-124) and informed consent was obtained from all individual participants or their legal guardians (when participants were under 18 years of age). Reference equations for FEF_{50} and FEF_{75} were established based on spirometry data from healthy subjects collected between January 2007 and June 2010 at 24 centers throughout China. The detailed introduction of the study design, inclusion, and exclusion criteria for healthy subjects, standards for PFT, and data collection process were successfully published (8).

The supplementary information for this study was that the values for FEF_{50} and FEF_{75} were extracted from the best curve with the largest sum of forced expiratory volume in 1 second (FEV_1) and FVC. Data from patients who underwent bronchodilator responsiveness (BDR) test between January 1st, 2017 to April 12th, 2022, in the center of PFT of First Affiliated Hospital of Guangzhou Medical University were extracted. Only the first report was selected for subjects who completed a BDR test more than once. The data was primarily reviewed using the standard terminology of the International Classification of Diseases Volume 10 (ICD-10) and the Systematised Nomenclature of Medicine Clinical Terms (SNOMED). In the review of electronic medical records, asthma was diagnosed based on the Global Initiative for Asthma (GINA) guidelines and COPD was defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines (1,2). Patients with interstitial lung disease, pulmonary tuberculosis, obliterative bronchiolitis, lung tumors, pneumoconiosis, bronchiectasis, and asthma-COPD overlap were excluded. Cases with missing key values such as sex, age, height and baseline lung function were also excluded from some analyses. For patients with suspected COPD, only those with a FEV_1/FVC ratio of less than 0.7 after bronchodilation were included (1).

BDR test

Standards for spirometry have been reported previously (8). In this study, we mainly introduced the procedures of the BDR test followed by the standards from ERS and American Thoracic Society (ATS) (14). Before performing the bronchodilation test, a detailed history of the subjects should be obtained, especially concerning allergy to bronchodilators or contraindications to other medications and the presence of significant cardiac disease. In addition, medications that could affect test results should be discontinued before testing. Baseline pulmonary function should also be measured before testing. The preparation, precautions, quality control, and procedure for baseline lung function measurement are the same as for spirometry. After baseline lung function measurement, a bronchodilator such as salbutamol 400 µg or ipratropium bromide 160 µg was administered by inhalation, and lung function was measured again later. The report of BDR test included patient information (such as age, height, sex, and weight), numerical values for pulmonary function indices (including predicted values, best values, the ratio of best to predicted values, and three times pulmonary function data obtained after bronchodilator administration, including measured values, the ratio of measured to predicted values, and the rate of improvement after bronchodilator inhalation), and flow-volume and volume-time curves for each measurement. Data of quality control indicators [such as forced expiratory time (FET) and extrapolated volume], large airway indices [FVC, FEV_1, FEV_1/FVC, and peak expiratory flow (PEF)], and small airway indices (MMEF, FEF_{50}, and FEF_{75}) were also reported (14-16).

Establishment of the reference equations

The LMS method in GAMLSS was used to establish the reference equations. In the LMS method, the data were normalized using the Box-Cox power transformation, which ensured that the transformed data were approximately normally distributed. The transformed data were then modeled by three smooth functions: the L-function (lambda), the M-function, and the S-function (sigma). The L-function modeled the skewness of the data, the M-function modeled the median or mean of the data, and the S-function modeled the variability or spread of the data. By modeling these three functions, the LMS method could capture the complex distribution patterns of the data and produced smoothed percentile curves or percentile values that could be used in growth charts. In this study, the Box-Cox-Cole-Green distribution was used to build the model, and the Schwarz Bayesian Criterion (SBC) was used to select the best model. The setting of the parameters, the evaluation for the performance of the model, the methods for calculating the lower limit of normal (LLN) and the z-scores were the same as the previously published standards (8,10).

Comparison with other equations

The reference equations for FEF_{50} and FEF_{75} in our study were compared with widely used equations established by the ECSC in 1993 and by the GLI in 2012 (12,13). According to the previous standards, we defined that the equations were not applicable to Chinese individuals if the standardized means (Z values) exceeded ±0.4 or the percentage errors (PE) exceeded ±5.0% (17). Z values = (measured value − predicted value)/standard deviation,

Table 1 Characteristics of healthy individuals

Characteristics	Value (n=7,115)
Center	
North	2,956 (41.5)
South	4,159 (58.5)
Sex	
Female	3,622 (50.9)
Male	3,493 (49.1)
Age (years)	24.1±17.9
Range	4 to 80
Height (cm)	151.4±19.1
Range	95.0 to 190.0
Body mass index (kg/m^2)	20.1±4.0
MMEF (L/s), n=6,874	2.9±1.2
FEF_{50} (L/s), n=7,050	3.5±1.4
FEF_{75} (L/s), n=7,034	1.5±0.7

Continuous data are described as mean ± standard deviation; categorical data are presented as frequency (percentage). n, sample size; MMEF, maximal mid-expiratory flow; FEF_{50}, forced expiratory flow at 50% of forced vital capacity; FEF_{75}, forced expiratory flow at 75% of forced vital capacity.

where the standard deviation is the standard deviation of the difference between the measured value and the predicted value. PE = Σ (measured value − predicted value)/ Σ measured value × 100%.

Evaluation of SAD

In patients with suspected asthma and COPD, the proportion for two of the three small airway indices (FEF_{50}, FEF_{75}, and MMEF) that was less than 65% of predicted values was calculated using the present equations (9). Additionally, differences in the use of 65% and 80% as thresholds for classifying SAD were assessed, with the LLN classification adopted as the gold standard. Differences in the improvement of small and large airway indices after bronchodilator inhalation were analyzed. The absolute change = $\text{value}_{(\text{post-BD})} - \text{best value}_{(\text{pre-BD})}$. Improvement rate = $[(\text{value}_{(\text{post-BD})} - \text{best value}_{(\text{pre-BD})})/\text{best value}_{(\text{pre-BD})}] \times 100\%$, where "BD" represents bronchodilator.

Statistical analyses

Continuous data were described as mean and standard deviation or range, while categorical data were presented as frequency and percentage. The GAMLSS package (Version 5.4-10) was used to establish the reference equations. Comparisons were performed using the Fisher exact probability method for categorical data, and the Mann-Whitney test for continuous data. A P value of less than 0.05 was considered significant for all tests. Statistical analyses were performed with R version 4.0.5 (http://CRAN.R-project.org, R Foundation, Vienna, Austria).

Results

Characteristics of healthy individuals and reference equations

A total of 7,115 healthy subjects from 24 centers in China were included. Among them, 3,622 (50.9%) were females, with the mean age of 24.1 years (range, 4–80 years) and the height of 95 to 190 cm. *Table 1* shows the details. Figure S1 shows the distribution of age among genders. Figure S2 shows the non-linear relationships between FEF_{50}, FEF_{75} and age or height in the healthy population. The values of FEF_{50} and FEF_{75} both reached a high level at about 20 years old. Regarding the establishment of reference equations for FEF_{50} and FEF_{75}, the best models required a logarithmic transformation of height and age (*Figure 1* and Table S1). The attached document shows the information on the Mspline, Sspline, and Lspline parameters with 0.2-year intervals (Tables S2-S5).

Comparison with other equations

Results showed that the present reference equations for FEF_{50} and FEF_{75} could satisfy the condition for use in the Chinese population [all mean Z values =−0.0 (<0.4) and PE ranged from 2.0% to 4.2% (<5.0%)]. The values predicted by ECSC 1993 showed a greater deviation from the measured values (Z values: range, −0.7 to −0.2; PE: range, −23.4% to −4.5%). The values predicted according to GLI 2012 were close to the measured values (Z values: range, 0.0 to 0.1; PE: range, 0.6% to 3.2%) (*Table 2*).

Information on the BDR test dataset

A total of 4,356 patients with clinical suspicion of asthma

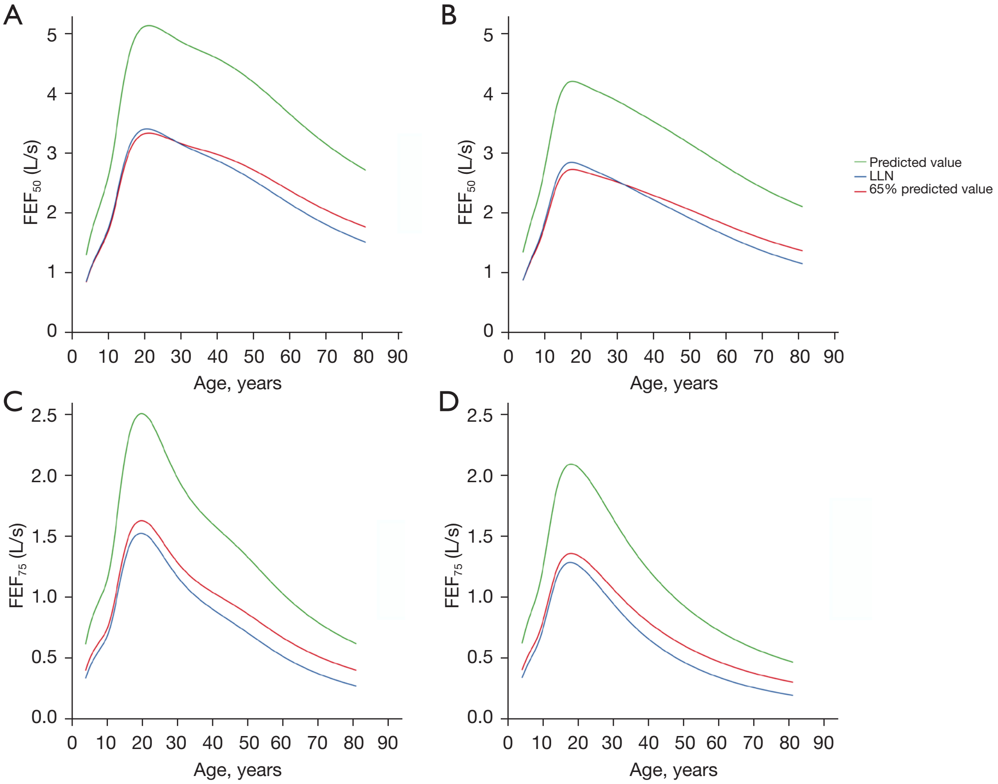

Figure 1 The predicted values, lower limit of normal and 65% of predicted values for forced expiratory flow at 50% and 75% of forced vital capacity in males and females. (A) Predicted values, LLN and 65% of predicted values for FEF$_{50}$ in males; (B) predicted values, LLN and 65% of predicted values for FEF$_{50}$ in females; (C) predicted values, LLN and 65% of predicted values for FEF$_{75}$ in males; (D) predicted values, LLN and 65% of predicted values for FEF$_{75}$ in females. FEF$_{50}$, forced expiratory flow at 50% of forced vital capacity; FEF$_{75}$, forced expiratory flow at 75% of forced vital capacity; LLN, lower limit of normal.

and 6,558 patients with suspected COPD and a FEV$_1$/FVC ratio of less than 0.7 after bronchodilation were included. The suspected asthma group included 2,224 (51.1%) female patients, with the mean age of 45.4 years (range, 6–80 years) and the height of 107.7 to 190.5 cm. The COPD group included 665 (10.1%) female patients, with the mean age of 65.0 years (range, 36–80 years) and the height of 132.5 to 188.5 cm. *Table 3* shows detailed information.

Patients with suspected asthma

In the BDR dataset, a total of 3,360 patients with suspected asthma had all small airway indices available at baseline. According to the present equations, the measured values were below 65% of the predicted value (94.6%, 95.8% and 95.7% of 3,360 cases had FEF$_{50}$, FEF$_{75}$ and MMEF <65% of the predicted value) or LLN (93.3%, 90.0% and 94.2% of 3,360 cases had FEF$_{50}$, FEF$_{75}$ and MMEF < LLN) in the majority of cases. SAD was defined in 3,214 cases (95.7%) when 65% of the predicted value was used as the threshold (*Figures 2,3*), and a total of 3,321 asthma patients (98.8%) were classified as SAD when at least two of the FEF$_{50}$, FEF$_{75}$, and MMEF parameters dropped to 80% below the predicted value (P<0.05). Compared to the LLN classification as a gold standard, both 80% (sensitivity =100.0%, accuracy =95.0%) and 65% (sensitivity =99.9%, accuracy =98.1%) of the predicted value as a threshold had high sensitivity and accuracy. However, the false positive rate reached 81.2% when 80% of the predicted value was used as the threshold, while it was 30.4% when 65% of the predicted value was used as the threshold (*Table 4*).

Patients with suspected COPD and a FEV$_1$/FVC ratio of less than 0.7 after bronchodilation

All small airway indices were available at baseline in a

Table 2 The deviation between the predicted and measured values obtained by the reference equations

Organization	Lung function indices	Age (range), years	Standardized means (Z values)	Percentage errors, %
Sex: male				
Present study	FEF_{50}	4–80	−0.0±1.0	2.2
	FEF_{75}	4–80	−0.0±1.0	4.2
ECSC 1993	FEF_{50}	18–70	−0.2±1.0	−4.5
	FEF_{75}	18–70	−0.4±1.0	−12.7
GLI 2012 (Northeast Asia)	FEF_{75}	25–80	0.1±1.0	2.7
GLI 2012 (Southeast Asia)	FEF_{75}	25–80	0.0±1.0	0.6
Sex: female				
Present study	FEF_{50}	4–80	−0.0±1.0	2.0
	FEF_{75}	4–80	−0.0±1.0	4.1
ECSC 1993	FEF_{50}	18–70	−0.5±1.0	−11.8
	FEF_{75}	18–70	−0.7±1.0	−23.4
GLI 2012 (Northeast Asia)	FEF_{75}	25–80	0.1±1.0	3.2
GLI 2012 (Southeast Asia)	FEF_{75}	25–80	0.0±1.0	1.2

Standardized means (Z values) = (measured value − predicted value)/standard deviation, where the standard deviation is the standard deviation of the difference between the measured value and the predicted value. Z values are described as mean ± standard deviation; Percentage errors = Σ (measured value − predicted value)/Σ measured value × 100%. ECSC, European Community for Steel and Coal; FEF_{50}, forced expiratory flow at 50% of forced vital capacity; FEF_{75}, forced expiratory flow at 75% of forced vital capacity; GLI, Global Lung Initiative.

total of 4,674 patients with suspected COPD and a FEV_1/FVC ratio of less than 0.7 after bronchodilation. The present reference equations showed that in most cases the measured values were below 65% of the predicted value (99.8%, 99.3% and 99.9% of 4,674 cases had FEF_{50}, FEF_{75} and MMEF <65% of the predicted value) or LLN (99.1%, 95.9% and 99.2% of 4,674 cases had FEF_{50}, FEF_{75} and MMEF < LLN). SAD was defined in 4,668 cases (99.9%) (*Figures 2,3*) and in 4,674 (100.0%) cases when at least two of the FEF_{50}, FEF_{75} and MMEF values were less than 65% or 80% of the predicted value, with no significant difference ($P>0.99$) (*Table 4*).

Comparison of the improvement rates between small and large airway indices

After bronchodilator inhalation, the mean improvement rate in small airway indices (mean ± SD =48%±47%) was greater than that in large airway indices (mean ± SD =13%±13%) in patients with suspected asthma ($P<0.05$). For large airway indices, the greatest mean improvement rate was observed in FEV_1 (mean ± SD =19%±16%), while it reached about 50% for all small airway indices (Table S6). Compared to the large airway indices, a greater improvement rate in small airway indices (mean ± SD =20%±30%, $P<0.05$) was also observed in patients with suspected COPD and a FEV_1/FVC ratio of less than 0.7 after bronchodilation, even when stratified by sex. The improvement rates in FEV_1, FVC, and FEV_1/FVC were comparable (mean ± SD =10%±10%), while they were approximately 20% to 30% for the small airway indices (Table S7).

Sensitivity analyses

When the geographical factor was added as a covariate, the SBC score of the models improved (an increase from 11.2 to 187.9), but no significantly different variability was found between the southern and northern regions (differences

Table 3 Characteristics of patients with suspected asthma and chronic obstructive pulmonary disease

Characteristics	Suspected asthma group (n=4,356)[†]	Suspected COPD group (n=6,558)[‡]
Sex		
Female	2,224 (51.1)	665 (10.1)
Male	2,132 (48.9)	5,893 (89.9)
Age (years)	45.4±17.7	65.0±7.9
Weight (kg)	58.3±14.4	59.1±10.8
Height (cm)	159.0±11.6	163.7±7.0
Body mass index (kg/m^2)	22.7±4.1	22.0±3.5
FEV_1 (L)		
Baseline	1.6±0.6	1.2±0.6
After bronchodilator	1.8±0.7	1.3±0.6
FVC (L)		
Baseline	2.7±0.9	2.6±0.8
After bronchodilator	2.9±1.0	2.8±0.8
FEV_1/FVC (%)		
Baseline	58.5±12.9	45.7±12.1
After bronchodilator	59.0±22.1	45.0±16.9
FEF_{75} (L/s)		
Baseline	0.4±0.3	0.2±0.1
After bronchodilator	0.5±0.4	0.2±0.1
FEF_{50} (L/s)		
Baseline	1.1±0.7	0.6±0.4
After bronchodilator	1.3±1.0	0.7±0.5
MMEF (L/s)		
Baseline	0.8±0.5	0.5±0.3
After bronchodilator	1.0±0.8	0.5±0.4

Continuous data are described as mean ± standard deviation; categorical data are presented as frequency (percentage). Sample size: FEV_1/FVC (%), FEF_{75} (L/s), FEF_{50} (L/s) and MMEF (L/s) were available in 4,002, 3,778, 3,837 and 3,714 cases with suspected asthma and 6,151, 5,413, 5,945 and 5,456 cases with suspected COPD. [†], patients with clinical consideration for asthma; [‡], patients with suspected COPD and a FEV_1/FVC ratio of less than 0.7 after bronchodilation. COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; FEV_1/FVC, the ratio of forced expiratory volume in 1 second to forced vital capacity; FEF_{75}, forced expiratory flow at 75% of forced vital capacity; FEF_{50}, forced expiratory flow at 50% of forced vital capacity; MMEF, maximal mid-expiratory flow.

ranged from 0.5% to 4.6%).

Discussion

Key findings

Based on data from healthy individuals, the reference equations for FEF_{50} and FEF_{75} were established. The use of 65% in predicted values for FEF_{50} and FEF_{75} was close to their LLN for individuals younger than 20 years old, although the bias increased with age. Compared with foreign equations, the present equations were more suitable for the Chinese population. Using the present equations, a large proportion of SAD was defined in patients with suspected asthma or COPD. In addition,

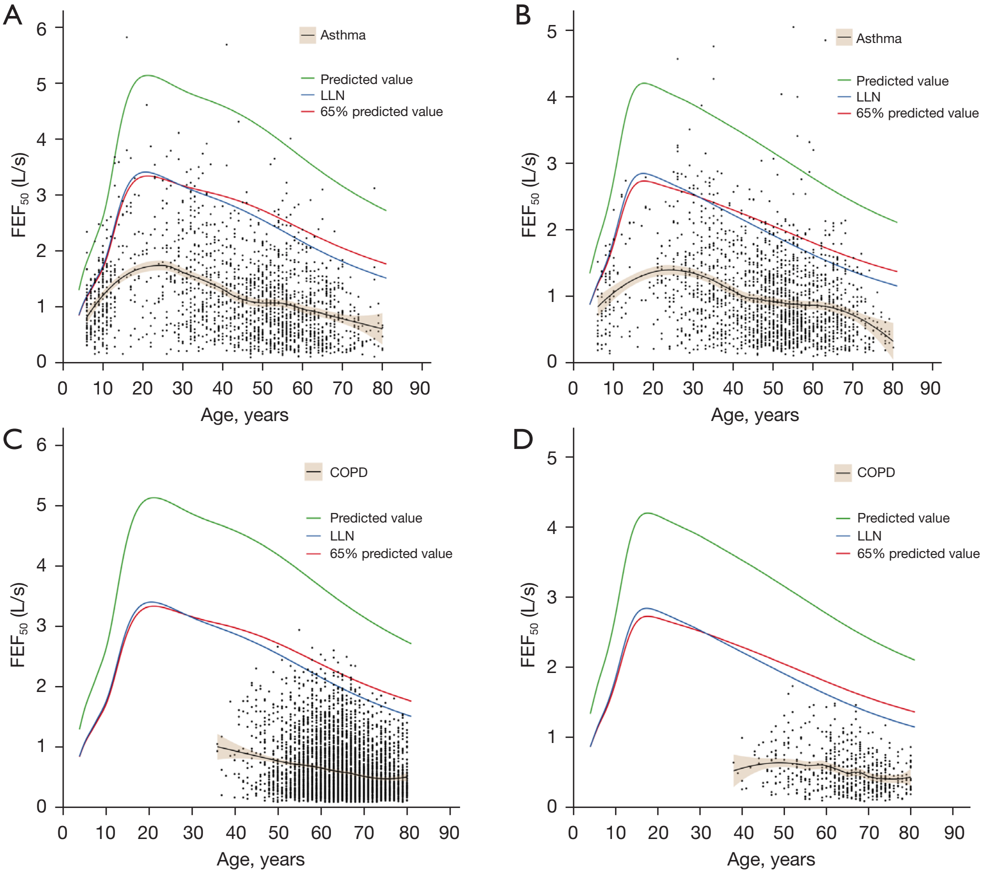

Figure 2 The measured values of forced expiratory flow at 50% of forced vital capacity in patients compared with the predicted values, 65% of predicted values and lower limit of normal. Black dots represent the measured values of FEF_{50} in patients; black lines are generated by the smoothing splines models; green lines, blue lines, and red lines represent the predicted values, LLN, and 65% of predicted values, respectively, generated by the present reference equations. (A) Male patients with suspected asthma; (B) female patients with suspected asthma; (C) male patients with suspected COPD; (D) female patients with suspected COPD. FEF_{50}, forced expiratory flow at 50% of forced vital capacity; LLN, lower limit of normal; COPD, chronic obstructive pulmonary disease.

greater improvement in small airway indices was found after bronchodilator inhalation.

Strengths and limitations

The major strength of this study was that reference equations for FEF_{50} and FEF_{75} were given based on a certain sample size of healthy subjects. However, there were several limitations in our study. First, patients with asthma or COPD included in this study were not clearly diagnosed. As there is no definitive, highly accurate diagnostic test for SAD, the ability of current equations in spirometry to distinguish patients with SAD from healthy individuals has yet to be validated. Second, the differences between spirometry and other examination methods for detecting SAD or the effects of combined use also need to be discussed further. Third, a fixed percentage of predicted values is commonly chosen for the sake of convenience in clinical practice. However, the suitability of this threshold still needs to be investigated. Fourth, only the Han population in China was analyzed. Whether there are differences in the reference values for other ethnic groups remains unclear. Fifth, the reference equations appropriate for Chinese need to be incorporated into the examination equipment, and our study has provided important clues for the following work.

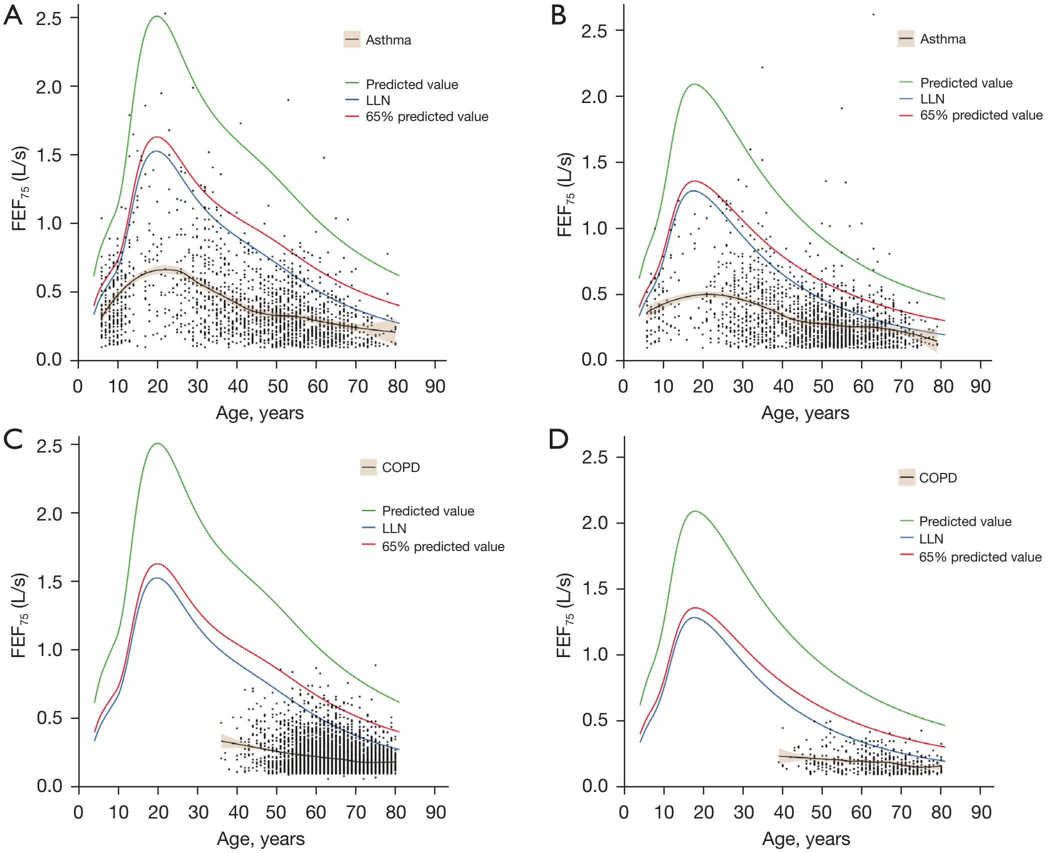

Figure 3 The measured values of forced expiratory flow at 75% of forced vital capacity in patients compared with the predicted values, 65% of predicted values and lower limit of normal. Black dots represent the measured values of FEF_{75} in patients; black lines are generated by the smoothing splines models; green lines, blue lines, and red lines represent the predicted values, LLN, and 65% of predicted values, respectively, generated by the present reference equations. (A) Male patients with suspected asthma; (B) female patients with suspected asthma; (C) male patients with suspected COPD; (D) female patients with suspected COPD. FEF_{75}, forced expiratory flow at 75% of forced vital capacity; LLN, lower limit of normal; COPD, chronic obstructive pulmonary disease.

Table 4 The performance of using 80% and 65% of the predicted value as the threshold to calculate the proportion of small airway dysfunction compared to using classification of the lower limit of normal

Variables	Suspected asthma group† (%)		Suspected COPD group‡ (%)	
	80% of the predicted value	65% of the predicted value	80% of the predicted value	65% of the predicted value
Calculating the proportion of small airway dysfunction	98.8	95.7	100.0	99.9
Sensitivity	100.0	99.9	100.0	100.0
Specificity	18.8	69.6	0.0	15.4
False negative rate	0.0	0.0	0.0	0.0
False positive rate	81.2	30.4	100.0	84.6
Accuracy	95.0	98.1	99.2	99.3

†, all small airway indices were available at baseline in a total of 3,360 patients with suspected asthma. ‡, all small airway indices were available at baseline in a total of 4,674 patients with suspected COPD and a FEV_1/FVC ratio of less than 0.7 after bronchodilation. COPD, chronic obstructive pulmonary disease; FEV_1/FVC, the ratio of forced expiratory volume in 1 second to forced vital capacity.

Comparison with similar researches, explanations of findings, and implications and actions needed

The equations from GLI 2012 also showed good performance in Z values and PE. Although GLI 2012 was an important step forward because all ethnic groups could be included in the model, it was still difficult to use as a uniform reference equation in China. This is because GLI 2012 divided the lung function data of healthy people previously provided in China into southern and northern parts, according to a commonly accepted boundary line called the Qinling-Huaihe line in China. In combination with data from other Asian countries or regions, equations for Northeast Asia and Southeast Asia have been established (12). It was difficult to choose the appropriate equations based on each province, which took into account the fact that the city of residence after birth could often be different from the city of birth. And the cities where the parents come from are probably also different. Equations that refer to regions could be confusing. In addition, reference equations for the FEF_{50} were missing in GLI 2012. In our study, sensitivity analysis was performed to assess the impact of including geographic location as a covariate in the equation. The variability between southern and northern regions was small. Moreover, the regional differences in China could be mainly reflected by the altitude differences, which were already taken into account in the construction of the present equations to avoid bias. Thus, the present equations are relevant for nationwide use in almost all age groups.

Our results showed that using 65% of predicted values was closer to the LLN, which was consistent with previous studies, especially in the Chinese population (5,18-22). Some studies also used 80% of predicted values as a threshold (23). However, our results suggested that it did not improve accuracy but led to a large number of misdiagnoses, which was debatable.

Impaired small airway function is a sign of early respiratory injury and plays an important role in the diagnosis of asthma and COPD (24-26). It was reported that several small airway parameters, including MMEF and FEF_{50}, are correlated with exacerbations in patients with asthma (27). Based on the large sample size of bronchodilator test data, our results suggested that the improvement in small airway indices was more sensitive than that in large airway indices, which was consistent with previous studies (28,29). However, it should be noted that the clinical significance of the small airway indices remains controversial. Compared to FEV_1, small airway indices may vary even in the same individual and may be reduced due to decreased lung volume (30,31). This disadvantage was also reflected in our results when we analyzed the improvement rate after bronchodilator inhalation. A larger standard deviation in small airway indices was observed. Additionally, other methods of detecting SAD could be more sensitive, such as the use of impulse oscillometry and optical coherence tomography (32,33). However, these techniques required more advanced and expensive equipment and more specialized training that was not widely available in clinical practice. Therefore, if clinicians could make good use of interpretations of routine PFTs, they could have a good impact on earlier diagnoses of asthma and COPD, but interpretation of abnormal small airway indices should be considered with caution (1-3).

Conclusions

The reference equations for small airway indices in spirometry established in this study should be considered for use in China. Further studies are needed to validate the utility of spirometry alone or in combination with other investigations in the early diagnosis or prognosis of chronic respiratory diseases.

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Footnote

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1219/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1219/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This retrospective study was approved by the ethics committee of the First Affiliated Hospital of Guangzhou Medical University (No. 2020-124) and informed consent was obtained from all individual participants or their legal guardians (when participants were under 18 years of age).

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