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The accuracy of FEF_{25-75}/FVC for primary classification of pulmonary function test

Majid Mirsadraee*[1], Amir Asnashari[2], Davood Attaran[2]

[1]*Pulmonologist, Islamic Azad University, Mashhad Branch, Mashhad, Iran.*
[2]*Pulmonologist, Lung Disease Research Center, Faculty of Medicine Mashhad University of Medicine Sciences, Mashhad, Iran*

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ABSTRACT

Introduction: The forced expiratory flow at 25 and 75% of the pulmonary volume/forced vital capacity ratio (FEF_{25-75}/FVC) as a spirometry parameter has been successful in the early diagnosis of chronic obstructive pulmonary disease (COPD) and the methacholine challenge test for assessing airway responsiveness. To determine the accuracy of FEF_{25-75}/FVC for the classification of spirometry lung disease.

Materials and Methods: Eighty subjects with clinical diagnosis of COPD and idiopathic pulmonary fibrosis (IPF) were entered into this case-control study. Forty normal volunteers in the control group with a PC_{20} of more than 8 mg/dl were also enrolled in this study. Spirometry, lung volumes, and diffusing capacity (DLCO) were measured for all the subjects by the body plethysmograph. Final diagnosis of COPD and IPF was confirmed according to patient's history, pulmonary function test, computed tomography of the lungs, and histopathology (in IPF subjects). The FEF_{25-75}/FVC ratio was determined in each group, and test accuracy was compared with lung volumes and DLCO as the gold standard.

Results: FEF_{25-75}/FVC was able to divide the subjects into four categories and its agreement with the clinical diagnosis (kappa= 0.486) was more than the ratio of forced expiratory volume in one second per forced vital capacity (FEV1/FVC) and residual volume (RV). Accuracy assessment showed that FEF_{25-75}/FVC had the highest likelihood ratio (133) followed by FEV1/FVC. Mid-expiratory flow parameters including FEF_{25-75} and FEF_{25-75}/FVC displayed the highest sensitivity, positive predicted value, negative predicted value, and accuracy.

Conclusion: FEF_{25-75}/FVC is helpful in diagnosing difficult cases such as mixed-type spirometry or spirometry results that are not matched with clinical findings and require lung volume measurement.

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Introduction:

Interpretation of routine spirometry requires several steps; an important step is the classification of the spirometry results into two major classes of pulmonary disease, the obstructive and restrictive pattern (1). Several methods were used for this step, such as the ratio of forced expiratory volume in one second per forced vital capacity (FEV1/FVC), lung volumes, and the configuration of flow volume curve(2). European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines for the interpretation of

*Corresponding *author: Majid Mirsaraee, Islamic Azad University, Mashhad Branch, Mashhad, Iran.Tel and Fax: +985118416694*
E-mail: majidmirsadraee@mshdiau.ac.ir

pulmonary function tests (PFT) used forced expiratory volume in one second per vital capacity (FEV1/VC) instead of FEV1/FVC for increasing the accuracy of the test (1). Lung volume parameters such as total lung capacity (TLC) and residual volume (RV) can also improve the interpretation of the result (3) and is necessary for mixed-type abnormalities (1), but this method requires expensive instruments. In obstructive lung disease, the earliest change is decreased airflow in the second half of the spirogram and flow volume curve; this finding is best shown by forced expiratory flow in 75 percent of vital capacity ($FEF_{75\%}$) and forced expiratory flow between 25% and 75% of vital capacity (FEF_{25-75})(1). Moreover, FEF_{25-75} is a more sensitive parameter than FEV1 and is capable of showing small airway disease (4).

Its usefulness is affected by its low specificity due to a wide normal range and changing its result with elongation of the FVC maneuver (1).

Therefore, this parameter shows diverse results in one person when the FVC result is different. Some investigators have tried to correct this drawback by dividing FEF_{25-75} to FVC (5).

FEF25-75/FVC showed more accurate results and good correlation with dysanapsis and PC_{20} in the methacholine challenge test (6). This test was also able to diagnose chronic bronchitis in the stage that FEV1 and FEV1/FVC (as defined by Global Initiative for Chronic Obstructive Lung Disease [GOLD] criteria) cannot be detected (7) and it has also been entered in epidemiological studies such as the Framingham study (8).

FEF_{25-75}/FVC was used for the detection of dysanapsis (the disproportional airway size in relation to lung volume) (9).

In this situation, FEF_{25-75}/FVC decreased when the airway caliber decreased or lung volume increased.

This finding is anticipated in obstructive lung disease, in which airway caliber decreases, but the lung volume increases due to air trapping.

In contrast, in restrictive lung disease, lung volume decreases, but the increased elastic recoil prevents airway collapse during the second half of the FVC maneuver; therefore, the FEF_{25-75}/FVC tends to increase[2].

On the other hand, we should consider that flow in the second half of expiration is higher than normal in restrictive lung disease, and in contrast, it is lower in obstructive disorders (10). Therefore, corrected FEF_{25-75}/FVC might differentiate obstructive from restrictive lung diseases by the two physiologic mechanisms mentioned above, and it is worthwhile to assess this parameter for the classification of lung disease.

The aim of this study was to compare the value of FEF_{25-75}/FVC in the normal group and obstructive and restrictive lung disease groups and determine the accuracy of this test for the diagnosis of lung disease.

Materials and Methods

Patients

Sample size was 120 subjects in three groups. Two groups were recruited from three pulmonary subspecialty clinics as case groups. One group consist of 40 subjects suffering from COPD (GOLD Stage II or more) as representative of obstructive lung disease, and 40 subjects suffering from idiopathic pulmonary fibrosis (IPF) as representative of restrictive lung disease.

The COPD was diagnosed considering typical history of smoking, clinical findings, and spirometry results that showed an obstructive pattern in which their bronchodilator response was less than 12%. IPF subjects were selected from typical subjects whose high resolution computed tomography (HRCT) showed a peripheral lower part honeycomb pattern and histopathology results were consistent with usual interstitial pneumonia. IPF subjects whose PFT showed an obstructive pattern were excluded from this group and were used as a forth group named mixed pattern. This group was not entered in the main study, but their results were compared with the above groups and mentioned in the results section separately. Control subjects were selected from the staff of Ghaem Medical Centre (N=40), who showed PC20 FEV1 more than 8 mg/ml and had no past or present history of respiratory complaints or any clinical symptoms or signs of pulmonary disorders. The exclusion criteria consisted of upper airway diseases (determined by clinical findings, imaging, and maximum inspiratory flow), neuromuscular disorders, recent lung infections, and un-cooperative

subjects during spirometry.The Ethics Committee of our university approved the experiment, and each subject signed an informed consent form.

Methods

This case-control study was performed in the pulmonary function laboratory of Chronic Obstructive Pulmonary Disease Research Center, Mashhad, Iran, from May 2014 until April 2016. We employed STARD checklist for reporting diagnostic accuracy.

Study design

A questionnaire on respiratory symptoms, history of smoking, pulmonary radiology (including chest roentgenogram and HRCT) and, if available, histopathology was designed and completed. The pulmonary function test was evaluated by measuring baseline slow vital capacity (VC), FVC maneuver, lung volumes (including RV and TLC), and diffusing capacity (DLCO). Equipment used was a body plethysmograph (Sensormedics, Model Vmax 6200, California Co. Ltd., and USA). Before the FVC maneuver and lung volumes measurement, the operator demonstrated the required maneuver, and the subjects were encouraged and supervised throughout the test performance. Standards outlined by the American Thoracic Society and European Respiratory Society (11) were used for determining the acceptability of the test. The FEF_{25-75}/FVC ratio was calculated manually after the FVC test.

Criteria used for the classification of PFT

The criteria used for major classification of the subjects into normal, obstructive, and restrictive groups were as follows: 1. Classic: Using FVC, FEV1 (less than 80%), and FEV1/FVC (obstructive < 75% and restrictive normal or higher) as described by Hyatt et al (2). 2. ATS/ERS guidelines: According to the data from the control group, for the diagnosis of an obstructive pattern, FEV1/VC less than the 5th percentile of normal subjects (calculated in this study less than 75%) and post-bronchodilator FEV1 less than 79% were used (1). 3. Lung volumes: RV and/or TLC within the range of 80-120% of predicted were used for the diagnosis of normal subjects. Values more than 120% of RV or TLC were used to confirm the obstructive pattern, and values less than 80% of RV or TLC were used to confirm the restrictive pattern.4. FEF_{25-75}/FVC: A range of FEF_{25-75}/FVC between 20% and 80% of the control group was considered as normal, values less than this range were used for marking obstructive lung disease, and values more than this range were used for diagnosing restrictive disorders. The range of FEF_{25-75}/FVC between 5% and 95% of the control group was wide and had too much overlap, therefore it was not used.

Mixed pattern was diagnosed by low FEV1/VC similar to the obstructive pattern (lower than the 5th percentile of the normal distribution) and low lung volumes (TLC less than the 5th percentiles of their relevant predicted values) (1). These subjects were not selected separately and, if diagnosed accidentally during the study, they were separated from the main groups and analyzed in a separate group.

Statistical analysis

Sample size was calculated according to mean of FEF_{25-75}/FVC ratio obtained from our previous study (7). Normal distribution of the data was examined using the Kolmogorov–Smirnov test. Categorical variables were compared using the Chi-square test. Agreement between clinical diagnosis as gold standard and spirometric parameters were determined by Kappa agreement coefficient. Analysis of variance (ANOVA) was carried out for the comparison of spirometry parameters between the four major groups. The range between 20% and 80% of one spirometric parameter was used to determine the cut-off point as recommended before (12). Receiver operator characteristic (ROC) curve was plotted for four diagnostic categories and the area under the curve was compared. Accuracy of FEF_{25-75}/FVC ratio, likelihood ratio, and Roc analysis as discussed by Metz (13) were determined and compared with the other three criteria. SPSS version 16 was used for statistical analysis. Data were expressed as mean ± SD, and *P*-value less than 0.05 was considered statistically significant.

Results

Baseline values

In addition to the three main groups that consisted of 40 subjects, there were also eight subjects with mixed pattern who were diagnosed accidentally during this study and considered as the fourth group. The mean age of the normal subjects was significantly lower than the patient groups, who were mostly in the 6th and 7th decades of their lives (F=22.3, P=0.001; Table 1).

Male gender and smoking were very predominant in the COPD group. Air pollution in the working place was also more frequent in COPD subjects, although the difference was not significant. Cough and dyspnea were the most prevalent symptoms in the patient groups with no significant difference between these groups. Phlegm was significantly more frequent in the COPD group. Hemoptysis was reported in only one subject in the COPD group. Physical examination showed wheezing as the most frequent sign in COPD subjects; however, rales was commonly detected in IPF and mixed pattern subjects.

Comparison of spirometric parameters between the groups

Comparison of mean of spirometric parameters is shown in Table 1. The difference in FEV1 between normal and abnormal conditions was significant, but the differences between the subclasses of abnormal conditions were not significant. FEV1/FVC was the only parameter with a significantly different mean in all the groups (the normal and three abnormal groups; Figure 1). Means of FEF_{25-75}, FEF_{25-75}/FVC, FRC, and RV were significantly different in the three major groups (i.e., obstructive, restrictive and normal; figures 1 and 2), but the FEF_{25-75} and FEF_{25-75}/FVC showed no significant differences between obstructive and mixed pattern group, and FRC and RV showed no significant differences between restrictive and mixed pattern groups (Table 1).

Determining the cut-off point for $FEF_{25-75\%}$/FVC

For determining the normal range of $FEF_{25-75\%}$/FVC, values between 20% and 80% of FEF_{25-75}/FVC of the control group were identified. In this regard, the range of 0.75 to 1.09 was considered as normal, higher values were considered as restrictive, and lower values were considered as obstructive. Using this method and excluding the mixed pattern, agreement of FEF_{25-75}/FVC and clinical categories as determined by the Kappa agreement coefficient was 0.639 (P< 0.001). Similarly, the Kappa agreement coefficient was 0.745 (P<0.0001)for FEV1/FVC (normal range: 0.75-0.84) and 0.472 for RV (P= 0.01) normal range: 80% to 119% of predicted).

According to Figure 1, FEF_{25-75}/FVC allowed patients to be divided into four groups and the mixed group was taken from the obstructive group. In this regard, the value of upper 80% of FEF_{25-75}/FVC in the COPD subjects was used to determine the cut-off point between the obstructive and mixed pattern. Therefore, 0.6 was used as a cut-off point, and all of the subjects were classified into four categories: Including the mixed pattern in clinical classification decreased the Kappa agreement coefficient to 0.385 (P= 0.03) for FEV1/FVC, 0.303 (P= 0.04) for RV, and 0.486 for FEF_{25-75}/FVC (P= 0.032). Kappa agreement coefficients for agreement between RV as the gold standard of diagnosis and FEV1/FVC and FEF_{25-75}/FVC were 0.274 (P= 0.4) and 0.251 (P= 0.5), respectively. Table 2 demonstrates the frequency of accurate clinical diagnosis by the introduced parameters (conforming to true positive). FEF_{25-75}/FVC revealed high results for the diagnosis of patient groups, although it was not successful in evaluating the normal group (like TLC). Comparison of accuracy of FEF25-75/FVC with traditional parameters Accuracy of the exploited parameters was determined by different methods (Table 3). Likelihood ratio of FEF25-75/FVC was the highest (133). ROC curve was plotted for determining the accuracy of potential diagnostic parameters from the pulmonary function test (Figure 3). Areas under the curve of FEF25-75% and FEV1/FVC plus RV were higher than the other parameters (Table 3). Mid-expiratory flow parameters including FEF25-75 and FEF25-75/FVC showed the highest sensitivity and positive and negative predicted values, but TLC showed the best specificity (Table 3). Overall accuracy showed the best results for FEF25-75 and FEF25-75/FVC (0.79 and 0.75, respectively).

Table 1- Comparison of spirometry parameters including FEF_{25-75}/FVC and lung volumes in four major categories of pulmonary disease (Mean of values and percent of predicted).

	Obstructive	***Mixed***	***Restrictive***	***Normal***
Age (Year)	59.3±11.7*	56.8±8.6*	61.3±15.3*	38.5±12.9
VC (L)	2.9±1.1	2.5±0.79*	1.6±0.6*†	3.7±0.7
%predicted	81.9±25.9	81.7±16.3	63.5±24*†	100.1±17.1
FVC (L)	3±1.2*	2.6±0.8*	1.6±0.63*†	3.9±0.85
%predicted	84.1±23.8*	88±21.8	66±24*†	104±12.2
FEV1 (L)	1.8±0.9*	1.9±0.5*	1.5±0.5*	3.2±0.6
%predicted	61.8±22.1*	77.5±14.7*	73±27.3*	100.7±10.1
FEV1/FVC (%)	58.3±10.3*	73.1±4.9*†	89.6±5.7*†	82±5.7
FEF25-75 (L/Min)	1.1±0.9*	1.4±0.47*	2.3±0.9*†	3.4±0.9
%predicted	29.7±22.4*	47.6±9*	85.9±38.2†	88.9±20
FEF25-75/FVC	0.33±0.18*	0.57±0.11	1.45±0.53*†	0.91±0.24
FEF25-75 pred. /FVC % pred.	0.33±0.18*	0.55±0.11	1.36±0.56*†	0.86±0.22
TLC (L)	6.6±2	4.2±0.87*†	3.4±1.2*†	5.9±1.3
%predicted	111.3±26.4	81.6±13.3*†	69.3±21.5*†	106±19
FRC (L)	4.8±1.8*	2.2±0.68†	2±0.72*†	3±0.86
%predicted	137±46.6*	74±21.6†	80±26.8†	105±30
RV (L)	3.6±1.8*	1.8±0.58†	1.6±0.72†	1.9±0.8
%predicted	160±71*	83.7±34.2†	85±42*†	120±52.4

*= Significant difference between parameter and control group (Normal), †= Significant difference between parameter and COPD group

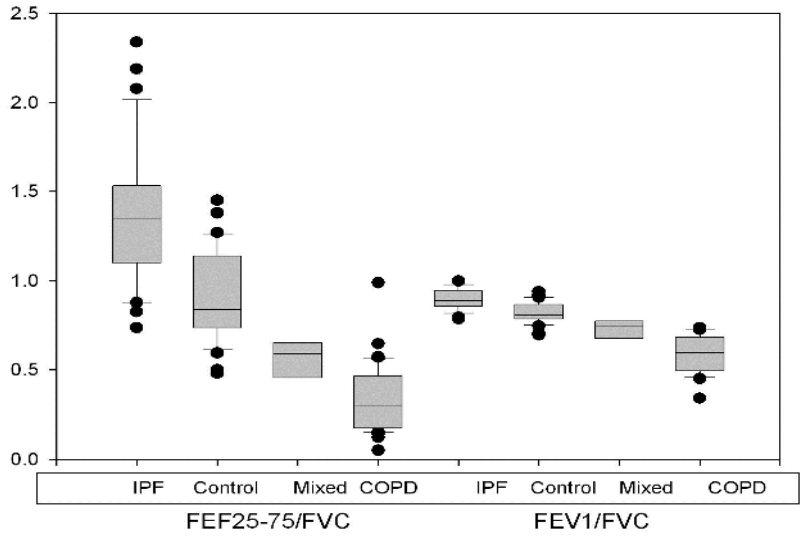

Figure 1: Comparison of means of FEF_{25-75}/FVC and FEV1/FVC between the four major categories of lung disease

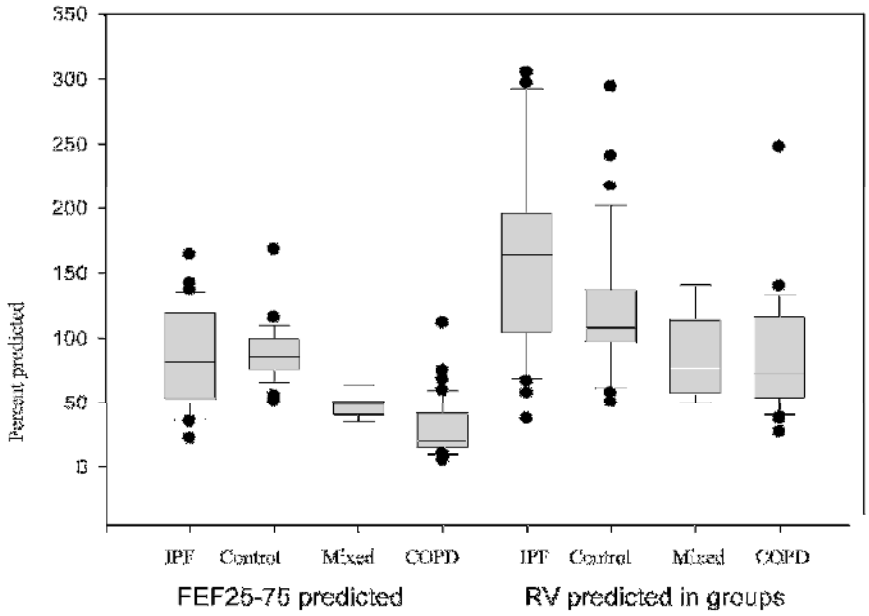

Figure 2. Comparison of means of FEF_{25-75} and RV percent of predicted between the four major categories of lung disease

Table 2: True positive subjects in different categories of pulmonary disease with applied parameters

	Obstructive	Mixed	Normal	Restrictive
FEV1/FVC	36 (97%)	9 (92%)	22 (62%)	25 (67%)
FEF_{25-75}/FVC	38 (95%)	4 (50%)	17 (48%)	30 (78%)
Predicted RV (%)	14 (60%)	12 (58%)	17 (48%)	21 (55%)
Predicted RV (%) + FEV1/FVC	26 (72%)	3 (37%)	16 (45%)	21 (55%)
Predicted FEF_{25-75} (%)	27 (100%)	21 (100%)	22 (62%)	13 (34%)
Predicted TLC (%)	8 (36%)	7 (33%)	28 (80%)	26 (68%)

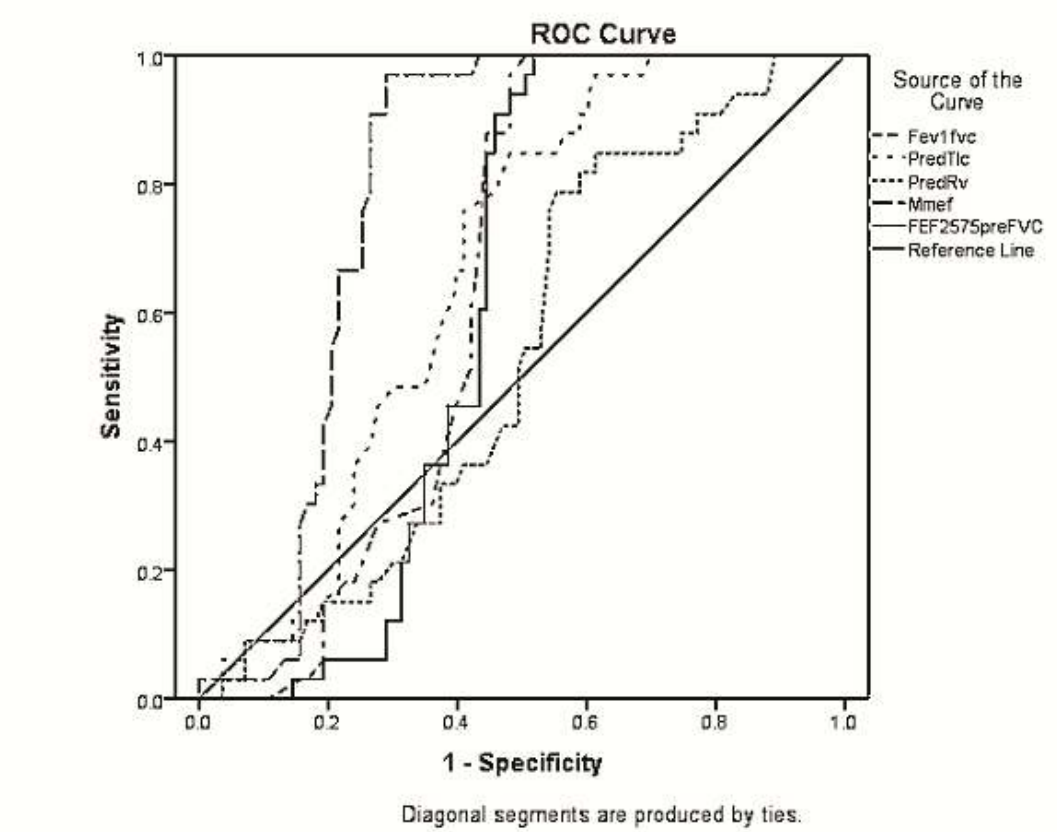

Figure 3. ROC curve for detecting the accuracy of FEF_{25-75}/FVC, FEV1/FVC, FEF_{25-75} (MmEF), predicted TLC, and predicted RV

Table 3- Comparison of accuracy of FEF_{25-75}/FVC and traditional spirometry parameters

	Likelihood ratio	Area under roc curve	Sensitivity	Specificity	PPV	NPV	accuracy
FEV1/FVC	119	0.635	71%	57%	85%	36%	0.68
FEF_{25-75} /FVC	133	0.610	83%	48%	85%	44%	0.75
FEV1/FVC + RV	74	0.676	78%	45%	76%	39%	0.71
Predicted RV†	29	0.533	70%	48%	82%	32%	0.64
Predicted FEF_{25-75}†	90	0.791	84%	62%	88%	53%	0.79
Predicted TLC†	75	0.665	49%	80%	89%	31%	0.55

†= Three group categorization.PPV= positive predicted value, NPV= negative predicted value

Discussion

In the present study, the accuracy of $FEF_{25-75\%}$/FVC was evaluated in 80 COPD and IPF subjects as candidates of obstructive and restrictive pulmonary disease and was compared with that in 40 normal volunteers. The clinical diagnosis of the patient groups was confirmed by their history, spirometry, imaging, and histopathology (in the IPF subjects). The normal volunteers reported no lung diseases and their spirometry, lung volumes, and methacholine challenge test were within the normal range. In addition

to multifactorial clinical diagnosis, FEV1/FVC plus RV was used as the gold standard for spirometry diagnosis as discussed by ATS/ERS guidelines[1]. Crude analysis of FEF_{25-75}/FVC as shown in Figure 1 revealed that the value of this parameter in different clinical diagnoses was different and this test could divide the subgroups. In the second step, ROC curve and values between 20% and 80% of the control group were used to separate the three major groups. Finally, the mixed group was separated from the obstructive group by the same methods. Results of this study showed that FEV1/FVC has the best agreement with the three-class categorization. This result could be expected because FEV1/FVC was used in the inclusion criteria and was the main criterion for classification of the recruited subjects. FEF25-75/FVC was the second parameter that showed significant agreement with the clinical diagnoses. These parameters were also able to differentiate subjects into four categories. The mean of FEV1/FVC value was significantly different in these four categories, including the mixed pattern, but the values were very close to each other. In contrast, the value of FEF25-75/FVC showed a wider range. Therefore, we suspected that FEF25-75/FVC had more potency to distinguish between different categories. In this regard, considering the four category classification, FEF25-75/FVC showed higher agreement with the clinical diagnosis than FEV1/FVC and RV. FEF25-75/FVC also demonstrated comparable agreement with FEV1/FVC according to the complete pulmonary function test (FEV1/FVC plus RV).

Strengths and limitations of this study:

To determine the accuracy of FEF_{25-75}/FVC, some analyses were performed. FEF_{25-75}/FVC revealed the highest likelihood ratio than the other parameters. The ROC curve showed that the area under the curve of mid-expiratory flow parameters, including FEF_{25-75} and FEF_{25-75}/FVC were the highest. In this regard, FEF_{25-75}/FVC showed the highest sensitivity, positive predicted value, negative predicted value, and Rand accuracy. Therefore, cumulative evidence was in favor of the accuracy of FEF_{25-75}/FVC for the diagnosis and categorization of pulmonary diseases, especially with respect to its potency to divide patients into four categories, which was previously executable exclusively with the aid of lung volume measurement.

Interpretation of the findings in relation to previously published work:

FEF25-75 and MEF50 can measure the flow in the most effort-independent part of the flow volume curve. This portion is very sensitive in peripheral airways when chronic airflow obstruction is present (14). In this study, FEF25-75 again showed satisfactory results, but two problems with FEF25-75 exist. First, we could not divide subjects into four categories, and secondly, Borrill et al (15) suggested that with treatment and improvement of COPD patients, FEF25-75 shifts along the flow volume loop and may paradoxically decline. Therefore, FEF25-75% should be corrected when FVC improves, namely FEF25-75/FVC.

Conclusion

Although FEF_{25-75}/FVC does not revolutionize the spirometry interpretation, but in difficult subjects, such as mixed-type spirometry or spirometry results that are not matched with clinical findings and require lung volume measurement, considering FEF_{25-75}/FVC may be helpful and resolve the problem without further testing.

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Conflicts of interest

The authors declare that they have no competing interest.

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