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Comparison of New Spirometry Measures to Diagnose COPD

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BACKGROUND: COPD is diagnosed by using FEV_1/FVC, which has limitations as a diagnostic test. We assessed the validity of several measures derived from the expiratory phase of the flow-volume curve obtained from spirometry to diagnose COPD: the slopes that correspond to the volume expired after the 50% and 75% of the FVC, the slope formed between the peak expiratory flow (PEF) and the FVC, and the area under the expiratory flow/volume curve. METHODS: We conducted a cross-sectional diagnostic test study in 765 consecutive subjects referred for spirometry because of respiratory symptoms. We compared the reproducibility and accuracy of the proposed measures against post-bronchodilator $FEV_1/FVC < 0.70$. We also evaluated the proportion of respiratory symptoms for the FEV_1/FVC, FEV_1 per FEV in the first 6 s (FEV_6), and the PEF slope. RESULTS: The subjects had a mean age of 65.8 y, 57% were women, and 35% had COPD. The test-retest intraclass correlation coefficient values were 0.89, 0.85, and 0.83 for FEV_1/FVC, FEV_1/FEV_6, and the PEF slope, respectively. The area under the curve values were 0.93 (expiratory flow/volume), 0.96 (potential expiratory flow/volume), 0.97 (potential expiratory flow/volume at 75% of FVC), and 0.82 (potential expiratory flow/volume at 50% of FVC). The area under the receiver operating characteristic curve was 0.99 for FEV_1/FEV_6, 0.99 for the slope at 50% of the FVC, and 0.98 for the PEF slope. CONCLUSIONS: The FEV_1/FEV_6, PEF slope, and 50% FVC slopes had similar diagnostic performances compared with FEV_1/FVC. *Key words: spirometry; pulmonary disease; chronic obstructive; early diagnosis; ROC curve*. [Respir Care 0;0(0):1–●. © Daedalus Enterprises]

Introduction

COPD is a preventable, treatable, and worldwide frequent pathology characterized by persistent respiratory symptoms and air-flow limitation. This limitation is due to abnormalities in the respiratory tract, usually caused by long exposure to harmful particles or gases.[1] Its prevalence is estimated to be between 7.8% and 19.7% in Latin America, with considerable morbidity and mortality, which increases with aging.[2] The estimated prevalence of COPD in Colombia is 8.9% in individuals > 40 years old, and it is higher in men (13.6%) than women (6.6%), and the costs related to COPD are substantial.[3] COPD also has a high economic and social burden.[4] It has a slow and long evolution and a growing global disease burden.[4] This disease can be present in any patient with dyspnea, chronic cough or expectoration, recurrent lower airway infections, or a history of exposure to risk factors.

The national and international guides recommend using spirometry to diagnose COPD.[1,5] The criteria for COPD diagnosis are the presence of ≥1 risk factors and post-bronchodilator $FEV_1/FVC < 0.7$.[1] Nonetheless, this measure has some limitations. For example, it requires a prolonged expiratory time, which is hard to achieve for many patients. This affects the reproducibility of the FVC and also requires spirometers that can detect extremely low air flows (common at the end of the expiration). In addition, the test requires trained staff to assess test quality and interpret the results.[1,5] These limitations can prevent an early and adequate COPD diagnosis.[6]

Such limitations demand the search for spirometry measures that can detect air-flow obstruction and have better reproducibility; also, a measure that is less dependent on the FVC, with better-operating characteristics, is required.[7] Some studies have attempted to determine indices capable of improving the diagnosis of the disease. FEV_1 per FEV in the sixth second (FEV_6) has been analyzed within these studies and has been identified as a possible substitute for FEV_1/FVC.[8] Other investigators explored graphic analysis, particularly the areas under the flow-volume curve and found a good correlation between the findings and the 6-min walk test.[9] The principal aim of this study was to assess the diagnostic validity of several measures derived from the

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expiratory phase of spirometry for COPD diagnosis. The secondary aim was to assess the relationship of this new measure with subjects' respiratory symptoms.

Methods

Study Design and Participants

This study was performed by following the Declaration of Helsinki and was approved by Comité de ética de la Clínica Universidad de La Sabana. Adult participant consent was not required because these adults were part of the repository of the Clínica Universidad de La Sabana. We recruited a total of 765 consecutive subjects referred for spirometry because of chronic respiratory symptoms at Clínica Universidad de La Sabana between November 2015 and August 2019 (Fig. 1). All the subjects answered questions about respiratory symptoms by using questionnaires valid for COPD diagnosis (Chronic Obstructive Pulmonary Disease-Population Screener [COPD–PS] and Career Development Questionnaire [CDQ]). The inclusion criteria were the following: the subjects were asked to perform a spirometry test given a suspicion of any airway pathology, >40 years old, included in the research repository of Clínica Universidad de La Sabana, and who had authorized the use of their personal data. The exclusion criteria were the following: patients who did not have respiratory symptomatology, missing data in spirometry, and patients with differences in time between spirometry and the symptoms > 2 months.

Test Methods

We extracted the raw signals of each spirometry test (CareFusion, Yorba Linda, California) to process all the trials done by the subjects. In the FEV_1/FVC estimation, the slopes and areas were performed simultaneously. We selected the 2 best flow/volume curves per subject, defined as those with the highest values. We then calculated the following measures: area under the potential expiratory flow/volume curve at 75% FVC, area under the potential expiratory flow/volume curve, area under the expiratory flow/volume curve, area under the expiratory, flow/volume curve at 75% FVC, FEV_1/FVC, FEV_1/FEV_6, peak expiratory flow (PEF) slope, 50% FVC slope, and 75% FVC slope.

All areas under the curve were approximated according to the following equation:

$$\text{Area under the curve} \approx \sum_{i}^{N} (volume_i - volume_{i-1}) * flow_i$$

where the *i* index represents every point of the flow/volume curve; that is, the total area under the curve was approximated by retrieving each individual area of the rectangles formed between every point of the spirometry.

The slopes were estimated through a simple linear regression as follows:

$$flow_i = \beta_0 + \beta_1 volume_i + \epsilon_i$$

where the coefficient β_1 index represents every point of the flow/volume curve; the regressions were estimated through ordinary least squares. As an exception, the slope formed from the highest flow peak was not estimated from a regression model but rather from the classical slope formula between 2 points. A visual representation of all the measures proposed in this study is presented in Figures 2 and 3. We decided to analyze these measures because the last portion of the expiratory phase gives some notion of the size of the small airway caliber (terminal bronchioles, bronchioles, alveolar ducts, and alveoli), which is related to the COPD physiopathology.[9]

Statistical Analysis

The quantitative variables according to distribution were summarized by means and standard deviation (SD) or medians and interquartile ranges. Categorical variables were described with absolute and relative frequencies. We assessed the test-retest concordance by using the intraclass correlation coefficient for absolute agreement with its 95% CI by comparing the 2 best spirometries per subject. We also assessed the test-retest concordance of the spirometry metrics by using the Bland-Altman method of tolerance limits.

The diagnostic accuracy of the spirometry metrics for COPD was assessed by using the receiver operating

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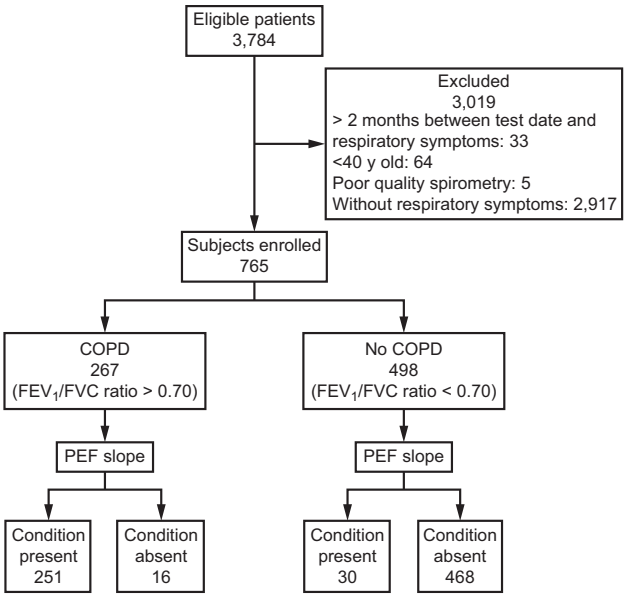

Fig. 1. Flow chart.

characteristic (ROC) curves based on the COPD diagnosis according to the post-bronchodilator $FEV_1/FVC < 0.70$. We estimated the diagnostic accuracy of the thresholds for each measure based on the sensibility, specificity, and Youden index. A 2-tailed $P < .05$ was considered statistically significant. Data were processed by using Python version 3.9 (Python Software Foundation, Wilmington, Delaware) and subsequently analyzed by using Rstudio version 4.0.5 (R Foundation for Statistical Computing, Vienna, Austria).

Sample Size Calculation

The minimum sample size selected according to the most demanding of all statistical tests to be performed, in this case, the ROC curve with a 95% CI; a sensitivity of proportions without disease and with disease of 80% and 20%, respectively; a percentage of false-positive and false-negative results of 30% and 80%, respectively; which required a sample size of 600 subjects.[10]

Results

In 765 subjects, 35% (267/765) had COPD. Fifty-seven percent were women, and the average age was 65 years. Most of the subjects (85%) reported respiratory symptoms. Twenty-seven percent of the subjects had a previous COPD diagnosis before the beginning of the study, and 14% were diagnosed with asthma (Table 1). The average age of the group of the subjects diagnosed with COPD by post-bronchodilator $FEV_1/FVC < 0.7$ was 69 years old, and they reported an average of 5 years of schooling. COPD severity was classified by using the Global Initiative for Chronic Obstructive Lung Disease (GOLD): GOLD 1, 46%; GOLD 2, 45%; GOLD 3, 7%; and GOLD 4, 2%.

Most of the subjects (87%) in this group reported respiratory symptoms, with dyspnea the most frequent. Forty-two percent of the subjects classified with COPD were previously diagnosed with COPD, and 19% of them reported being diagnosed with asthma during their lives. The most common history of exposure was to wood smoke (68%), followed by tobacco (48%), with an average pack-year index of 11 for the subjects with COPD (Table 1). The prevalence of COPD in this study was 35% (defined by an $FEV_1/FVC < 0.7$), 36% (defined by the FEV_1/FEV_6), or 36% (defined by the PEF slope).

With regard to the spirometry measures, the FEV_1/FVC median was 0.63 in the subjects with COPD and 0.78 in the subjects without COPD. The median percentage of predicted FEV_1 was 92% for the total population (78% and 98% for the subjects with and without COPD, respectively). The lowest coefficient of variation was obtained for FEV_1/FEV_6, FEV_1/FVC, and PEF slope (ranging from 0.12 to 0.36) (Table 2). The rest of the measures proposed in this study ranged from 0.5 to 0.9 (Table 2). The test-retest reliability measured through the intraclass correlation coefficient showed better reliability for the area under the potential expiratory flow/volume curve at 75% FVC, area under the potential expiratory flow/volume curve, and area under the expiratory flow/volume curve (Table 3). FEV_1/FVC, FEV_1/FEV_6, and PEF slope showed similar reliability values (Table 3).

The diagnostic accuracy was assessed by comparing the spirometry metrics with a post-bronchodilator $FEV_1/FVC < 0.70$. We found an area under the ROC curve of 0.99 for FEV_1/FEV_6, 0.99 for the slope of the last 50% of the FVC, and 0.98 for the PEF slope (Table 4). The sensibility and specificity of the diagnosis at the Youden index cutoff value ranged from 0.92 to 0.97 and from 0.94 to 0.98, respectively (Table 4). We compared the area under the ROC curve of FEV_1/FEV_6 (area under the curve, 0.99) versus the slope of the last 50% of the FVC (area under the curve, 0.99) and the PEF slope (area under the curve, 0.98) by using the DeLong test, and their differences were not statistically significant ($P = .06$ for FEV_1/FEV_6 vs the PEF slope; $P = .48$ for FEV_1/FEV_6 vs 50% of the FVC slope; and $P = .09$ for PEF slope vs 50% of the FVC slope). Based on the Youden index to classify subjects with and without COPD with a post-bronchodilator $FEV_1/FVC < 0.70$, post-bronchodilator $FEV_1/FEV_6 < 0.73$, and a post-bronchodilator PEF slope > -1.76, we found a similar proportion of subjects with respiratory symptoms (Table 5).

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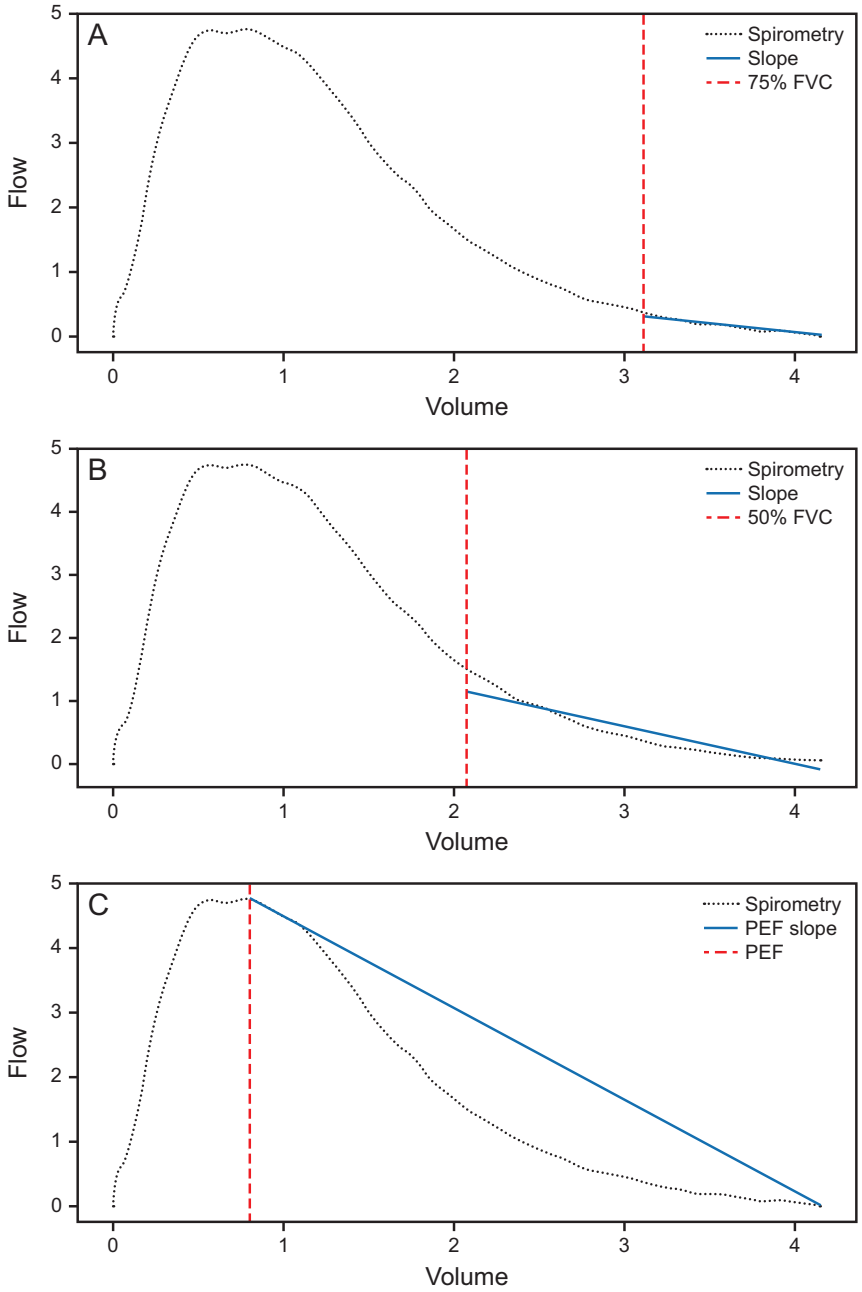

Fig. 2. Graphic representation of the slope measures proposed in this study. A and B: The estimated slopes through ordinary least squares (OLS), from 75% and 50% of the FVC and above, respectively. It is worth noting that the 75% and 50% FVC slopes do not necessarily start at the intersection between the FVC threshold and the expiratory flow/volume curve because it is calculated by regression and captures the average behavior of those portions of the curve. C: The line slope between the peak expiratory flow (PEF) and the FVC.

Discussion

We explored various metrics based on the graphic analysis of the flow-volume curve; we found that measures such as the FEV_1/FEV_6, the PEF slope, and the slope of the final 50% of the FVC achieved similar reproducibility when compared with FEV_1/FVC with outstanding accuracy. Also, the operating characteristics of FEV_1/FEV_6, the slope of the final 50% of the FVC, and PEF slope, showed that their diagnostic performance is similar to the current GOLD-COPD standard.

With regard to the population included in the analysis, we found a COPD prevalence of 35% by using the current accepted standard ($FEV_1/FVC < 0.7$), 36% by using

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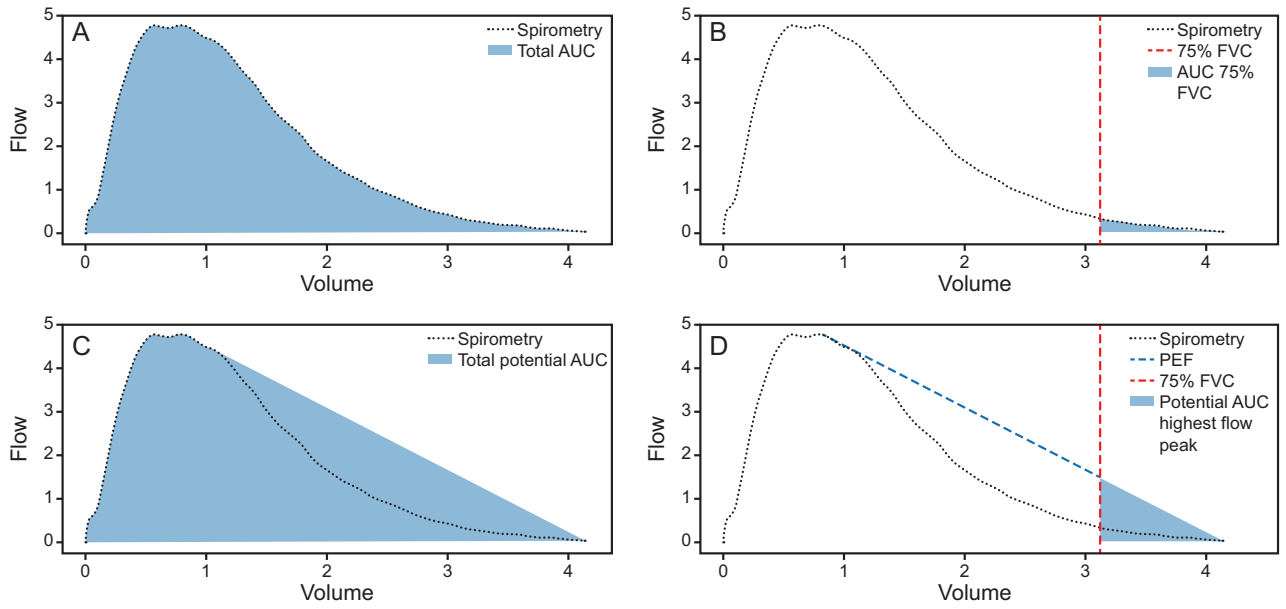

Fig. 3. The proposed area under the curve measures. A and C: The area under the flow/volume curve of the whole expiratory phase and the volume above the 75% FVC, respectively. B and D: The same areas under the curve but the line formed between the highest flow peak and the FVC.

$FEV_1/FEV_6 < 0.73$, and 36% by using PEF slope > -1.76. When compared with the literature, our results are in the middle of the range of disease prevalence for subjects with respiratory symptoms or risk factors.[11,12] In Latin America, there are studies in different primary care and specialized care centers that report a prevalence of 20%.[2] However, Bhatt et al[13] conducted a multi-center cohort study, in the United States, with subjects who smoke and found a COPD prevalence of 44.7% based on FEV_1/FVC and 38% based on the lower limit of normal. Furthermore, another study found a prevalence of the disease, a disease prevalence of 50% for subjects who consulted specialized centers and these were based on symptomatology questionnaires such as the COPD–PS or CDQ.[14] This is important given the effect that prevalence has on positive and negative predictive values.[2]

Despite COPD being more prevalent in men, we found a similar proportion of men and women diagnosed with air-flow obstruction, and 49% of the subjects diagnosed with COPD were women, which is slightly higher than previous studies. Bhatt et al[13] found that 44% of the subjects diagnosed with COPD were women, both with FEV_1/FVC and FEV_1/FEV_6. However, Börekçi et al[15] found that 27.9% of the subjects diagnosed with COPD through FEV_1/FVC were women. This could be a consequence of a high proportion of exposure to wood or biomass smoke in the women in our population. The proportion of women exposed to wood or biomass smoke is higher in Colombia than in other countries and that is a risk factor for COPD,[16] which may affect the balance of COPD frequency in men and women.

There also is literature on a poor relationship between COPD diagnosis based on FEV_1/FVC and subjects' symptomatology.[17] Most of the new indices to diagnose COPD in the literature seek to maximize the identification of subjects who are symptomatic. Bhatt et al,[13] in a study based on FEV_1/FEV_6, found a greater number of subjects with COPD and with airway obstruction, increased airway thickness, worse lung capacity, and more exacerbations. We found a similar proportion of subjects who were symptomatic based on the forced spirometric maneuvers (FEV_1/FEV_6 and PEF slope), which indicated that, perhaps the main advantage of the new metrics seems to take advantage of all the information that the expiratory flow-volume curve has to offer.

With regard to the calculated areas and slopes in this study, we found that some showed intraclass correlation coefficients higher than that for a post-bronchodilator FEV_1/FVC, which means that they have greater reproducibility than the current standard. Due to the underdiagnosis or late diagnosis of COPD, multiple studies focused on providing a more-accurate COPD diagnosis through several indices or graph analyses of the flow/volume curve.[6,9,13,18] Currently, there are studies that evaluated non-traditional spirometric measures against traditional measures; Bhatt et al[7] introduced the D parameter (measured in the curve volume vs time) and reported a diagnostic significant correlation for COPD when compared with FEV_1/FVC

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Table 1. Baseline Characteristics of the Study Population

	All Subjects ($N = 765$)	COPD ($FEV_1/FVC < 0.70$) ($n = 267$)	No COPD ($FEV_1/FVC > 0.70$) ($n = 498$)	P
Age, mean ± SD y	66 ± 11	69 ± 11	64 ± 11	<.001*
Men	330 (43)	136 (51)	194 (39)	.002†
Height, mean ± SD cm	160 (10)	160 (10)	160 (10)	.98*
Weight, mean ± SD kg	70.8 ± 14.3	67.9 ± 13.5	72.4 ± 14.5	<.001*
BMI, mean ± SD kg/m^2	27.8 ± 5	26.7 ± 5.1	28.4 ± 4.8	<.001*
Full years of schooling, median (IQR)	4 (2–5)	3 (2–5)	4 (2–5)	.01‡
Severity of COPD by GOLD				
GOLD 1	ND	123 (46)	NA	ND
GOLD 2	ND	118 (45)	NA	ND
GOLD 3	ND	19 (7)	NA	ND
GOLD 4	ND	5 (2)	NA	ND
Respiratory symptoms	656 (86)	233 (87)	423 (85)	.44†
Age of onset of symptoms, median (IQR)	60 (40–80)	63 (41–85)	60 (42–78)	.038†
Wheezing	223 (29)	103 (39)	120 (24)	<.001†
Dyspnea	446 (58)	168 (63)	278 (56)	.058†
Chronic cough	348 (45)	136 (51)	212 (43)	.01†
Chronic expectoration	215 (28)	89 (33)	126 (25)	.02†
Smoker	352 (46)	129 (48)	223 (45)	.39†
Pack-year index, median (IQR)	5 (1–22)	11 (2–33)	4 (1–11)	<.001‡
Passive smoker	158 (21)	48 (18)	110 (22)	.20†
Exposure to wood smoke	451 (59)	182 (68)	269 (54)	<.001†
Years of exposure, median (IQR)	17 (10–30)	20 (10–30)	15 (10–25)	.01‡
History of atopy	186 (24)	74 (28)	112 (22)	.13†
Previous diagnosis of COPD	209 (27)	113 (42)	96 (19)	<.001†
Previous asthma diagnosis	107 (14)	50 (19)	57 (11)	.008†

Data shown as *n* (%) unless otherwise specified.
* The *t*-test for independent samples.
† Chi-square test.
‡ Mann-Whitney U test.
BMI = body mass index
IQR = interquartile range
GOLD = Global Initiative for Chronic Obstructive Lung Disease
ND = no data
NA = not available

($r = 0.83$, $P < .001$). Li et al[6] present a new parameter, termed the AUC3/AT3, which is the area under the descending limb of the expiratory flow-volume curve before the end of the first 3 s (AUC3) divided by the area of the triangle before the end of the first 3 s (AT3), which describe the concave shape of the maximal expiratory flow-volume curve in the first 3 s exhibited a strong correlation with the FEV_1/FVC ($r = 0.88$, $P < .001$).

As to the diagnostic accuracy, the operative characteristics of several of our metrics obtained from the flow-volume curve showed a diagnostic performance that was close to the current standard, with an under the ROC curve > 0.9 and a sensibility and specificity $> 80\%$. Some researchers focused on describing different measures of the shape of the flow-volume curve. Oh et al[19] proposed a measure called flow decay, which is defined as the slope of volume versus the natural logarithm of the reciprocal of the flow (ln [1/flow]) in mid exhalation, to quantify dynamic airway resistance. This measure was found to have an accuracy of 0.94, a sensitivity of 0.95, and a specificity of 0.92 when compared with $FEV_1/FVC <$ lower limit of normal and plethysmography. However, Zapletal et al[20] used the area under the expiratory flow-volume in children with asthma to assess bronchoconstriction and bronchodilation, and found that it was more sensitive than changes in FEV_1, PEF, and other spirometric parameters for detecting bronchial hyper-responsiveness and airway obstruction reversibility.

One of the limitations of this study was that it was conducted at a single center, which limits the extrapolation of the results. Since the beginning of our research, we have considered the current standard as an imperfect method, so it is not sufficient to compare these indices against a potentially imperfect standard as the post-bronchodilator FEV_1/FVC could be. This same limitation is also present in several studies that explored the behavior

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Table 2. Coefficient of Variation of Variables of Interest (post-bronchodilator)

Variable (post-bronchodilator)	Coefficient of Variation
FEV_1/FEV_6	0.12
FEV_1/ FVC	0.15
FEV_6	0.31
FVC	0.31
FEV_3	0.32
FEV_1	0.34
PEF slope	0.36
50% FVC slope	0.51
Area under the potential expiratory flow/volume curve	0.60
Area under the potential expiratory flow/volume curve at 75% FVC	0.61
75% FVC slope	0.65
Area under the expiratory flow/volume curve	0.65
FEF_{75}	0.70
Area under the expiratory flow/volume curve at 75% FVC	0.91

FEV_6 = FEV in the sixth second
FEV_3 = FEV in the third second
PEF = peak expiratory flow
FEF_{75} = forced expiratory flow at 75%

Table 3. ICC of Variables of Interest

Variable (post-bronchodilator)	ICC	95% CI	*P*
FEV_3	0.99	0.99–0.99	<.001
FEV_1	0.98	0.98–0.99	<.001
FEV_6	0.98	0.98–0.99	<.001
FVC	0.98	0.98–0.98	<.001
FEF_{75}	0.22	0.16–0.29	<.001
Area under the potential expiratory flow/volume curve at 75% FVC	0.97	0.96–0.97	<.001
Area under the potential expiratory flow/volume curve	0.96	0.95–0.96	<.001
Area under the expiratory flow/volume curve	0.93	0.91–0.93	<.001
FEV_1 / FVC	0.89	0.87–0.90	<.001
FEV_1/FEV_6	0.85	0.83–0.87	<.001
PEF slope	0.83	0.81–0.85	<.001
50% FVC slope	0.82	0.80–0.84	<.001
Area under the expiratory flow/volume curve: 75% FVC	0.81	0.79–0.84	<.001
75% FVC slope	0.79	0.76–0.82	<.001

ICC = intraclass correlation coefficient
FEV_3 = FEV in the third second
FEV_6 = FEV in the sixth second
FEF_{75} = forced expiratory flow at 75%
PEF = peak expiratory flow

Table 4. Areas Under the ROC Curve of Variables of Interest vs GOLD-COPD Standard (FEV_1/FVC post bronchodilator < 0.70)

Variable	Area Under the Curve	95% CI	Cut Point of the Youden Index	Sensitivity	Specificity
FEV_1/FEV_6	0.99	0.987–0.997	≤ 0.73	0.97	0.96
50% FVC slope	0.99	0.983–0.995	> −0.95	0.92	0.98
PEF slope	0.98	0.977–0.991	> −1.76	0.94	0.94
75% FVC slope	0.95	0.934–0.964	> −0.51	0.89	0.87
Area under the expiratory flow/volume curve - 75% FVC	0.81	0.776–0.839	≤ 0.16	0.85	0.64
Area under the expiratory flow/volume curve	0.78	0.749–0.818	≤ 7.55	0.75	0.68
Area under the potential expiratory flow/volume curve at 75% FVC	0.71	0.666–0.746	< 0.50	0.52	0.81
Area under the potential expiratory flow/volume curve	0.69	0.652–0.733	≤ 7.59	0.53	0.78

ROC = receiver operating characteristic
GOLD = Global Initiative for Chronic Obstructive Lung Disease
FEV_6 = FEV in the sixth second
PEF = peak expiratory flow

of the flow/volume curve; some investigators attempted to overcome this limitation by comparing their results with symptoms, the 6-min walk distance, and diagnostic imaging. Nevertheless, given that the main objective of this study was to make an initial exploration of measures extracted from the flow/volume curve, we did not make any further analysis, and the adjustment for an imperfect standard should be performed in future studies to make a

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Table 5. Proportion of the Subjects With Respiratory Symptoms

Symptom	FEV_1 / FVC < 0.7 (n = 267)	FEV_1 / FEV_6 < 0.73 (n = 244)	PEF Slope > −1.76 (n = 261)
Respiratory symptoms	233 (87.3)	218 (89.3)	228 (87.4)
Wheezing	104 (39)	98 (40.2)	104 (39.8)
Dyspnea	168 (62.9)	154 (63.1)	160 (61.3)
Chronic cough	136 (50.9)	123 (50.4)	131 (50.2)
Chronic expectoration	89 (33.3)	80 (32.8)	87 (33.3)

Data are shown as n (%).
FEV_6 = FEV in the sixth second
PEF = peak expiratory flow.

fair comparison of the new spirometry metrics with a post-bronchodilator FEV_1/FVC.[21]

Conclusions

This study explored the behavior of several metrics obtained from the flow/volume curve to diagnose COPD. We found that FEV_1/FEV_6, PEF slope, and 50% of the FVC slope had a similar diagnostic performance as FEV_1/FVC. Their diagnostic accuracy could be higher than FEV_1/FVC, but such a hypothesis should be tested in a future study by using a method to adjust for an imperfect standard, which will allow for a fair comparison with FEV_1/FVC.

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