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Original Article

Diagnostic score for COPD: Validation of the DS-COPD in clinical settings

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ARTICLE INFO

Article history:

Received 23 February 2013

Accepted 21 April 2013

Available online 29 April 2013

Keywords:

Diagnosis

COPD

Case-control

Cost-effectiveness

ABSTRACT

Background: Diagnosing Chronic Obstructive Pulmonary Disease (COPD) without spirometry is difficult; we had developed previously a scale (DS-COPD) in an epidemiological setting. It allowed diagnosing COPD confidently when scored high, and excluded confidently when low. **Aim:** To validate the DS-COPD in clinical setting through a case-control study, and to evaluate the cost saving by its use.

Methods: In two tertiary care hospitals, we calculated the DS-COPD scale in suspected COPD and controls; COPD was predicted in the study sample and in symptomatic individuals. COPD status was confirmed by post-bronchodilator spirometry.

Results: From the ROC curve, the Area Under Curve was 0.945. The Positive Predictive Value was 79% if DS-COPD was >17 and the Negative Predictive Value was 83% if DS-COPD was <10 in symptomatic individuals. A DS-COPD of 10–17 represented a gray zone mostly suggestive of no COPD. For every 100 symptomatic patients 4150\$ were saved combining spirometry and scale when inconclusive compared to systematic use of spirometry.

Conclusions: We were able to validate a scale (DS-COPD) for COPD diagnosis in clinical setting. It would be valuable in primary care settings, where spirometry may not be available and in clinical settings before availability of spirometry results. Future prospective studies are still needed to confirm its value.

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1. Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a condition with high burden of disease, expected to further increase the upcoming years.¹ However, underdiagnosis is common² and

diagnosis is difficult, due to complexity of its symptoms and differential diagnosis.^{3,4} Spirometry is required for final diagnosis,^{5,6} but is not always feasible in non-tertiary care hospitals; even if available, it still requires expertise for results interpretation.⁷ Not to mention that portable spirometry

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devices may be expensive, require high technical skills and patients' learning efforts.^{7,8} Moreover, using systematic testing for early detection without pre-selection of at-risk patients result in wasting healthcare resources.⁷ For these reasons, many authors tried to predict COPD on the basis of scoring systems, taking symptoms into account.^{9–14}

We had previously developed a scale to diagnose COPD in an epidemiological setting, based on a cross-sectional study performed over Lebanon^{15,16}: the Diagnostic Score of Chronic Obstructive Pulmonary Disease (DS-COPD). This score had good properties and comprised twelve items. In this epidemiological setting, the Area Under Curve (AUC) was 0.849; the Positive Predictive Value (PPV) was 76% if DS-COPD > 20 and the Negative Predictive Value (NPV) was 97% if DS-COPD < 10. COPD could thus be diagnosed confidently when DS-COPD scored high, and could be excluded confidently when low. A DS-COPD of 10–19 represented a gray zone, mostly suggestive of no COPD (77%), but needing complementary spirometry to exclude or confirm COPD. However, application in clinical settings was still necessary to further validate this scale. We aimed to clinically validate the devised tool; a secondary objective was to calculate the cost saved when using it.

2. Methods

2.1. Study design

A case-control study was performed between July 2009 and June 2010, involving consecutive outpatient individuals consulting for respiratory symptoms in two tertiary care hospitals in Beirut: cases had to complain from one or more chronic respiratory symptoms. The control group included those with no respiratory diseases; consulting for other problems or accompanying other patients. All participants agreed to be part of the study after informed consent. The Ethical committee waived the need for ethical clearance because the study was observational, and the Helsinki declaration was adhered to.

2.2. Study participants

The "COPD group" included outpatients consulting in pulmonology departments for respiratory symptoms and confirmed as having COPD by spirometry.⁶ They were included if they were ≥40 years of age, free of other respiratory diseases, diagnosed as COPD by a chest physician, and had a post-bronchodilator FEV1/FVC <0.7. They were classified functionally according to GOLD guidelines.⁶ A secondary definition of COPD was adopted, according to the Lower Limit of Normal (LLN5; FEV1/FVC post-bronchodilator <5th percentile of healthy people having similar age and gender to the individual).¹⁷ Chronic bronchitis was defined as suffering from morning cough and sputum production for more than 3 months a year for at least two years.⁶ Spirometric quality was checked, and FEV6/FVC was ≤100% in more than 99.2% of measurements. An "intermediate status" group was also included in the analysis: they were those consulting pulmonologists for chronic respiratory symptoms, suspected to have COPD but not fulfilling its definition by spirometry criteria.⁶

Outpatients consulting for various extra-pulmonary problems were included as controls if they were ≥40 years of age, free of any respiratory disease or symptom. Some were consulting for diverse extra pulmonary problems. People accompanying patients (family members or friends) could also be taken as controls. Exclusion criteria included having previous or current diagnosis of chronic bronchitis or COPD, or any other diagnosed respiratory diseases.

2.3. Procedure and tool

After informed consent, subjects had baseline spirometry (MicroLab, MicroMedical Limited, England) by a trained technician and answered a standardized questionnaire. Thirty minutes after inhaling 2 puffs of albuterol sulfate (103 µg/actuation) (Ventolin®) in a pressurized metered-dose aerosol unit, post bronchodilator spirometry was performed. The best of 3 trials was taken. A significant reversibility was considered a change of FEV1 from baseline of 12% or more and an increase in absolute volume of FEV1 from baseline of 200 ml or more.¹⁸ As stated in the score development publication,¹⁶ we used the questionnaire of the American Thoracic Society (ATS) to evaluate chronic pulmonary diseases and respiratory symptoms,¹⁹ and the Medical Research Council (MRC) score for dyspnea.²⁰ Moreover, data were collected concerning socio-demographic characteristics, and cigarette and waterpipe smoking history (current, previous or never smokers). Waterpipe smoking was defined as a cumulative dose of more than 15 waterpipe – year; calculated by multiplying the number of waterpipe/week by the duration in years of smoking. Additional environmental and occupational toxic exposures were also evaluated. Additional methodological details are in another publication.²¹

3. Statistical analysis

SPSS version 17.0 was used to enter and analyze the data. We first applied a scale based on COPD symptoms without risk factors (the COPD Symptoms Index (CSI)), as generated in the epidemiological setting.¹⁶

For multiple linear regression model with one continuous outcome (DS score) and a set of k independent predictors (i.e. X_i 's which may be continuous or categorical), the equation is usually expressed as:

$$Y = \alpha + B_1X_1 + B_2X_2 + B_3X_3 + \dots + B_kX_k$$

The parameters – α and β 's (B) represent an intercept and regression coefficients respectively. The regression coefficients were taken from the logistic regression rounded adjusted OR that best predicted COPD in the epidemiological setting.¹⁶

The DS-COPD was computed using the following equation: DS-COPD = (previous waterpipe smoking × 3) + (MRC score) + (age class) + (gender) + (heating home by diesel × 2) + (cooking on wood × 3) + (low birth weight) + (current cigarette smoking × 3) + (previous cigarette smoking × 3) + (all day coughing × 2) + (chronic bronchitis × 2) + (all day wheezing × 2).

The calculated score was applied on the sample: ROC curves were used to evaluate the possibility of a threshold for the index with best sensitivity (Se) and specificity (Sp). Concordance Kappa value was calculated to evaluate concordance between two dichotomous variables. The Chi² test was used for cross tabulation of qualitative variables, to evaluate the Positive Predictive Value (PPV) and the Negative Predictive Value (NPV) of the score after dichotomization. ANOVA was also used to compare means of quantitative variables between groups, and Somers' D test was used to evaluate trends of ordinal variables. A *p*-value of less than 0.05 was considered significant.

On the whole sample encompassing COPD individuals, control and intermediate status individuals, a linear regression equation was derived between the score on one hand and post-bronchodilator FEV1/FVC, post bronchodilator FEV1 and percentage of expected FEV1 on another hand (after ensuring variables normality and association linearity). A subgroup analysis on symptomatic individuals was also performed.

4. Economical analysis

A cost effectiveness analysis was performed, comparing two situations:

- the systematic use of spirometry for 100 symptomatic patients
- the combined use of the scale systematically and spirometry only in case the scale was inconclusive, i.e. in case the DS-COPD was between 10 and 17.

Costs of spirometry and for scale application were estimated from the Lebanese market current prices used in medical laboratories. Moreover, underdiagnosis (percentage of false negative cases) and overdiagnosis (percentage of false positive cases) proportions were calculated in both situations.

5. Results

5.1. Sample description

The sample included 527 control individuals, 211 COPD patients, and 338 individuals who had chronic respiratory symptoms without COPD (intermediate status). Their post-bronchodilator FEV1/FVC measures are presented in Table 1. COPD patients were classified as follows: 38 (17.9%) grade I, 121 (57.6%) grade II, 45 (21.2%) grade III, and 7 (3.3%) grade IV COPD GOLD grade.

Intermediate group included: 21.3% of medically confirmed asthmatic with significant reversibility on spirometry, 45.3% of declared chronic wheezing, 43.8% of chronic bronchitis patients, and 19.2% of restrictive profile on spirometry, all without COPD according to spirometry.

As for controls, 323 (63.2%) declared themselves totally healthy with no chronic diseases; the rest were classified as follows: 42 (8%) were consulting for cardiology problems, 15 (2.9%) for endocrine, 19 (3.6%) for dermatology, 9 (1.7%) for hematology/oncology, 8 (1.5%) for nephrology, 9 (1.7%) for

urology, 19 (3.6%) for gastroenterology, 8 (1.5%) for gynecology, 17 (3.2%) for ophthalmology, 3 (0.6%) for ear, nose and throat problems and 15 (2.9%) for pre-surgery consultation. Forty patients (7.6%) did not declare the reason for their medical consultation, but they were free of any chronic respiratory disease or symptom. A random sample of 30 control individuals performed spirometry; they all had a post-bronchodilator FEV1/FVC of more than 0.7 (Table 1).

The socio-demographic and smoking characteristics of all three groups are presented in Table 1: cases were significantly older, included more males, more widow or divorced, less educated and non working individuals (*p* < 0.001). The intermediate group showed demographics that were intermediate between cases and controls. Cases included more previous and current cigarette smokers, and more previous waterpipe and mixed smokers (*p* < 0.001) (Table 1).

5.2. Scale properties

The scale has a minimum of two and a maximum of 33 points. In the sample, the minimum was two and the maximum was of 27. In individuals with COPD, the mean was 14.98 ± 4.64 , and the median was 15. In controls, the mean was 6.09 ± 2.96 , and the median was 6. In intermediate status individuals, the mean was 10.74 ± 3.94 (*p* < 0.001). Moreover, in the intermediate status group, individuals with chronic bronchitis had a mean score of 12.51 ± 3.72 , those with chronic wheezing a mean of 11.91 ± 3.99 , while those with asthma had a mean score of 8.95 ± 3.95 .

5.3. DS-COPD properties

Before going to DS-COPD evaluation, we tried to apply the CSI, considering it as a sensitivity analysis: we found a sensitivity of 80% and a specificity of 42% in symptomatic individuals. The values were again deemed of low interest as in previous publication,¹⁶ and we went on applying the DS-COPD. In Fig. 1, we present the ROC curves of COPD prediction, comparing COPD patients with control individuals. The AUC was high: 0.945 [0.928–0.963]; *p* < 0.001; the value that gave the best sensitivity and specificity was 10: Se = 84.9% and Sp = 90.2%.

After applying this threshold, we obtained a very good concordance between the COPD score and COPD according to spirometry: Kappa = 0.748 (*p* < 0.001). Individuals with a positive score (DS-COPD ≥ 10) have an infinitely high possibility of being a true COPD: OR = 58.47 [36.11–94.67]. In this situation, the PPV was 82% and the NPV was 92.8%.

5.4. DS-COPD and prediction of COPD

In Fig. 2, we present COPD prediction in the whole sample; there is a significant increase in COPD prediction per 5 points increments of DS-COPD (*p* < 0.001 for trend). Since the sample encompassed controls, COPD and intermediate status patients, the threshold of 10 had to be changed to take into account the three types of clinical presentations. We thus selected two thresholds: the score category of zero to 9 best represented control individuals (74.7% control, 21.1% respiratory symptoms without COPD and 4.2% COPD), 10 to 17 was mostly suitable for intermediate status (16.8% control, 51.1%

Table 1 – Socio-demographic and smoking characteristics of the study participants.

Characteristic	Controls ^a N = 527	Intermediate ^a N = 338	Cases ^a N = 211	p-Value cases vs controls excluding intermediate	p-Value cases vs intermediate versus controls
Age				<0.001	<0.001
40–44 Years	190 (36.1%)	50 (14.8%)	4 (1.9%)		
45–49 Years	139 (26.4%)	58 (17.2%)	10 (4.7%)		
50–54 Years	70 (13.3%)	39 (11.5%)	21 (10.0%)		
55–59 Years	42 (8.0%)	50 (14.8%)	30 (14.2%)		
60–64 Years	33 (6.3%)	46 (13.6%)	29 (13.7%)		
65 Years +	53 (10.1%)	95 (28.1%)	117 (55.5%)		
Gender				0.004	0.016
Males	233 (44.3%)	165 (48.8%)	118 (55.9%)		
Females	293 (55.7%)	173 (51.2%)	93 (44.1%)		
Education				<0.001	<0.001
Never been to school	6 (1.1%)	14 (4.2%)	9 (4.3%)		
Primary or less	39 (7.4%)	69 (20.8%)	51 (24.3%)		
Complementary or less	64 (12.2%)	54 (16.3%)	52 (24.8%)		
Secondary or less	170 (32.4%)	107 (32.4%)	67 (31.9%)		
University degree	246 (46.9%)	87 (26.3%)	31 (14.8%)		
Working status				<0.001	<0.001
Currently working	354 (67.2%)	170 (50.3%)	65 (30.8%)		
Retired	47 (8.9%)	53 (15.7%)	62 (29.4%)		
Not finding a job	5 (0.9%)	4 (1.2%)	1 (0.5%)		
Does never work	121 (23.0%)	111 (32.8%)	83 (39.3%)		
Marital status				<0.001	<0.001
Married	437 (83.6%)	283 (85.2%)	175 (83.7%)		
Single	70 (13.4%)	33 (9.9%)	13 (6.2%)		
Widow or divorced	16 (3.1%)	16 (4.8%)	21 (10.0%)		
Previous smoking				<0.001	<0.001
Never smoking ^b	245 (70.6%)	54 (32.5%)	10 (8.2%)		
Cigarette	71 (20.5%)	83 (50.0%)	84 (68.9%)		
Waterpipe	21 (6.1%)	9 (5.4%)	10 (8.2%)		
Cigarette & waterpipe	10 (2.9%)	20 (12.0%)	18 (14.8%)		
Current smoking				<0.001	<0.001
Never smoking ^b	245 (56.7%)	54 (22.9%)	10 (9.2%)		
Cigarette	98 (22.7%)	157 (66.5%)	82 (75.2%)		
Waterpipe	55 (12.7%)	8 (3.4%)	4 (3.7%)		
Cigarette & waterpipe	34 (7.9%)	17 (7.2%)	1 (1.9%)		
FEV1/FVC M ± SD	0.85 ± 0.07	0.79 ± 0.08	0.60 ± 0.08	<0.001	<0.001

^a Numbers may sum inferior to the total (100%) due to missing values.

^b Never smokers are the same individuals.

respiratory symptoms and 32.1% COPD), and 18 or more corresponded to COPD patients (77% COPD, 20.2% respiratory symptoms without COPD and 2.4% control).

Moreover, if the score is only applied among symptomatic individuals suspected of COPD (individuals with respiratory symptoms, with or without COPD, excluding control individuals), the first category gave 82.5% with no COPD versus 17.5% of COPD, the second 39.9% COPD and the third 79.3% COPD (Fig. 3).

5.5. DS-COPD and disease severity

There were significant differences in number of emergency visits in the previous year for respiratory problems between the three groups defined above: 0.066 versus 0.35 versus 0.45 for incremental score classes ($p < 0.001$). An analogous trend was found for number of hospitalizations for >1 day for respiratory problems: 0.13 versus 0.38 versus 0.41 ($p < 0.001$).

Moreover, to show that the score does predict the severity of the disease, we calculated the regression equation after

ensuring relationship linearity between DS-COPD score and post-bronchodilator FEV1/FVC. We derived the equation: $[FEV1/FVC] = 83.5 - (0.85 \times [DS-COPD])$. Based on this equation, a DS-COPD of zero would predict a FEV1/FVC of 83.5%, and a DS-COPD of more than 17 would predict lower than normal FEV1/FVC ratio (70%); the regression coefficient was $r = -0.472$ ($p < 0.001$).

Similar results were obtained for post-bronchodilator FEV1 ($r = 0.494$; $p < 0.001$). The obtained equation was: $[Post-bronchodilator FEV1] = 3.47 - (0.105 \times [DS-COPD])$.

For the percentage of expected FEV1, we found: $r = -0.343$; $p < 0.001$ and the equation was: $[Percentage of expected FEV1] = 89.16 - (1.09 \times [DS-COPD])$ (Fig. 4).

5.6. Economic analysis

Among symptomatic individuals, 26.6% are expected to have a score lower than 10, 57.5% a score between 10 and 17, and 15.9% a score higher than 17. Compiled with the PPV and NPV found above, and given that the cost of a spirometry

Fig. 1 – ROC curve for threshold selection of DS-COPD score. COPD patients and control individuals were analyzed. Area under the curve = 0.945 [0.928–0.963] ($p < 0.001$); at value = 10, Se = 84.9% and Sp = 90.2%.

measurement is 100\$ while the cost of applying the scale is estimated at 1\$ according to the Lebanese market prices, we calculated a cost saving of 4150\$ for 100 symptomatic individuals; this constitutes a relative reduction compared to systematic spirometry of 41.5%.

Furthermore, this reduction is accompanied by a 3.3% overdiagnosis of COPD (false positive) and a 3.4% underdiagnosis (false negative) of COPD cases (Table 2).

The overdiagnosed cases by the scale were all cigarette smokers; among them, 76.5% had chronic bronchitis, while 23.5% had post bronchodilator FEV1/FVC lower than the 5th

Fig. 2 – Percentages of COPD by 5 points category of DS-COPD. Among individuals with or without respiratory symptoms.

Fig. 3 – Percentage of COPD per DS-COPD categories according to selected thresholds. Controls were excluded.

percentile Lower Limit of Normal. Inversely, 62.5% of the underdiagnosed cases by the scale were not classified as COPD when using the LLN5 definition and 75% of them did not have chronic bronchitis.

6. Discussion

In this study, we validated in a clinical setting the previously developed tool for COPD diagnosis.¹⁶ The DS-COPD demonstrated even better properties than in the epidemiological setting.¹⁶ Our scale properties are also better than those of other researchers^{9–13}: we obtained in a case finding situation a sensitivity of 84.9% and a specificity of 90.2%, and an AUC of 0.945. These excellent results may be due to the fact that we compared individuals with COPD versus others with no respiratory disease. Nevertheless, when we worked on the whole sample and on symptomatic individuals suspected with COPD to take into account the risk of overestimating the DS-COPD properties, results were still satisfactory.

Fig. 4 – Scatter plot of Percentage of expected FEV1 versus DS-COPD. $r = -0.242$; $p < 0.001$; [percentage of expected FEV1] = $89.16 - (1.09 \times [\text{DS-COPD}])$.

Table 2 – Cost effectiveness of DS-COPD scale use in clinical setting.

	Using systematic spirometry for all individuals consulting for respiratory symptoms	Combining DS-COPD and spirometry when useful ^a
Total cost for 100 symptomatic individuals	10,000\$	5850\$
Percentage of individuals diagnosed as COPD	40.2%	38.8%
Cost/COPD diagnosed	248.76\$	149.29\$
Percentage of COPD cases detected (sensitivity)	100%	96.6%
Under-diagnosed COPD ^b	0%	3.4%
Over-diagnosed as COPD ^c	0%	3.3%

^a DS-COPD is applied for all symptomatic individuals, while spirometry is only carried out in case DS-COPD is between 10 and 17.
^b Percentage of false negative cases.
^c Percentage of false positive cases.

This could be due to computing risk factors added to symptoms, which was not the case in other studies; therefore a higher percentage of disease variability could be explained. As shown in the scale, age, low birth weight and gender, added to behavioral/environmental factors such as previous and current cigarette smoking, and cooking on wood and heating home by diesel (known risk factors for COPD) were also included.^{22–25} Another specificity of this scale is that previous waterpipe smoking of more than 15 waterpipes-years found to be a risk factor for COPD by our team²¹ and others²⁵ has been also included.

In addition, taking the timing for all symptoms such as morning sputum production and cough for chronic bronchitis and all day wheezing and coughing added a unique dimension to our score, except for Price et al¹⁹ who took morning sputum production into account, but with no timing reported for other symptoms. In fact, COPD symptoms do have a circadian rhythm, with morning symptoms being mostly reported by patients,²⁶ while for other chronic respiratory diseases such as asthma, symptoms are known to worsen during the night and early morning hours.²⁷ All these properties have improved the specificity of the scale (from 42% in the CSI scale to 90% in the DS-COPD scale), as shown in the sensitivity analysis.

To note also that the scale gave its best predictive ability of COPD in symptomatic patients seeking physicians help, while its use in asymptomatic individuals is useless (in this case, the COPD prevalence is 0.7% and PPV = 0.4%; results not shown). Overall, when used in symptomatic patients of a clinical setting, a score of 18 or more is highly suggestive of COPD (PPV = 79%); as expected, the high PPV was obtained in this setting because of the high prevalence of COPD. A score of 9 or less applies mainly to individuals with no COPD (NPV = 83%; high PV of no COPD).

A score between 10 and 17 seems a zone of symptomatic respiratory diseases other than COPD (60%); in the latter doubtful subgroup, individuals should be referred for spirometry testing. In this situation, a cost reduction of 41.5% resulted from combining the scale to spirometry when the scale results were inconclusive, with minimal percentages of over- and underdiagnosis compared with systematic spirometry. This conservative approach is acceptable, particularly that these percentages would decrease if the adopted definition of COPD is switched to the LLN5, considered more appropriate by some authors.^{17,28,29}

In this study sample, no single threshold for COPD detection could be defined. This threshold in the clinical setting (DS-COPD ≥ 18) also differed from that of epidemiological setting (DS-COPD ≥ 20).¹⁶ The 2 points difference may be related to the higher proportion of severe respiratory diseases other than COPD seeking physicians' help in the clinical setting, or to samples' fluctuations. Additional studies are required to further refine the COPD threshold issue.

Moreover, the DS-COPD score was correlated with exacerbation history and obstruction severity, showing dose-effect relationships. If showing higher ER visits and hospitalization in the COPD group compared to the intermediate and control group is an expected finding, the interesting finding remains within the COPD group. In fact, poor correlation was found between the COPD stage and exacerbation rate in literature.⁶ That was a key finding in ECLIPSE study³⁰ where the only correlation with COPD exacerbation was an exacerbation in the previous year. Another interesting finding was that the higher the DS-COPD the more severe the obstruction, whereas in other studies it has been difficult to find a steady correlation between symptoms and severity of obstruction.^{5,30} Concerning the rate of hospitalization, it seems high even in mild stages in our population, compared to other studies³⁰; the explanation might be that in our developing country with small role for preventive medicine, patients seek medical help at later stages of their disease.

Nevertheless, the value of this new scale should further be tested in prospective studies, because our study may suffer from several drawbacks: a selection bias might exist since it was not possible to get detailed information about non responders; however, answer refusals are expected to be mainly non-motivation or illiteracy, but not related to disease status. This may introduce a selection bias of more educated persons, but we do not expect this bias to affect the results. Results may also be subject to recall and subjectivity bias; moreover, in 0.8% of individuals, post-bronchodilator FEV6/FVC was $>100\%$, which may slightly add to the classification bias. However, the fact that our results were confirmed in both epidemiological and clinical settings and the demonstrated dose-effect relationship underline the strong points of this study. Nevertheless, factors specific to the Mediterranean region such as cooking on wood and smoking a waterpipe may not be generalized to the worldwide COPD population; this has to be taken into account in other countries and cross-cultural

adaptation and validation of the scale is suggested. Issues of generalizability of the study findings are also crucial as relative contribution of the risk factors used in such scoring system may vary from study to study and population to population.

In conclusion, we were able to validate a scale for COPD diagnosis in clinical setting among symptomatic individuals. It had good ability to differentiate between COPD and non-COPD patients. It correlated with exacerbations and obstruction severity. This tool would be useful in settings where spirometry is unavailable or before availability of spirometry results; its value for COPD diagnosis remains to be confirmed in future prospective studies.

Ethics statement

The Institutional Review Board of the Lebanese University waived approval to the original study due to its observational nature.

Funding

This study was funded by in-house resources.

Author contributorship

Pascale Salameh has made substantial contributions to conception and design, and acquisition analysis and interpretation of data. She drafted the submitted article and revised it critically for important intellectual content, and has provided final approval of the version to be published.

Georges Khayat has made substantial contribution to analysis and interpretation of data. He also revised the submitted article critically for important intellectual content, and has provided final approval of the version to be published.

Mirna Waked has made substantial contributions to conception and design, and acquisition of data and interpretation of data. She also drafted part of the submitted article and provided final approval of the version to be published.

Conflicts of interest

All authors have none to declare.

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