Comparison of Three Screening Questionnaires for Chronic Obstructive Pulmonary Disease in the Primary Care

Dionisios Spyrtatos^a Anna-Bettina Haidich^a Diamantis Chloros^a
Dionisia Michalopoulou^b Lazaros Sichletidis^a

^aPulmonary Department, Aristotle University of Thessaloniki, “G. Papanikolaou” Hospital, Exohi, and

^bPrimary Care Center, Municipality of Thessaloniki. Thessaloniki, Greece

Keywords

Chronic obstructive pulmonary disease · Primary care · Screening questionnaires · Underdiagnosis

Abstract

Background: Even though the diagnosis of chronic obstructive pulmonary disease (COPD) is easy and based mainly on spirometry and symptoms, the prevalence of underdiagnosis is extremely high. The use of simple screening tools (e.g., questionnaires, hand-held spirometers) has been proved to be a simple method for case finding of COPD. Nevertheless the most appropriate target group of the general population has not been specified yet. **Objectives:** The aim of the present study was to compare 3 screening questionnaires among smokers aged >40 years in the primary care setting. **Methods:** We excluded all subjects with a previous medical diagnosis of bronchial asthma or chronic pulmonary disease other than COPD. All participants were in a stable clinical condition, filled in the International Primary Care Airways Group (IPAG) questionnaire, the COPD Population Screener (COPD-PS) questionnaire, and the Lung Function Questionnaire (LFQ) and underwent spirometry. Medical diagnosis of COPD was established by an experienced pulmonologist. **Results:** We studied 3,234 subjects during a 3.5-year period. COPD

prevalence was 10.9% (52.1% underdiagnosis). All 3 questionnaires showed extremely high negative predictive values (94–96%), so in this case the diagnosis of COPD could be safely excluded. The area under the curve was similar across the 3 questionnaires (AUC_{ROC}: 0.794–0.809). The COPD-PS questionnaire demonstrated the highest positive predictive value (41%) compared to the other 2. On the other hand, the IPAG questionnaire and LFQ demonstrated higher sensitivities than COPD-PS resulting in lower percentages of missed cases. **Conclusions:** Three validated screening questionnaires for COPD demonstrated different diagnostic characteristics.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a common disease and one of the main causes of morbidity, mortality and health-related financial burden worldwide [1–3]. It is estimated that it will be the fourth cause of death in 2030 globally [4]. Even though the diagnosis of COPD is easy and based mainly on spirometry and clinical status [1], the prevalence of underdiagnosis is extremely high – >50% of cases for almost all countries –

with geographic variation and it is reversely related with the disease severity [5–7]. This phenomenon could be attributed to underestimation of symptoms by the majority of patients and the underuse of spirometry in the primary care [8]. In most countries, general practitioners (GPs) and not pulmonologist are the physicians who initially come in contact, diagnose and treat patients with respiratory symptoms [9]. Even though short-term educational courses of GPs on spirometry could lead to improvement in their diagnostic accuracy for asthma and COPD similar to pulmonologists, adoption of the procedure in everyday clinical routine is not feasible [10].

Increasing age and the presence of respiratory symptoms such as chronic cough and dyspnea during exercise could increase the possibility of COPD diagnosis [11, 12]. The use of simple screening tools (e.g., questionnaires, hand-held spirometers) that have been validated in the primary care setting has been proved to be an effective method for case finding of COPD [13–18]. A common characteristic of these tools is their high negative predictive value (NPV) – in most studies it exceeds 90% – while the positive predictive value (PPV) is about 25–35%. The aim of the present study was to compare 3 of the most recently developed questionnaires among a large sample of smokers (ex- and current), aged >40 years in the primary care.

Methods

Subjects from the general population were invited to participate in the present study by advertisement posters that had been distributed across a network of primary care practices in the city of Thessaloniki, Greece, and in the counties of Pella, Kilkis and Halkidiki covering a radius area of approximately 100 km around Thessaloniki. The study was performed during a 3.5-year period (January 2012 to June 2015). The Medical Ethics Committee of “G. Papanikolaou” Hospital, Exohi, Thessaloniki, Greece, approved the study protocol.

Participants eligible for this cross-sectional study were subjects aged >40 years, current and former smokers (≥ 10 pack-years). Only the inclusion criteria were printed on the posters (age and smoking status) and there was no reference to respiratory symptoms or regular use of inhaled medications.

Exclusion criteria were a previous medical diagnosis of bronchial asthma or chronic pulmonary disease other than COPD (e.g., bronchiectasis, lung cancer, tuberculosis, and interstitial lung disease). Patients with a previous medical diagnosis of COPD who suffered from a recent (≤ 8 weeks) exacerbation leading to hospitalization or prescription of antibiotics and/or corticosteroids were also excluded.

We used 3 different screening COPD questionnaires: (a) the International Primary Care Airways Group (IPAG) questionnaire [13, 14] that has already been validated in the Greek population [16], (b) the COPD Population Screener (COPD-PS) question-

naire [15], and (c) the Lung Function Questionnaire (LFQ) [17, 18]. We translated the last 2 questionnaires into Greek while the IPAG questionnaire is already in use in the primary care in Greece. We tested the reliability of the COPD-PS questionnaire and LFQ by calculating the reproducibility rate based on the first 120 participants as these 2 questionnaires had not been used in the Greek population in the past (participants filled in the questionnaires on their own twice, 15 days apart). Cutoff points for a positive response were: ≥ 17 for the IPAG questionnaire, ≥ 5 for the COPD-PS questionnaire and ≤ 18 for the LFQ based on previous studies.

All subjects filled in the questionnaires unassisted at the primary care clinics (they asked GPs only in case of uncertainties) and they also signed the informed consent form. We recorded all subjects with a previous medical diagnosis of COPD according to their health care booklet. Spirometry was always performed after completion of the questionnaires and informed consent form.

On the same day, all participants underwent spirometry by a group of experienced board-certified pulmonologists (MIR Spiro-Lab II, Roma, Italy, CE0476, before and 15–30 min after inhalation of 400 μ g salbutamol via a pressurized metered-dose inhaler with spacer for those with an abnormal prebronchodilation spirometry). Spirometers had been calibrated on the same morning before the visit to the primary care clinic. All measurements were performed according to the criteria of the American Thoracic Society/European Respiratory Society task force [19]. We used the predicted values for FVC, FEV₁ and FEF_{25–75} according to the Global Lung Function 2012 equations [20]. All spirometric tests were interpreted by an experienced pulmonologist (criteria for acceptability and reproducibility as well as final diagnostic evaluation of the spirometry) who was blinded to the scores of the 3 COPD screening questionnaires.

Subjects with an FEV₁/FVC <0.7 following bronchodilation were defined as COPD patients according to GOLD guidelines [1]. The final medical diagnosis of COPD was based on spirometric criterion, clinical status (medical history, symptoms and physical examination), and exclusion of other diseases [1]. A recent chest X-ray was evaluated for COPD patients, whenever one was available, in order to exclude other undiagnosed diseases. We also collected data for the subgroup of COPD patients about: (a) the modified Medical Research Council (mMRC) Dyspnea Scale and the COPD Assessment Test (CAT) questionnaire score, (b) exacerbations during the last year, and (c) comorbidities that were recorded in the health care booklet. We categorized them to groups A, B, C, and D based on FEV₁ % predicted, MRC Dyspnea Scale or CAT score, and exacerbation history during the last year.

We retrieved all prescribed inhaled drugs – via the national electronic platform – during the last 12 months for all participants. Overdiagnosis was defined as lung function within predicted values or restriction (post FEV₁/FVC >0.7, FCV and FEV₁ <80% of predicted values), previous medical diagnosis of COPD recorded in the health care booklet, and prescription of inhaled drugs for at least 12 consecutive months during the last 5 years.

Statistical Analysis

Normally distributed quantitative data were prescribed with mean and standard deviation (SD) and were analyzed within the dependent *t* test. When data were not normally distributed, they were described with a median and interquartile range (IQR) and analyzed with the Mann-Whitney U test (in the case of comparison between 2 groups) or the Kruskal-Wallis test (in the case of com-

Table 1. Comparison of demographic, spirometric and screening questionnaire scores between subjects with and without COPD

	Non-COPD subjects (<i>n</i> = 2,883)	COPD patients (<i>n</i> = 351)	<i>p</i> value
Gender, <i>n</i> (%)			<0.001 ^a
Males	1,812 (62.9)	290 (82.6)	
Females	1,071 (37.1)	61 (17.4)	
Mean age ± SD, years	59 ± 13.2	65.7 ± 11.7	<0.001 ^b
BMI ± SD	29.5 ± 5.4	28.4 ± 5.0	<0.001 ^b
Smoking, <i>n</i> (%)			0.172 ^a
Current/former	1,540 (53.4)	201 (57.3)	
Smokers	1,343 (46.6)	150 (42.7)	
Median pack-years (IQR)	24 (30)	50 (55)	<0.001 ^c
Mean FVC, L (SD)	3.36 ± 1.03	3.02 ± 1.0	<0.001 ^b
Mean FVC ± SD, %pred.	95 ± 17.6	85.6 ± 21.5	<0.001 ^b
Mean FEV ₁ ± SD, L	2.8 ± 0.8	1.9 ± 0.7	<0.001 ^b
Mean FEV ₁ ± SD, %pred.	97.4 ± 17.0	68.5 ± 18.8	<0.001 ^b
Median FEV ₁ /FVC, % (IQR)	82.9 (10)	64.9 (7.8)	<0.001 ^c
Median MMEF, %pred. (IQR)	90.1 (41.7)	38.7 (16.1)	<0.001 ^c
Mean score IPAG ± SD [13, 14]	13.5 ± 5.8	21.1 ± 6.7	<0.001 ^b
Mean score COPD-PS ± SD [15]	3.3 ± 1.6	5.4 ± 2.1	<0.001 ^b
Mean score LFQ ± SD [17, 18]	19.2 ± 2.6	15 ± 4.1	<0.001 ^b

SD, standard deviation; IQR, interquartile range. ^a Pearson χ^2 . ^b Independent *t* test. ^c Mann-Whitney test.

parison between 3 groups). The Bonferroni correction was applied for multiple comparisons. The Pearson χ^2 test was used for qualitative data. The intraclass correlation coefficient was calculated to evaluate the reproducibility rate between the same questionnaires. The 95% confidence intervals were calculated for the diagnostic proportions results. The Youden index was used to find the optimal cutoff point for sensitivity and specificity. The Delong test was used for comparing 2 areas under the curve (AUCs) except for comparison of curves with different direction, where the bootstrap method was used. The confidence level was set as $\alpha = 0.05$. A subgroup analysis was performed excluding those with a previous medical diagnosis of COPD and receiving inhaled drugs at the time of the study. The statistical analysis was conducted using R and SPSS statistical packages.

Results

The study sample consisted of 3,319 subjects totally. Eighty-five participants were excluded because their spirometric maneuvers did not fulfill the American Thoracic Society/European Respiratory Society criteria. The eligible sample for the final analysis consisted of 3,234 subjects (65% males, 54% current and 46% former smokers).

A subgroup of 351 patients (10.9%) presented with clinical symptoms as well as postbronchodilation spirometric values compatible with a diagnosis of COPD. De-

mographics, spirometric values and scores of the 3 screening questionnaires of the subjects with and without COPD are shown in Table 1. Patients with COPD achieved worse scores across all questionnaires as it was anticipated. One hundred and eighty-three patients had no previous medical diagnosis of COPD (underdiagnosed, 52.1%), while 168 (47.9%) had already been diagnosed and were receiving inhaled drugs at the time of the study. Overdiagnosis was the case for 307 subjects (9.5%).

We also estimated severity according to the combined COPD assessment system as proposed by GOLD (spirometry, exacerbation rate, and symptoms). The patients were divided into group A (240 patients), group B (58 patients), group C (20 patients), and group D (33 patients) based on the mMRC Dyspnea Scale. On the other hand, using the CAT for evaluating symptoms, we estimated the following classification: group A (160 patients), group B (138 patients), group C (14 patients), and group D (39 patients). Comorbidities of COPD patients were: arterial hypertension (*n* = 133, 37.9%), coronary artery disease (*n* = 73, 20.8%), hyperlipidemia (*n* = 60, 17.1%), diabetes (*n* = 48, 13.7%), depression (*n* = 23, 6.6%), and cerebrovascular accident (*n* = 13, 3.7%).

The reproducibility rate of the COPD-PS questionnaire and LFQ was calculated to be 89% (95% CI: 83–95)

Table 2. Characteristics of the 3 case-finding COPD questionnaires for the whole study sample

	IPAG (≥ 17)	COPD-PS (≥ 5)	LFQ (≤ 18)	<i>p</i> value
Sensitivity	0.74 (0.69–0.79)	0.56 (0.51–0.61)	0.79 (0.75–0.84)	
Specificity	0.72 (0.70–0.74)	0.90 (0.89–0.91)	0.68 (0.66–0.69)	
PPV	0.24 (0.22–0.27)	0.41 (0.37–0.45)	0.23 (0.21–0.26)	
NPV	0.96 (0.95–0.97)	0.94 (0.93–0.95)	0.96 (0.96–0.97)	
Diagnostic accuracy	0.72 (0.71–0.74)	0.86 (0.85–0.88)	0.69 (0.67–0.71)	
AUC	0.802 (0.776–0.828)	0.794 (0.767–0.822)	0.809 (0.783–0.835)	
QA-QB (Delong test)				$z = 0.7705, p = 0.441$
QA-QC (bootstrap method, $n = 10,000$)				$p = 0.4085$
QB-QC (bootstrap method, $n = 10,000$)				$p = 0.0613$
Best cutoff point				
Based on Youden method	19.5	4.5	17.5	
Based on Closest Top Left method	16.5	4.5	17.5	

QA, IPAG questionnaire; QB, COPD-PS questionnaire; QC, LFQ.

Fig. 1. ROC curves for the 3 questionnaires analyzing the whole study sample. QA, International Primary Care Airways Group questionnaire; QB, Chronic Obstructive Pulmonary Disease Population Screener questionnaire; QC, Lung Function Questionnaire. **Fig. 2.** ROC curves for the 3 questionnaires after excluding subjects with a previous medical diagnosis of COPD. QA, International Primary Care Airways Group questionnaire; QB, Chronic Obstructive Pulmonary Disease Population Screener questionnaire; QC, Lung Function Questionnaire.

and 91% (95% CI: 88–97), respectively, based on a subsample of the first 120 subjects who filled in the questionnaires twice (15 days apart).

As it is shown in Table 2, the possibility of a patient to suffer from the disease was higher if he/she had a positive COPD-PS questionnaire (PPV = 41% compared with 23 and 24% for the other 2 questionnaires). On the other hand, it is important to mention that all 3 questionnaires

had extremely high NPVs (94–96%) so in this case the diagnosis of COPD could be quite safely excluded. The AUC was similar across the 3 questionnaires as it is shown by the ROC curves (Fig. 1). We also calculated the same diagnostic characteristics of the 3 questionnaires after excluding those with a previous medical diagnosis of COPD and those receiving inhaled drugs (correctly diagnosed and those with an overdiagnosis) at the time of the study

Table 3. Characteristics of the 3 case-finding COPD questionnaires after excluding those with a previous medical diagnosis of COPD and those receiving inhaled drugs

	IPAG (≥ 17)	COPD-PS (≥ 5)	LFQ (≤ 18)	Comparison of AUC
Sensitivity	0.66 (0.59–0.73)	0.50 (0.43–0.58)	0.74 (0.67–0.80)	
Specificity	0.74 (0.72–0.75)	0.91 (0.90–0.93)	0.69 (0.68–0.71)	
PPV	0.15 (0.13–0.18)	0.29 (0.24–0.35)	0.15 (0.12–0.17)	
NPV	0.97 (0.96–0.98)	0.96 (0.95–0.97)	0.97 (0.97–0.98)	
Diagnostic accuracy	0.73 (0.71–0.75)	0.89 (0.88–0.90)	0.70 (0.68–0.71)	
AUC	0.769 (0.731–0.807)	0.766 (0.727–0.805)	0.777 (0.741–0.814)	
QA-QB (DeLong test)				$z = 0.195, p = 0.845$
QA-QC (bootstrap method, $n = 10,000$)				$p = 0.5163$
QB-QC (bootstrap method, $n = 10,000$)				$p = 0.3264$
Best cutoff point				
Based on Youden method	18.5	4.5	18.5	
Based on Closest Top Left method	15.5	3.5	18.5	

QA, IPAG questionnaire; QB, COPD-PS questionnaire; QC, LFQ.

Table 4. Questionnaire scores for subgroups of diagnosed and underdiagnosed COPD patients as well as overdiagnosed subjects

	Patients with previous diagnosis of COPD ($n = 168$)	Underdiagnosed patients with COPD ($n = 183$)	Overdiagnosed subjects ($n = 307$)	p value*
Score IPAG questionnaire; median (IQR)	22.5 $\pm$ 6.2; 23 (9)	19.7 $\pm$ 6.9; 20 (9)	16.3 $\pm$ 6.1; 15 (8)	<0.001
Patients with a positive QA	139/168 (82.7%)	121/183 (66.1%)	128/307 (41.7%)	
Score COPD-PS questionnaire; median (IQR)	5.9 $\pm$ 2.3; 5.5 (4)	4.9 $\pm$ 1.9; 5 (2)	4 $\pm$ 1.7; 4 (1)	<0.001
Patients with a positive QB	105/168 (62.5%)	92/183 (50.3%)	64/307 (20.8%)	
Score LFQ; median (IQR)	13.9 $\pm$ 4.2; 14 (6)	16.1 $\pm$ 3.6; 17 (5)	18.1 $\pm$ 3.2; 19 (3)	<0.001
Patients with a positive QC	144/168 (85.7%)	135/183 (73.8%)	139/307 (45.3%)	

QA, IPAG questionnaire; QB, COPD-PS questionnaire; QC, LFQ. All data are presented as mean values $\pm$ SD if not otherwise noted. * Kruskal-Wallis test, multiple pairwise comparisons (using the Mann-Whitney test with Bonferroni correction) found significant differences ($p < 0.001$) for all comparisons.

($n = 2,676$, COPD prevalence = $186/2,676 = 6.8\%$). We performed this subgroup analysis as these subjects did not have any previous medical diagnosis of respiratory disease and may seek support in case of worrisome symptoms in the future. The results were similar as the 3 questionnaires had a comparable AUC and NPV, while the COPD-PS questionnaire had a better PPV (Table 3; Fig. 2). We performed another subgroup analysis based on patients with COPD stages B, C, and D as they need regular treatment with inhaled drugs according to the GOLD guidelines. We also found that the COPD-PS questionnaire had a better PPV (0.33) compared to the other 2 (0.19 for the IPAG and 0.18 for the LFQ).

Trying to determine the best cutoff point (the Youden index method calculating the maximal combination of sensitivity and specificity), we found that the previously proposed scores for a positive test [14, 15, 17] were exactly the same as in the present study for the COPD-PS questionnaire and the LFQ. We also calculated that the best cutoff point for the IPAG questionnaire should be raised to ≥ 19 based on the Youden method (Table 3).

It is interesting to mention that the subgroup with an overdiagnosis of COPD had the lowest scores across all questionnaires while those with a previous correct diagnosis achieved the highest scores (Table 4). On the other hand, patients with an underdiagnosis of COPD were fre-

quently symptomatic (50–74% had positive questionnaires) even though they had not sought medical advice until the time of the study.

Discussion

Simple questionnaires that are easy for everyone to understand and complete are useful tools in order to identify patients at risk for COPD. National and international websites related with COPD could use these questionnaires as a first-level screening method of the general population and advise subjects with a positive test to visit their physician and perform spirometry.

In the present study, we compared the ability of 3 different screening questionnaires to discriminate between subjects with and without COPD. The main findings are: (a) overall the diagnostic characteristics were similar among the 3 questionnaires (diagnostic accuracy and AUC), (b) the NPV for all questionnaires was extremely high making spirometry unnecessary in that case, (c) the IPAG questionnaire and the LFQ demonstrated higher sensitivities than the COPD-PS questionnaire resulting in lower percentages of missed cases, and (d) the cutoff point for the IPAG questionnaire should be raised to 19 points in order to improve its diagnostic accuracy. To our current knowledge, this is the largest population-based study on case finding of COPD patients using different screening questionnaires among smokers (current and former) in the primary care.

Price et al. [13] developed the IPAG questionnaire based on 818 subjects, 45% current smokers, with no prior history of respiratory disease and COPD prevalence of 18.6%. Using the cutoff point of 17 [14], the questionnaire had a sensitivity of 58.7%, a specificity of 77%, an NPV of 89%, a PPV of 37% and an ROC_{AUC} of 0.8158. In our study, the ROC_{AUC} was quite similar (0.802 and 0.769) based on the whole study sample (COPD prevalence: 10.9%) and after excluding those with prior COPD diagnosis (COPD prevalence: 6.8%). Using the above questionnaire as a telephone interview is also possible and the percentage of new COPD cases was higher among those who achieved the high-risk score [21]. On the other hand, we should mention that an external validation study of the IPAG questionnaire [22] showed that its usefulness was too low (ROC_{AUC} 0.65) among 676 current smokers with a high prevalence of COPD (41.1%).

Martinez et al. [15] studied 295 subjects – 38% of whom had persistent airflow obstruction – and developed the COPD-PS questionnaire which achieved an ROC_{AUC}

of 0.73 (0.794 in the present study) for the cutoff point of 5. Hanania et al. [18] showed that the main advantage of the LFQ was its high sensitivity (82.6%), although it was not too specific. In everyday clinical practice, this means that it could identify more patients with COPD but at the same time more subjects should undergo spirometry because of a positive test.

The low COPD prevalence in the present study could give an explanation for the differences in PPV. We calculated that the LFQ had a PPV of 0.23, which was very close to the original study (0.26) as the prevalence of COPD was quite similar (10.9 vs. 18.6%). We should mention that the COPD prevalence of our study was comparable with that of the BOLD study [2].

Screening questionnaires is a validated way for finding new cases of COPD; however, offering spirometry to subjects with tobacco/occupational exposure and at least one respiratory symptom (e.g., dyspnea, cough, wheeze, and phlegm) seems to be a very effective screening strategy. One study performed by the Danish GPs who followed the above criteria found that more than one-third of participants had airway obstruction [23]. The same screening program seems to be feasible and effective if implemented out of general practices (e.g., municipalities) [24]. Additional screening tools such as differential diagnosis questionnaires for those with prior evidence of respiratory medical history have been developed for use in the primary care [25].

Screening programs and ongoing education of GPs to use simple tools among high-risk populations in primary care is the only feasible way to reduce the percentage of underdiagnosed COPD. At the same time, finding mild and moderate COPD cases may increase the long-term effectiveness of inhaled drugs in altering the natural history of the disease.

Financial Disclosure and Conflicts of Interest

All authors state that they do not have any financial or other relationships for the present study that might lead to a conflict of interest.

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