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Diagnostic values of bronchodilator response versus 9-question questionnaire for asthma

Abstract

Introduction: Several studies have investigated different tools for asthma diagnosis in order to reduce the cost and improve its early recognition. The goal of this study is to establish a short questionnaire to be used in practice for asthma screening and compare diagnostic values between this method and spirometric response to bronchodilators.

Material and method: 208 patients presenting with chronic stable dyspnea (> 6 months) and definite clinical diagnosis of chronic obstructive pulmonary disease, bronchiectasis, pulmonary fibrosis or asthma, were enrolled. 9 questions out of 43 based on the literature search were selected by regression analysis. Patients were asked to complete the questionnaire and then their spirometric responses to bronchodilators were evaluated.

Results: Of all, 53.8% of cases were diagnosed clinically to have asthma. For establishing diagnosis of asthma, the bronchodilator test had 48.2% sensitivity, 78.1% specificity, 72% positive, 56.4% negative predictive values, 2.2 positive, 0.66 negative likelihood ratios, and false positive, false negative and accuracy of 21.9%, 51.8% and 62.01%, respectively. The revised 9 questions from the questionnaire had 97.3% sensitivity, 77.1% specificity, 83.2% positive, 96.1% negative predictive values, 4.24 positive, 0.03 negative likelihood ratios, 22.9% false positive, 2.7% false negative and 87.98% accuracy.

Conclusions: The 9-question questionnaire had better diagnostic values in defining asthma in patients with chronic dyspnea than reversibility of airway obstruction to salbutamol and can be used as a useful screening test for diagnosis of asthma in clinical practice and for investigational purposes.

Key words: asthma, spirometry, questionnaire

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Introduction

Asthma is a commonly encountered disorder that imposes a great burden on patients and their family members if not diagnosed and treated properly. Its misdiagnosis causes a great cost for patients, health care institutions and local or national health service. On the other hand, asthma's definite pathophysiology is not clearly known so far, thus current diagnosis is based on signs and symptoms, and objective pulmonary function evaluations [1–4]. Spirometry is not available in all institutions, and it needs patient's cooperation. There are some reports that confirm the reversibility of airway obstruction in response to short-acting bronchodilators, which is one of the inclusion criteria for diagnosis of asthma, cannot be seen in some patients suffering from asthma. Moreover, limited reversibility of the airways is present in some other respiratory disorders, which must be included in differential diagnosis of asthma. Hence, spirometry is not

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a definite test for diagnosis of asthma [5–9]. There are several studies published till date which have investigated different tools with sufficient sensitivity and specificity in order to reduce the cost of recognition of asthma and to be applicable in clinical practice all around the world.

Similar investigations into chronic obstructive pulmonary disease (COPD) showed that brief questionnaires are valuable in differentiating COPD from other pulmonary disorders as screening tools in primary health care centers [10, 11]. Also, there are various surveys in which asthma was defined by a questionnaire, but none of them were used in clinical practice. So, in this study, our efforts went into designing a practical and appropriate questionnaire for asthma screening which can be applicable in other primary health care units. We assessed other questionnaires and the usage of our clinical experiences. Also, we compared its diagnostic power to response to bronchodilators in spirometry.

Material and methods

213 patients from the outpatient pulmonary clinic of Masih Daneshvari Hospital who had history of chronic dyspnea for more than 6 months and consented to enroll in the study, were assigned for the research. All subjects were examined by a pulmonologist and their asthma was defined in line with the GINA (Global Initiative for Asthma) [2] and the Saudi Initiative for Asthma [12] guidelines. Other respiratory disorders like COPD, pulmonary fibrosis and bronchiectasis were confirmed by history, physical examination and chest radiographies. Then, each patient was interviewed and assessed for airway reversibility by spirometry before and 20 minutes after inhalation of 4 puffs (400 μ) of salbutamol as a short-acting bronchodilator through a spacer [2, 12, 13].

Exclusion criteria:

- exacerbation of disease which induced chronic cough such as COPD, bronchiectasis or asthma;
- inability to perform the spirometry properly;
- disagreement on continuing the research;
- probability of *Mycobacterium tuberculosis* infection based on symptoms or radiological findings;
- past history of hypersensitivity to salbutamol;
- patients without definite diagnosis according to the clinical evaluation for reason of chronic cough by a pulmonologist (as the gold standard to differentiate asthma or non-asthma in the disease groups).

5 patients met the exclusion criteria, hence were excluded from the study and the research continued with 208 patients who complied with the inclusion criteria. Data were collected and used for statistical analysis.

Airway reversibility: FEV1 (forced expiratory volume in one second) increased by ≥ 12% and ≥ 200 mL, 20 minutes after inhalation of bronchodilator [2, 12, 13].

Statistical analysis

Data were analyzed by SPSS® 16 (Statistical Package for the Social Science, for Windows, Chicago. Version 16) software with using the Chi^2, ANOVA, independent T-test and linear regression to reveal independent associations between questions and the study groups. Further analysis such as receiver operating characteristic (ROC) curve used to determine a cut-off point for diagnosis of asthma by questionnaire EPI® 6 was applied for its good sensitivity, specificity, positive/negative predictive value, positive/negative likelihood ratio and accuracy analysis. Significant level for α and β errors were 0.05 and 0.2, respectively.

Questionnaire

The initial questionnaire was designed by selecting questions according to symptoms, signs or complaints about diseases accompanied by chronic cough, which had the best sensitivity and specificity in establishing the diagnosis of asthma in previous studies (Table 1). Then the 43 items questionnaire (arranged in 26 questions) was reviewed by a group of experienced pulmonologists in Masih Daneshvari hospital (center of excellence in lung diseases in Iran) for content and validity. The study was approved by the National Research Institute of Tuberculosis and Lung Diseases (NRITLD) research committee (approval code: CRD9010).

All visits and interviews were performed by 3 trained counselors who were blinded for type of disease and the spirometry results. The standardized Cronbach's alpha, which measures the internal consistency of the components of a score, was 0.83 for the questionnaire (43 items). Regression analysis was performed on the initial questionnaire, and 9 out of 43 questions with independently significant correlation with asthma were described. So, the 9-question questionnaire (9-QQ) was adopted and correlation coefficients were used for questionnaire scoring (Table 2) and other types of analysis. We used both spirometric bronchodilator response and the 9-QQ as

Table 1. Complete questionnaire for determining asthma in patients with chronic dyspnea

1. Does your chest ever sound wheezy or whistling?	Yes ☐	No ☐
2. Does your chest ever sound wheezy or whistling, during last 12 months?	Yes ☐	No ☐
3. How many times does your chest ever sound wheezy or whistling during last 12 months? Not ever ☐ 1–3 times ☐ 4–12 times ☐ > 12 times ☐		
4. Have you ever woken up with a feeling of tightness in your chest first thing in the morning?	Yes ☐	No ☐
5. Have you ever woken up with a feeling of tightness in your chest first thing in the morning in the last 12 months?	Yes ☐	No ☐
6. Have you ever had a feeling of tightness in your chest that came on after you stopped exercising?	Yes ☐	No ☐
7. Have you ever had a feeling of tightness in your chest that came on after you stopped exercising in the last 12 months?	Yes ☐	No ☐
8. Have you ever had a period of being well without any symptoms?	Yes ☐	No ☐
9. Have you ever had asthma in your opinion?	Yes ☐	No ☐
10. Has a doctor ever told you that you have asthma?	Yes ☐	No ☐
11. Are your symptoms occur or worsen at night?	Yes ☐	No ☐
12. Have you ever been woken at night by an attack of symptoms?	Yes ☐	No ☐
13. How many times you been woken at night by an attack of shortness of breath/cough during last 12 months? Not ever ☐ < 1 night per week ☐ > 1 night per week ☐		
14. Have you ever had severe dyspnea as could not speech more than 2 words between your breaths during last 12 months?	Yes ☐	No ☐
15. Are your symptoms occur or worsen in a seasonal pattern?	Yes ☐	No ☐
16. If yes to 15, in which seasons? Spring ☐ Summer ☐ Autumn ☐ Winter ☐		
17. Have you ever had history of eczema, hay fever, dermatitis or atopic disease?	Yes ☐	No ☐
18. Have you ever had first degree family history of eczema, hay fever, dermatitis or atopic disease?	Yes ☐	No ☐
19. Are your symptoms relief by anti-asthma therapy (salbutamol inhaler)? Not used ☐	Yes ☐	No ☐
20. Are your colds take more than 10 days to clear up?	Yes ☐	No ☐
21. Are your colds go to the chest?	Yes ☐	No ☐
22. Have you ever had history of the any following?		
Recurrent coughs ☐ Recurrent wheeze ☐ Recurrent difficult breathing ☐ Recurrent chest tightness ☐		
23. Have your symptoms occur or worsen in the presence of:		
Animals with fur ☐ Aerosol chemicals ☐ Domestic dust mites ☐ Chang in temperature ☐ Drugs (aspirin, beta blockers) ☐ Respiratory (viral) infections ☐ Strong emotional expression ☐ Smells (perfumes, foods…) ☐ Pollen ☐ Exercise ☐ Cigarette smoke ☐ Vehicles smoke ☐		
24. Have you ever had cough and phlegm more than 3 months per year in more than 2 years?	Yes ☐	No ☐
25. Do you often have exertional dyspnea?	Yes ☐	No ☐

a combined screening test for more research, and in this setting asthma diagnosis was made when both tests were positive.

Results

208 patients with chronic dyspnea who visited pulmonary clinics of our center during 9 months were enrolled in the study. Demographic characteristics of the study cohort are listed in Table 3.

54 asthmatic cases (48.2%) and 21 non-asthmatic individuals (21.9%) had positive airway response to bronchodilator (P-value < 0.001). In 10 (20.8%) cases with bronchiectasis, 1 (8.3%) with pulmonary fibrosis and 10 (27.8%) patients with COPD from non-asthmatic patients airway reversibility with bronchodilators were noted. Regression analysis between a type of disease and questionnaire questions revealed that only 9 out of 43 questions had independent association.

Table 2. 9-question screening questionnaire for determining asthma in patients with chronic dyspnea

Question	Yes*	No*
1. Have you ever had a period of being well without any symptoms?	+0.218	−0.218
2. Have you ever had asthma in your opinion?	+0.484	−0.484
3. Have you ever been woken at night by an attack of symptoms?	+0.129	−0.129
4. Are your symptoms occur or worsen in a seasonal pattern?	−0.141	+0.141
5. Are your symptoms occur or worsen in springs?	+0.122	−0.122
6. Have your symptoms occur or worsen in the presence of respiratory viral infections?	+0.106	−0.106
7. Have your symptoms occur or worsen in the presence of vehicles smoke?	−0.124	+0.124
8. Have you ever had cough and phlegm more than 3 months per year in more than 2 years?	−0.309	+0.309
9. Do you often have exertional dyspnea?	−0.112	+0.112
Total score (summation of the coefficients by responses)**		

*Coefficients are getting by regression analysis; **If the questionnaire score is ≥ −0.14 then asthma is highly suggested

Table 3. Demographic characteristics of cases with chronic dyspnea and comparison of them by disease

		Asthma (112)	Not asthma				All cases (208)	P-value
			Bronchiectasis (48)	Fibrosis (12)	COPD (36)	Total (96)		
Age mean (SD)		48.9 (13.9)	43.4 (16.7)	55.1 (18.8)	62.4 (15.7)	52 (18.7)	50.3 (16.3)	0.195
Disease duration mean (SD)		9.6 (8.2)	17.8 (16.5)	4.8 (5.3)	9.1 (11.3)	12.9 (14.5)	11.2 (11.6)	0.055
Gender	Male	50 (44.6%)	32 (66.7%)	8 (66.7%)	30 (83.3%)	70 (72.9%)	120 (57.7%)	< 0.001*
	Female	61 (55.4%)	16 (33.3%)	4 (33.3%)	6 (16.7%)	26 (27.1%)	88 (42.3%)	
Smoking	Smoker	5 (4.5%)	5 (10.4%)	1 (8.3%)	11 (30.6%)	17 (17.7%)	22 (10.6%)	0.002*
	Passive smoker	17 (15.2%)	10 (20.8%)	1 (8.3%)	2 (5.6%)	13 (13.5%)	30 (14.4%)	
	Ex-smoker	14 (12.5%)	4 (8.3%)	2 (16.7%)	14 (38.9%)	20 (20.8%)	34 (16.3%)	
	Non smoker	76 (67.9%)	29 (60.4%)	8 (66.7%)	9 (25%)	46 (47.9%)	122 (58.7%)	
Pack × year (SD)		20.4 (23)	22.9 (19.2)	7.6 (0.5)	34.3 (21.3)	29.1 (21.2)	26.1 (22)	0.179

*Difference between asthma and not asthma groups was statistically significant.
COPD — chronic obstructive pulmonary disease

Further analysis such as receiver operating characteristic (ROC) curve (Figure 1) demonstrated that the 9-QQ had the score of ≥ −0.14 as a cut-off point for diagnosis of asthma. 109 (97.3%) asthmatic patients and 22 (22.9%) non-asthmatic subjects suggested asthma in 9-QQ (P-value < 0.001).

Finally, in patients with chronic dyspnea, in determining asthma, spirometric bronchodilator response had 48.2% sensitivity, 78.1% specificity, 62.01% accuracy, 2.2 and 0.66 positive and negative likelihood ratios. On the other hand, 9-QQ had 97.3% sensitivity, 77.1% specificity, 87.98% accuracy, 4.24 and 0.03 positive and negative likelihood ratios. Combination of both tests had 46.4% sensitivity, 94.8% specificity, 68.75% accuracy, 8.91 and 0.56 positive and negative

likelihood ratios, respectively. Their screening results and diagnostic values are reported in details in Table 4.

Discussion

Asthma is a common chronic condition without a diagnostic gold standard for establishing the disease. Its diagnosis is often based on the patients' symptoms, medical history, lung function measurements and/or provocation tests. Similar researches revealed that brief questionnaires are valuable in differentiating multiple pulmonary diseases from other pulmonary disorders in primary health care centers [10, 11]. Also, there are various surveys in which asthma was defined by a questionnaire, but none of them are simple and accurate enough to be used in clinical practice, especially in our country. So, our goal was to collect questions with the best power to differentiate asthma from other diseases in one accurate, simple and easily applicable questionnaire.

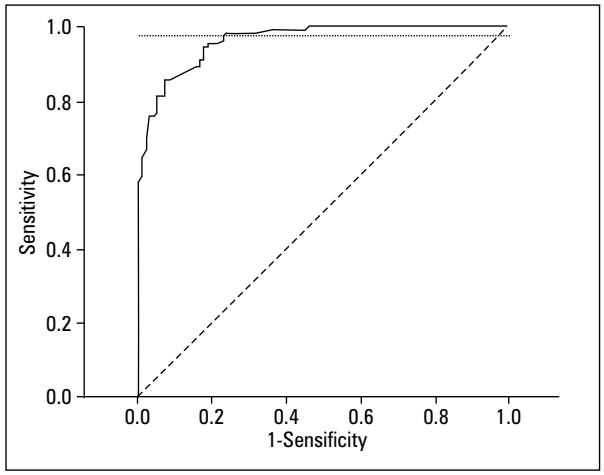

Figure 1. Receiver operating characteristic curve of 9-question questionnaire to determine asthma in patients with chronic dyspnea

In the study, 208 cases with chronic dyspnea were assessed and their demographic findings were similar to other researches [10, 11, 14–22], such as the mean age of our cases was 50.3 (SD = 16.3) years — the same as 58.7 (SD = 11.4) in Tinkelman's study [11] and trivial differences were due to different study groups such as in Santos's study [17] which was performed among 5 to 15-years-old children.

Diagnostic values of response to bronchodilator in asthma in our study were similar to Mehrabi *et al*. report with sensitivity of 64% and specificity of 60% (which is done in our country but only two groups of cases were assessed — COPD and asthmatic cases), and also the ones from the GINA's study (sensitivity of 55% and specificity of 59%) [15]. In Jenkins *et al*. study, bronchial hyperresponsiveness had 39% sensitivity, 90% specificity, 55% positive predictive value, 82% negative predictive value in adults and 54% sensitivity, 89% specificity, 64% positive predictive value, 85% negative predictive value in children [16]. So, it could be suggested that BHR in children may be more sensitive than in adults, but specificities are the same.

The 9-QQ in our study had 97.3% sensitivity, 77.1% specificity, positive predictive value of 83.2%, and negative predictive value of 96.1% and accuracy of 87.98%. Previous researches brought about variable results. Cunha and Santos conducted a study with a 4-question questionnaire and assessed its diagnostic values. They reported sensitivity of 17%, specificity of 89.6%, positive predictive value of 32%, negative predictive value of 79% and accuracy of 73.5% for this questionnaire [17]. So, our 9-QQ had the same accuracy as Santos questionnaire but had more sensitivity and less specificity. According to

Table 4. Comparison of diagnostic values between response to bronchodilator in spirometry and questionnaire in determining asthma in patients with chronic dyspnea (asthma prevalence = 53.8%)

Variables	Sen 95% CI	Spe 95% CI	PPV 95% CI	NPV 95% CI	FPER 95% CI	FNER 95% CI	Acc 95% CI	PLR	NLR
Bronchodilator response	48.2% 38.7–57.8%	78.1% 68.3–85.7%	72% 60.3–81.5%	56.4% 47.5–64.9%	21.9% 14.3–31.7%	51.8% 42.2–61.3%	62.01% 55.4–68.6%	2.2	0.66
9-question questionnaire	97.3% 91.8–99.3%	77.1% 67.2–84.8%	83.2% 75.5–89%	96.1% 88.3–99%	22.9% 15.2–32.8%	2.7% 0.7–8.2%	87.98% 83.5–92.4%	4.24	0.03
9-question questionnaire + bronchodilator response	46.4% 37–56.1%	94.8% 87.7–98.1%	91.2% 80–96.7%	60.3% 52–68%	5.2% 1.9%–2.3%	53.6% 43.9–63%	68.75% 62.4–75%	8.91	0.56

95% CI — 95% confidence interval; Acc — accuracy; FNER — false negative error rate; FPER — false positive error rate; NLR — negative likelihood ratio; NPV — negative predictive value; PLR — positive likelihood ratio; PPV — positive predictive value; Sen — sensitivity; Spe — specificity

differences in asthma prevalence in the studied populations (our cases were aged > 15 years and some were smokers with longer disease duration, but Santos's cases were aged 5−15 years, nonsmokers with shorter disease duration), PLR of our 9-QQ was more than Santos's (4.24 *vs* 1.64), so, our 9-QQ works better than theirs in defining asthma among patients with chronic dyspnea.

Jenkins and coworkers evaluated two questionnaires, the Tasmanian Asthma Survey (TAS) for adults and the International Study of Asthma and Allergies in childhood (ISAAC). They reported 80% and 85% sensitivities, 97% and 81% specificities, 89% and 61% positive predictive values and 94% and 94% negative predictive values [16]. Venables *et al*. also discovered 91% sensitivity and 95% specificity for a 9-question questionnaire [18]. Our 9-QQ had lower specificity than these questionnaires but other characteristics were found better.

In a review published by Toren *et al*., in articles with gold standard of clinical diagnosis, range of sensitivity was 48-100% with the average of 68%, and specificity was 78-100% with the average of 94% [19−22]. Sensitivity of our 9-QQ was more than their average, but specificity was slightly lower.

Question 2 has the biggest score in 9-QQ; which reflects the patient's opinion about his/her disease. This may be arising from insight of the subjects into their condition. Therefore, patients tend to research in the symptoms and pay more attention to them. So, one could say we may more relay on patients opinion in diagnosis of asthma.

In regards of questions 4 and 5 in the 9-QQ, the same as other reports, our analysis revealed that bronchiectasis and COPD have worsened in winter [23, 24], and in our study, they had more prominent seasonal pattern than asthma, so, worsening of symptoms in seasonal pattern is against diagnosis of asthma in our 9-QQ. On the other hand, in some reports, asthma worsens during spring [25]. Our analysis also cleared that worsening of symptoms only during spring is in favor of asthma, which is reflected in question 5.

Overall, our 9-QQ had acceptable sensitivity and specificity according to other articles, and could be used as a screening tool to distinguish between asthmatic cases and others with chronic dyspnea. It is important to emphasize that our questionnaire was used to differentiate asthma from other chronic respiratory disorders — not to screen the general population for diagnosing asthma. Similarly, we also evaluated the value of spirometry and bronchodilator response with this goal. According to Table 4, it is clear that 9-QQ is a better screening test than response to bronchodilator in lung function test for differentiating asthma from other chronic respiratory disorders which are characterized by chronic chough. Specificity, positive predictive value, false positive error rate and PLR improved together with combination of both tests.

As Toren *et al*. reported [19], it seems that the combined use of questionnaire and spirometric response to bronchodilator is a proper method for detection of asthmatic patients. According to 97.3% sensitivity of 9-QQ, it can properly be used as a screening test, thus all cases with 9-QQ's score ≥ −0.14 are highly suspicious of having asthma. If there is an imperative need to confirm diagnosis, response to bronchodilator in spirometry is recommended in those with positive test to label a person as an asthmatic patient. But cases with negative test need more evaluation with provocative tests as methacholine or histamine challenge test. So, this approach may achieve the best screening results and decrease the need for spirometry, and could be cost-effective. More studies are needed to assess the costs.

According to our findings, the use of the 9-question questionnaire may be recommended to differentiate asthmatic patients from other individuals with chronic dyspnea for all health care units, clinics, polyclinics, and epidemiological screening researches. Also, it is recommended to use reversibility of airway obstruction to bronchodilator in spirometry, not as a screening but as a confirmatory test.

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Conflict of interests

None declared.

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