Journal of Asthma and Allergy

Dovepress
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ORIGINAL RESEARCH

What is the Best Way to Diagnose Possible Asthma Patients with Negative Bronchodilator Reversibility Tests?

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Objective: The best method and strategy for the diagnosis of asthma remains unclear, especially in patients with negative bronchodilator reversibility test (BDRT). In our study, we aimed to investigate the diagnostic yield of peak expiratory flow (PEF) variability for this patient group.

Methods: A total of 50 patients with suspected asthma, all with negative BDR test, were included in the study. Demographic information and symptoms were recorded and PEF variability was monitored for 2 weeks. Metacolinbronchial provocation test (mBPT) was performed. Asthma was diagnosed when PEF variability ≥20% and/or positive mBPT was observed.

Results: 30 of 50 patients were diagnosed with asthma. After 1 month, 17 patients were evaluated for treatment outcomes. The sensitivity and specificity of PEF variability for different cut-off values (≥20%, >15% and >10%) were 61.5–83.3, 88.5–62.5 and 100–16.7, respectively. One of the most important findings of our study was the absence of variable airflow limitation or airway hyper reactivity in 39% patients with a previous diagnosis of asthma. Multiple logistic regression analysis revealed that a low baseline FEF_{25-75} value was an independent predictive factor for the diagnosis of asthma (p= 0.05).

Conclusion: The most efficient diagnostic test for asthma is still unclear due to many factors. Our study is one of the few studies on this subject. Although current diagnostic recommendations generally recommend a PEF variability of 10% for the diagnosis of asthma, this threshold may not be appropriate for the BDR-negative patient group. Our results suggest using a threshold value of <15% for PEF variability when excluding asthma and ≥20% when confirming the diagnosis of asthma in patients with clinically suspected but unproven reversibility. Furthermore, FEF_{25-75} is considered to be an important diagnostic parameter that should be included in diagnostic recommendations for asthma.

Keywords: diagnosis of asthma, reversibility, peak expiratory flow (PEF) variability, bronchial challenge test, forced expiratory flow $_{(25-75\%)}$

Introduction

Asthma is the most common chronic disease worldwide. More than 339 million people live with asthma.[1] It is estimated that 100 million people will be diagnosed with asthma by 2025.[2] It is a heterogeneous disease, usually characterised by chronic airway inflammation. It is characterised by variable airflow obstruction as well as adaptive respiratory symptoms that vary in time and intensity. The need to address the variable airflow limitation that characterises asthma before initiating treatment is emphasised in updated asthma management guidelines.[3,4]

Population-based studies in children, adults and the elderly show that 20–70% of people with asthma go undiagnosed and ultimately untreated. These studies also show that 30–35% of children are frequently misdiagnosed with asthma and that asthma is overdiagnosed in the general population[5] There are many studies investigating the use of testing methods such as spirometric reversibility, PEF monitoring and mBPT for the correct diagnosis of asthma.[6,7] However, the most

Received: 1 September 2023
Accepted: 8 February 2024
Published: 22 February 2024

appropriate test and strategy for diagnosis remains unclear, especially in patients in whom early reversibility cannot be demonstrated by spirometry.[6–8]

In our study, we aimed to draw attention to personalised PEF devices, which we believe may be helpful in the diagnosis and follow-up of asthma even during unprecedented events such as pandemic restrictions.[9] To increase the diagnostic efficiency and usability of PEF variability, we aimed to review the cut-off value of 10% recommended by GINA[3] and the cut-off value of 20%[10] recommended by other guidelines and to determine the most appropriate PEF variability cut-off value.

Materials-Methods

Patient Population

The people who applied to our outpatient clinic with complaints consistent with asthma between June 2016 and 2017 were evaluated. From this patient population, patients who had no problems in physical examination, whose early reversibility could not be demonstrated in simple spirometry, and who could not prove variable airway obstruction were targeted. Patients aged 18–65 years, with a smoking history <10 pack/year, who were not pregnant at the time of admission, who did not have respiratory tract infection in the last 6 weeks and who did not have any symptoms suggestive of other respiratory diseases (eg sarcoidosis, COPD, bronchiectasis) were included in the study. Patients who did not meet these criteria, who could not cooperate during spirometric evaluation, PEF monitoring and mBPT tests, or who had missing data were excluded from the study. A total of 58 patients were evaluated. All data of 50 patients were completed.

Study Design

Demographic information, history, symptoms, presence of atopy, eosinophil level, skin prick test and/or specific IgE results of all patients included in the study were recorded. The symptom severity score was calculated by scoring the number of daytime symptoms (<2 per month, 1–2 times per month, >2 per week) + activity restriction + nocturnal symptom (0–4).

PEF measuring devices were distributed to 50 patients at the first visit. Instructions for use of the device were explained to the participants. Electronic PEF meters were not used. The same type of PEF meters were used for each patient. They were asked to measure PEF 3 times a day, in the morning, in the evening and when there was a complaint, and to record their best values on the given chart. At the end of the second week, the patients were called for the 2nd visit. From the charts, thePEFvariability was calculated daily and the average was taken. Patients with PEF variability greater than 20% were considered as positive. The GINA asthma report was used to calculate the PEF variability. mBPT was administered using the two-minute tidal volume inhalation technique. BPT contraindications and preparation guidelines were followed. Individuals with PEF variability >20% and/or positive mBPT were diagnosed with asthma. PEF follow-up and mBPT tests were performed in all patients. 30 patients were diagnosed with asthma and treated according to GINA guidelines. The quality of life evaluations of the diagnosed patients were calculated based on the asthma control test (ACT), asthma quality of life scale (AQLQ) and short form 36 (SF-36). A total of 17 patients came for follow-up. 13 patients did not come for follow-up. Symptom scores, ACT, AQLQ, SF-36 quality of life questionnaires, and drug compliance status of the treated patients were checked at 1 month (Figure 1). The study was approved by the Medical Specialist Education Board and the Local Ethics Committee. (Approval number: 08–2018/1552). Informed consent forms were obtained from all patients before the tests.

Statistical Analyses

Statistical analyses were made by using the SPSS software. The conformity of the variables to the normal distribution was examined using visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov/Shapiro–Wilk tests). In descriptive statistics, mean and standard deviation were used for normally distributed variables, as well as a median and interquartile range for non-normally distributed variables. The difference between the groups in terms of these frequencies, if any, was tested by comparing them using Chi-square or Fisher tests. The correlation coefficients and statistical significance of the variables were subjected to the Pearson test for normally distributed variables and the Spearman test for at least one of the variables that were not normally distributed or ordinal. P values equal to or less than 0.05 were considered statistically significant.($p \leq 0.05$) Sensitivity, specificity and predictive values of the tests were calculated.

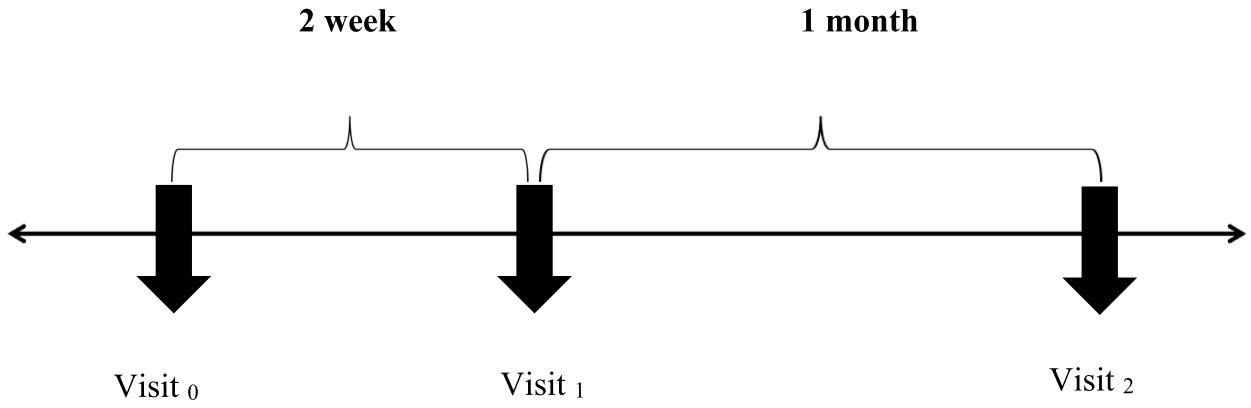

Figure 1 Material and method: Demographic characteristics, physical examinations, pulmonary function tests, asthma control tests, quality of life questionnaires were performed at the first application of the participants (Visit 0) who consented to participate in the study. PEF meters were provided to each of them, and their usage was explained. A chart was given to the participants for follow-up standardization. They were asked to perform PEF follow-up for 2 weeks. After 2 weeks, the participants were given mBPT appointments (Visit 1). According to the patients whose results were evaluated, treatment was started according to the recommendations of the GINA guideline. They were called for control after 1 month (Visit 2). Physical examination, pulmonary function tests, quality of life questionnaires, and asthma control tests were renewed and recorded.

Results

Of the 50 patients included in the study, 30 patients were diagnosed with asthma and 20 patients were followed up as patients with non-specific symptoms. There was no significant difference between the study groups in terms of demographic and clinical characteristics (Table 1).

When the cardinal symptoms of asthma were questioned, wheezing was statistically significant in the group diagnosed with asthma compared to the group with non-specific symptoms ($p = 0.021$) (Table 2). No significant difference was found in terms of other symptoms. When we compared asthma patients with non-specific respiratory symptomatic cases, a statistically significant difference was found in favor of asthma in terms of activity limitation ($p = 0.05$) and total symptom score ($p = 0.028$).

When pulmonary function tests were evaluated, baseline FEF_{25-75} measurements were significantly lower in the asthma group compared to the other group. There was no statistically significant difference between the two groups in terms of other parameters (Table 3). When the ACT, AQLQ and SF-36 were evaluated, no significant difference was found between the two groups. Baseline FEF_{25-75} measurement abnormality was found to be an independent predictor of asthma diagnosis ($p = 0.05$) (Table 4).

BPT alone was positive in 10 of 30 asthma cases. Both mBPT positivity and PEF variability were positive in 16 cases. Four of the 30 patients were diagnosed with asthma based on positive PEF variability. (Figure 2) When the sensitivity and specificity were evaluated for three different cut-off values of PEF variability, considering mBPT positivity as the baseline diagnostic test for the diagnosis of asthma, the sensitivity and specificity of PEF variability for different cut-off values (≥20%, >15% and >10%) were 61.5–83.3%, 88.5–62.5% and 100–16.7%, respectively (Table 5).

One of the important results of our study was the absence of variable airflow limitation or airway hyperreactivity in 39.28% of patients with a history of asthma diagnosed by a physician and previously treated for asthma.

Table 1 Demographic and Clinical Features of the Study Group

	Asthma (n=30)	Non-Specific Respiratory Symptoms (n=20)	Total (n=50)	p
Gender F, n(%)	20 (66.6)	14 (70)	34 (68)	0.804
Dr. diagnosed asthma	17 (%56.7)	11 (%55)	28 (%56)	0.907
BD treatment history	17 (%56.7)	11 (%55)	28 (%56)	0.907
Family history	10 (%33.3)	6 (%30)	16 (%32)	0.804
Comorbidity	16 (%53.3)	10 (%50)	26 (%52)	0.817
Atopy	21 (%70)	10 (%50)	31 (%62)	0.153
Age	32.73 (10.04)	33.25 (10.87)	32.94 (10.27)	0.864
BMI	26.6 (17–42)	26.45 (17–38.5)	26.45 (17–42)	0.692
Blood EOS level	200 (75–797)	200 (59–800)	200 (59–800)	0.546

Abbreviations: BMI, body mass index; BD, bronchodilator; EOS, eosinophil.

Table 2 Clinical Features of the Study Group

	Asthma (n=30)	Non-Specific Respiratory Symptoms (n=20)	Total (n=50)	p
Cough, n(%)	12 (60)	12 (60)	35 (70)	0.208
Wheezing, n(%)	19 (63.3)	6 (30)	25 (50)	0.021
Shortness of breath, n(%)	23 (76.7)	17 (85)	40 (80)	0.720
Tightness in the chest, n(%)	6 (20)	3 (15)	9 (18)	0.724
Total number of symptoms	2 (1–4)	2 (1–4)	2 (1–4)	0.068
Symptom duration (months)	11 (1–156)	15 (0.5–72)	11 (0.5–156)	0.766
Activity restriction, n(%)	10 (33.3)	2 (10)	12 (24)	0.050
Nocturnal symptom, n(%)	18 (60)	9 (45)	27 (54)	0.297
Total symptom weight score	2 (0–4)	1 (0–3)	2 (0–4)	0.028

Notes: Total symptom weight score: The number of daytime symptoms (0 = <2 per month, 1 = 2 times a month, 2 = >2 per week) + activity restriction + night symptom (0–4) were calculated by scoring.

Treatment was initiated in 30 patients diagnosed with asthma according to the GINA strategy report. Treatment was not given to 20 patients with non-specific respiratory symptoms. First month controls were planned after treatment.17 patients out of 30 patients came to the first month controls. 13 patients did not come to the controls. Medication compliance was questioned. Significant improvement was found in symptom scores, pulmonary function tests and quality of life of the patients compared to baseline (Table 6).

Table 3 Basal Spirometry and Survey Data of the Study Group (Visit 0)

	Asthma (n=30)	Non-Specific Respiratory Symptoms (n=20)	Total (n=50)	p
FEV_1, mean (SD)	91.13 (14.65)	96.75 (11.21)	93.38 (13.55)	0.153
FVC, mean (SD)	91.93 (14.73)	96.1 (10.20)	93.6 (13.16)	0.277
FEV_1/FVC, med (min-max)	83.5 (77–98)	87 (79–92)	85 (77–98)	0.393
PEF, mean (SD)	86.23 (12.15)	88.55 (16.39)	87.16 (13.89)	0.569
FEF_{25-75}, mean (SD)	81.90 (19.75)	93.75 (21.43)	86.64 (21.06)	0.050
Basal ACT, med (min-max)	14 (6–20)	13 (6–20)	14 (6–20)	0.510
Basal AQLQ, mean (SD)	148.37 (41.5)	151.65 (39.95)	149.68 (40.5)	0.782
Basal MCS, SF-36	155.9 (61–213)	167.9 (97.6–206)	165.9 (61–213)	0.898
Basal PCS, SF-36	269.5 (86.7)	286.88 (67.63)	276.45 (73.95)	0.454

Note: SF-36 test components.
Abbreviations: MCS, Mental Component Score; PCS, Physical Component Score; ACT, Asthma Control Test; AQLQ, Asthma Quality of Life Questionnaire; SD, Standart Deviation.

Table 4 Multivariate Linear Regression Analysis That Examines Various Parameters to Predict Asthma Diagnosis

	B Co-Efficient	Beta Co-Efficient	Standard Error	p	95% Confidence Interval
Wheezing	0.242	0.247	0.172	0.16	−0.105–0.589
Activity restriction	0.084	0.073	0.199	0.67	−0.318–0.485
Total symptom weight score	0.075	0.181	0.075	0.32	−0.076–0.226
FEF_{25-75}	−0.006	−0.264	0.003	0.05	−0.013–0.000

Notes: Total symptom weight score: The number of daytime symptoms (0 = <2 per month, 1 = 2 times a month, 2 = >2 per week) + activity restriction + night symptom (0–4) were calculated by scoring.

Discussion

Unfortunately, misdiagnosis of asthma is not uncommon.[5,8] In the patient group participating in the study, over diagnosis was found to be 39%, supporting the literature. In our study, it was aimed to provide diagnostic guidance, to draw attention to PEF follow-up, and to determine the diagnostic efficacy of PEF variability measurement, especially in the patient group whose early reversibility could not be proven. We think that this study conducted before the pandemic will add value to PEF follow-up in cases where pulmonary function tests cannot be performed, such as pandemics. We think that wheezing is the most distinctive symptom for the diagnosis of asthma and FEF_{25-75} measurement is an important spirometric marker in the diagnosis of asthma in patients with symptoms compatible with asthma. As an ideal predictive value recommendation, we think that using a cut-off value of <15% PEF variability to exclude the diagnosis of asthma or ≥20% PEF variability to confirm the diagnosis would increase the diagnostic value.

A high prevalence of under and over diagnosis of asthma has been reported in the literature, with important consequences for patients and healthcare systems.[8] José et al[11] showed that 54% of patients were underdiagnosed and 34% were overdiagnosed with asthma in primary care. Gershon et al[12] found that only 43% of patients diagnosed with asthma in Canada received a pre-diagnostic spirometric examination. Eguiluz-Gracia et al[13] conducted a survey with 339 participants to assess asthma management during the pandemic. During this period, 62%, 76%, 66%, 76%, 76% and 87% of healthcare workers, respectively, reported that they did not use spirometry, impulse oscillometry, bronchodilator

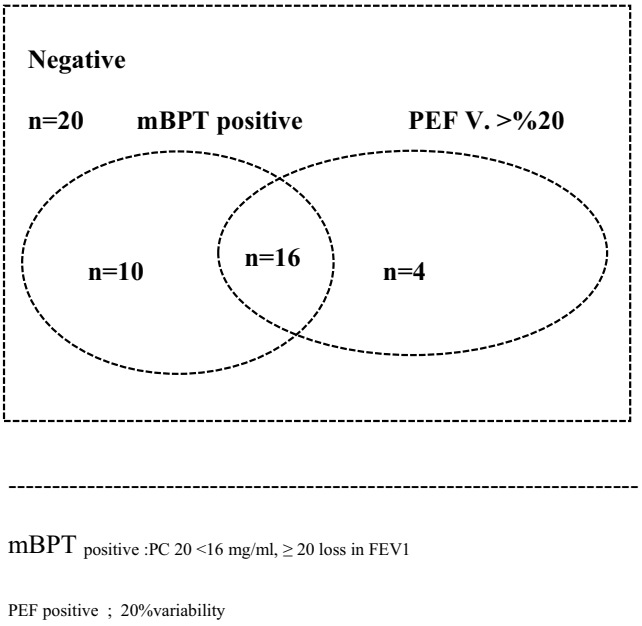

Figure 2 Results; BPT alone was positive in 10 of 30 asthma cases. Both mBPT positivity and PEF variability were positive in 16 cases. Only four out of 30 patients were diagnosed with asthma based on positive PEF variability. 20 patients were evaluated as non-specific respiratory symptoms. No treatment was given. At the end of the 1st month, 17 of the 30 treated patients attended visit 2. 13 patients did not attend visit 2. Treatment response of 17 patients was evaluated.

testing, FeNO or methacholine to diagnose asthma in adults. Furthermore, 73% of respondents reported that when they were first diagnosed with asthma, inhalation therapy was prescribed based on clinical parameters alone. Ambulatory peak expiratory flow (PEF) measurements were recommended for only 56% of asthma patients.10 In our study, similar to the literature, 39.2% of patients were diagnosed with over diagnosis of asthma despite a previous diagnosis of asthma.

Clinical use of standardised diagnostic algorithms and the development of new predictive biomarkers may help to reduce the prevalence of under diagnosis and over diagnosis of asthma.[8] Both traditional methods and innovative alternative pulmonary function tests should be investigated for use during these periods.[14] New digital health tools and mobile health technologies such as peak expiratory flow devices, electronic portable spirometers, portable exhaled nitric oxide meters, airwave oscillometry devices, and smart phone microphone spirometers have been proposed in the literature.[14]

Table 5 Correlation Rates Between Patients with BPT Positivity and Different Cut-off Values of PEF Variability

PEF Positivity in Those with mBPT(+)			Correlation of PEF Variability with mBPT		
PEF variability	**PEF (+)/BPT(+)**	**%**	**PEF variability**	**r**	**p**
>10%	26/26	100	>10%	0.307	0.03
>15%	23/26	88.5	>15%	0.530	<0.001
≥20%	16/26	61.5	≥20%	0.328	0.09
PEF variability	**Sensitivity**		**Specificity**		**CI**
≥20%	61.5%		83.3%		0.58–0.86
>15%	88.5%		62.5%		0.61–0.89
>10%	100%		16.7%		0.42–0.74

Notes: When BPT positivity is accepted as the gold standard in the diagnosis of asthma and Sensitivity and Specificity are evaluated for 3 different threshold values of PEF variability.
Abbreviations: PEF, Peak expiratory flow; mBPT, Methacolin bronchial provocation test; CI, Confidence interval.

Table 6 1st Month Control Results of Those Who Started Treatment with Asthma Diagnosis (n=17)

	$Visit_0$	$Visit_2$	p
FEV_1, mean (SD)	91.1 (14.6)	97.3 (16.9)	0.043
FVC, mean (SD)	91.9 (14.7)	97.9 (18.9)	0.021
PEF, mean (SD)	86.2 (12.1)	100.9 (10.2)	0.001
ACT, med (min-max)	14 (6–20)	22 (13–25)	0.001
SF-36 Physical function, med (min-max)	80 (20–100)	75 (40–100)	0.028
SF-36 PCS, mean (SD)	269.5 (86.6)	299.8 (61.6)	0.039
AQLQ, mean (SD)	148.3 (41.5)	162.1 (31.4)	0.028
Symptoms, mean SD	29.5 (8.9)	34 (6.4)	0.049
Activity restriction, mean SD	25.7 (6.1)	27.3 (5.5)	0.024

Note: SF-36 test components.
Abbreviations: MCS, Mental Component Score; PCS, Physical Component Score; ACT, Asthma Control Test; AQLQ, Asthma Quality of Life Questionnaire; SD, Standard Deviation.

In our study, no difference was found between the patient group with non-specific symptoms and the patient group with asthma in terms of symptom scores and quality of life questionnaires. Although the value of anamnesis in diagnosiswaswell recognised, it is important to assess patients' perceptions of their symptoms. Accordingly, symptoms should be confirmed by objective tests and asthma diagnosis based on clinical parameters alone should be a thing of the past.

Spirometry-based reversibility testing and detection of peak expiratory flow (PEF) variability by PEF metre monitoring can be used to reveal variable airway restriction. However, it is often not possible to demonstrate variable airway restriction by early spirometry-based reversibility testing, especially in patients with mild asthma in whom asthma symptoms are not prominent or are intermittent.[3] Diagnosis in this group is difficult and important due to studies on the rate of severe asthma attacks and mortality in patients with mild asthma.[3,15,16]

As emphasised in the guidelines, normal simple spirometric tests do not exclude the diagnosis of asthma.[3,17] In this situation, the most objective measurement, its applicability and cut-off value remain unclear.[6] Studies have showed that simple spirometry has a positive predictive value of 29% with a sensitivity of 53% and a negative predictive value of 77%.[18] In a similar study, the sensitivity, positive predictive value and negative predictive value of pre- and post-bronchodilator spirometry for the diagnosis of asthma were reported to be 49%, 85% and 29%, respectively.[9,17] In our study, there was no difference between the spirometrically diagnosed group and the non-specific symptomatic group in terms of baseline FEV_1, FVC, FEV_1/FVC, PEF ratios.

False negatives and false positives in the diagnosis of asthma can be reduced by performing direct and/or indirect mBPTs in individuals with asthma symptoms and normal respiratory examinations and spirometric tests.[19–22] Direct mBPT is a more useful test to exclude rather than diagnose asthma. Its value is higher than its positive predictive value. However, mBPTis mostly performed in specialised centres and is not easily accessible as it requires expertise and equipment and can only be performed by trained professional health assistants. This test, which has a preliminary preparation and confirmation phase, is impractical and cannot be used in pandemic-like situations.[9,20]

PEF measurement using a portable handheld device is an inexpensive option recommended by guidelines for the diagnosis of asthma and occupational asthma.[17] However, the optimal threshold for PEF variability remains unclear.[8] Several studies have also showed that serial measurements in asymptomatic children can be useful for early diagnosis, especially in those with a family history.[23] We believe that PEF measurements are valuable, reliable and more feasible in this and future life. With PEF measurements performed twice a day, daily PEF variability in healthy individuals was found to be 9% in adults and 12.3% in children with a 95% confidence limit.[3]

In our study, we found 100% sensitivity and 16.7% specificity when the threshold value of PEF variability in the diagnosis of asthma was a) >10%, b) 88.5% sensitivity and 62.5% specificity when it was >15%, and c) 61.5% sensitivity and 83.3% specificity when it was ≥20%. According to studies on the predictive value of PEF variability, after PEF monitoring with 5 measurements per day for 3 days in 100 stable asthmatic patients, a sensitivity of 64% and 51% and a specificity of 94.1% and 98.7% were found when the PEF variability threshold for the diagnosis of asthma was taken as 12.5% and 16.5%, respectively.[24] Similarly, in a study involving 122 asthma patients in Denmark, the sensitivity and specificity of >20% PEF variability for the diagnosis of asthma were found to be 39% and 58%, respectively.[25]

We believe that the diagnostic yield for PEF variability increases with a cut-off value of <15% to exclude the diagnosis of asthma and ≥20% to confirm the diagnosis of asthma.

We believe that baseline FEF_{25-75} measurement abnormality is an independent predictive factor that may be a predictor of asthma diagnosis when simple spirometry is available. Despite similar results presented by many studies, we think that it has not yet been included in the guidelines because it does not have a specific predictive value. FVC values, FEF_{25-75} and mBPT PD_{20} were associated with FEV_1 ($p < 0.001$). It was found that those with lower FEF_{25-75} values ($p < 0.001$) were more likely to have a positive mBPT test and that FEF_{25-75} may be a predictive marker in newly diagnosed asthma. When the demographic data and SFTs of 829 asthmatic patients over 18 years of age included in the SARP study[26] were analysed, low FEF_{25-75} was found to be an independent predictive factor for ICU admission, persistent symptoms, nocturnal symptoms, blood eosinophilia and AHR.[26,27] The limitation of our study may be that the FeNO test was not included because a similar study comparing peripheral eosinophilia and the combination of FeNO and mBPT in BDR-negative patients was performed in our clinic. We recommend using this combination as an exclusion test.[28]

The limitation of our study is the small sample size. This leads to a small number of subgroups. Our goal is to increase this number of patients. This was not possible due to the pandemic. The need for optimal testing for the diagnosis of asthma continues. Improvement of studies should be our goal.

Conclusions

The best method for diagnosing asthma and its predictive value are still uncertain. This leads to the problem of over- and under-diagnosis, which can be misleading when the diagnosis is based on symptoms and the patient's medical history. It is therefore important that variable airway obstruction is documented by objective diagnostic methods. Wheezing is a differential symptom for the diagnosis of asthma. In addition, FEF25-75 is an important predictive spirometric marker for the diagnosis of asthma in patients with symptoms compatible with asthma. The use of PEF meters should be promoted among specialists. We believe that the use of PEF variability with a threshold value of <15% to exclude the diagnosis of asthma or ≥20% to confirm the diagnosis will increase diagnostic yield.

Abbreviations

PEF, Peak Expiratory Flow; ACT, Asthma Control Test; PFT, Pulmonary Function Test; AQLQ, Asthma Quality of Life Questionnaires; SF36, Short Form 36; mBPT, Methacholin Bronchial Provocation Test; PC, Provocative Concentration; SAD, Small Airway Dysfunction.

Ethics Approval

We declare that our work is in conformity with the Declaration of Helsinki. Our study was approved by the ethics committee of Health Sciences University Kecioren Training and Research Hospital.

Funding

The authors did not receive support from any organization for the submitted work.

Disclosure

The authors have no relevant financial or non-financial interests to disclose for this work.

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