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Could FEF 25–75 levels or blood eosinophil counts predict the presence or absence of bronchial hyperreactivity?

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Abstract:

BACKGROUND AND AIM: The relationship between bronchial hyperreactivity (BHR) and lung function parameters and blood eosinophilia in suspected asthmatics is not clear. This study aimed to investigate the relationship between FEF 25-75 values and blood eosinophilia levels and BHR in patients with asthma symptoms.

MATERIALS AND METHODS: Demographic and spirometric data and blood eosinophil counts were compared between patients with and without significant BHR. Receiver operating characteristic (ROC) curve analysis was performed to evaluate FEF25–75 and blood eosinophil count cutoff values to distinguish BHR in these patients.

RESULTS: According to the data of 894 patients, with BHR in 182 (20.4%), FEF25%–75% were significantly lower and blood eosinophil counts were significantly higher in patients with BHR. The best discriminatory values to assess the nonevident BHR were 64.5% for FEF25–75 (sensitivity: 94.2% and specificity: 18.7%) and 164/μL for blood eosinophil count (sensitivity: 59.6% and specificity 60.2%). The rate of nonevident BHR was significantly different between patients with FEF25–75 <65% and ≥65% (54.7% and 81.9%, respectively, $P < 0.001$). Although significant, the rates of nonevident BHR in patients with blood eosinophil counts below and above the cutoff (85.5% and 72.6%, respectively, $P = 0.012$) were not as different as the rates in patients with FEF25–75 values below and above the cutoff.

CONCLUSION: FEF25–75 is associated with BHR in patients with asthma symptoms. Nonevident BHR is more likely if FEF25–75 ≥65 in suspected asthmatics. However, blood eosinophil count is not helpful in predicting the absence of BHR in suspected asthmatics.

Keywords:

Asthma, bronchial challenge test, eosinophilia, spirometry

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Introduction

Documentation of airflow limitation with variable airflow limitation is required for the diagnosis of asthma according to international guidelines. To document airflow limitation in patients with asthma symptoms, a low forced expiratory volume in 1 s/forced vital

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capacity (FEV1/FVC) ratio (<0.75–0.80 in adults) must be confirmed in at least one clinical visit. Documentation of a positive bronchodilator reversibility test is the most commonly appraised parameter to confirm the excessive variability in lung function for the diagnosis of asthma.[1] When no positive bronchodilator reversibility test is detected in patients with asthma symptoms, the bronchial provocation test is an alternative diagnostic method to document excessive variability in lung function.[1,2] Asthma diagnosis may be verified in patients if provocative concentration of methacholine producing a fall in FEV1 of 20% (PC_{20}) values are <4 mg/ml.[3]

With increasing awareness of the contribution of small airways in the pathogenesis of asthma, forced expiratory flow in 25%–75% of vital capacity (FEF25–75) measurements were suggested to be a more sensitive parameter compared to FEV1 for diagnosis and follow-up of asthmatics.[4-6] Impaired FEF25–75 may suggest bronchial hyperreactivity (BHR) in people who describe asthma symptoms. However, the main problem is that no guidelines are provided for finding normal FEF25–75 values.[7]

The eosinophilic inflammation is in part responsible for airway hyperreactivity. As for the increase in eosinophil counts and eosinophil activation markers in respiratory tract isolates, the increase in eosinophils in peripheral blood is also associated with asthmatic disease activity.[8-12] Eosinophilic airway inflammation may also be present in asthmatic patients with normal lung function and clinically well-controlled asthma.[13] Therefore, conventional assessments of airway obstruction may not be sensitive enough to reflect the extent of asthmatic activity.

This study was designed to evaluate the relationship between spirometric parameters, particularly FEF25–75 and blood eosinophil counts and BHR, in patients with asthma symptoms. More specifically, it was aimed to assess whether impairment of FEF25–75 and increased blood eosinophilia is related to a more severe BHR in suspected asthmatics with no apparent reversible airway obstruction in spirometric tests.

Materials and Methods

Data collection

A retrospective study was conducted to evaluate the data of patients who were examined for symptoms suggestive of asthma and underwent methacholine challenge test in an outpatient clinic of a tertiary chest diseases hospital between January and December 2017. Adult patients aged 18–80 years with complete spirometric data in the file information were included in the study. Demographic data, spirometric values, and blood eosinophil levels of the patients were obtained from the hospital files. PC_{20} values below 4 mg/ml in methacholine challenge tests were considered as significant BHR.[3]

Outcome measures

Demographic and spirometric data and peripheral blood eosinophil counts were compared between patients with and without significant BHR. The relationship between lung function parameters and peripheral blood eosinophil count and significant BHR was evaluated. Discriminative values of FEF25%–75% and eosinophil counts for nonevident BHR were assessed.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation, and categorical variables were expressed as numbers (percentages). For comparisons, independent student's *t*-test and Chi-square test were used for continuous and categorical variables, respectively. The relationship between the presence of BHR and continuous variables was evaluated by Spearman's correlation coefficient. A receiver operating characteristic (ROC) curve analysis was performed to assess the ability of the FEF25%–75% and peripheral blood eosinophil count levels to determine the absence of BHR. All statistical tests were two sided, and $P < 0.05$ was considered statistically significant. The analyses were performed using Statistical Package for the Social Sciences, IBM Corp., Armonk, NY, USA version 22.

Standard protocol approvals

The study was approved by the Ankara Keçiören Educational Research Hospital Clinical Research Ethics Committee (December 21, 2018/614).

Results

The present study included 894 adults with a median age of 44 years (range: 58 years) and the gender distribution of 581 females (65.0%) and 313 males (35.0%). Among the study population, 182 patients (20.4%) had significant BHR. While age and body mass index of patients with and without significant BHR were not different significantly, the proportion of females was significantly higher among patients with significant BHR compared to those without significant BHR ($P = 0.002$). Peripheral blood eosinophil counts were present in the file information of 258 patients. All spirometric values, including FEV1, FVC, and FEF25–75 values, were significantly lower in patients with significant BHR compared to those without significant BHR, and mean blood eosinophil counts were significantly higher [Table 1]. Evaluation of the relationship between lung functions and blood eosinophil counts and significant BHR revealed that FEF25–75 and FEF25%–75% values are weak to moderately related to

Table 3: Comparison of forced expiratory flow at 25%-75% of the forced vital capacity and blood eosinophil count values between patients with and without significant bronchial hyperreactivity

	Patients with significant BHR (*n*=182), *n* (%)	Patients without significant BHR (*n*=712), *n* (%)	*P*
FEF25%-75%			
<65	34 (45.3)	41 (54.7)	<0.001***
≥65	148 (18.1)	671 (81.9)	
Blood eosinophil count (/μL)	*n*=52	*n*=206	
≤164	21 (14.5)	124 (85.5)	0.012**
>164	31 (27.4)	82 (72.6)	

P significant at levels of **$P<0.05$, ***$P<0.001$. FEF25%-75%: Forced expiratory flow at 25%-75% of the forced vital capacity, BHR: Bronchial hyperreactivity. Chi-square test

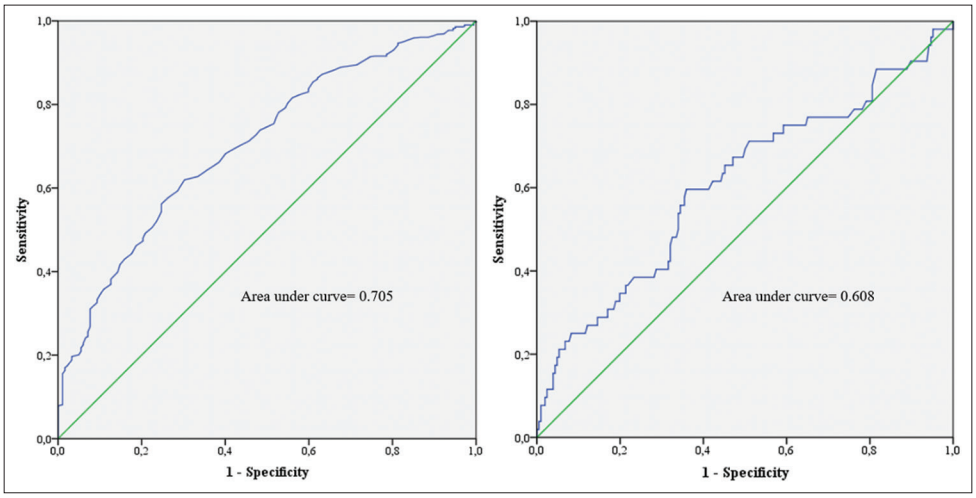

Figure 1: Receiver operating characteristic curves of force expiratory flow 25–75 measurement and eosinophil count in the diagnoses of bronchial hyperreactivity

for newly diagnosed asthma when conventional spirometry parameters are normal.[7,16] Studies have been conducted on whether impaired FEF25–75 values can be used in the early diagnosis of asthma, as it reflects small-airway obstruction. It was reported that FEF25%–75% predicted was well correlated with bronchodilator responsiveness in asthmatic children with normal FEV1 and that FEF25%–75% may be clinically relevant in predicting reversible airflow obstruction.[17] Two previous reports suggested that FEF25%–75% could potentially be a predictor of BHR. Patients with a positive methacholine challenge test were reported to have significantly lower FEF25%–75% compared to those with negative test results, and a low FEF25–75 could potentially predict BHR.[7,16] In the study conducted by Raji *et al*., to determine the relationship between baseline FEF25–75 and BHR, a FEF25–75 cutoff value was not found to distinguish patients with and without hyperreactivity.[7] In our study, patients with FEF25–75 ≥65% had significantly higher rates of cases without significant BHR than those with FEF25–75 <65%. Although the threshold value of FEF25–75 with high sensitivity and specificity could not be found in this study, the sensitivity of FEF25–75 values above 64.5% indicating the absence of significant BHR was found to be 94.2%. On the other hand, due to the low specificity of this threshold value, it was determined that FEF25–75 values below 64.5% could not indicate the presence of BHR. In a multicenter study, investigating whether the use of FEF25%–75% and FEF75% in spirometric examination adds more information than the FEV1, FVC, and FEV1/FVC ratio, it was concluded that it did not provide any superiority in clinical decision-making.[18]

Eosinophilia is another parameter that reflects asthmatic activity.[10-12] However, the relationship between blood eosinophilia and BHR is not fully enlightened. In 2000, Gibson *et al*. have reported that airway responsiveness is associated with the severity of airway inflammation in asthmatics.[19] Furthermore, a strong association was reported between peripheral eosinophilia and airway hyperresponsiveness assessed by methacholine challenge test.[20] In our study, mean blood eosinophil counts were significantly higher in patients with significant BHR compared to those without significant BHR. However, the threshold value of the blood eosinophil count to indicate the absence of significant BHR, calculated as 164/μL by ROC analysis, had a sensitivity of only 59.6% and a specificity of only 60.2%. Therefore, no cutoff value of the blood eosinophil count was determined to be relevant in predicting BHR in patients with suspected asthma.

The major limitation of the present study is the lack of long-term follow-up of patients to assess the development of overt asthma and the course of patients' asthma-related symptoms.

Conclusion

The present study demonstrates that FEF25–75 is associated with BHR in patients with asthma symptoms. It is more likely that BHR is not present in suspected asthmatics if FEF25–75 levels are ≥65. A FEF25–75 value above 65% in spirometric examination performed in patients with suspected asthma can rule out asthma, however with a low specificity.

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Conflicts of interest

There are no conflicts of interest.

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