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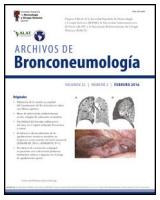

Scientific Letter

Identification of Fractional Exhaled Nitric Oxide Cutoff Values for the Diagnosis of Asthma

To the Director,

Despite the acknowledged importance of establishing a timely and accurate diagnosis, asthma diagnosis remains a challenge in clinical practice. The heterogeneity of symptoms, overlapped with other respiratory conditions, contribute to the complexity of achieving a definitive diagnosis.[1] Fractional exhaled nitric oxide (FeNO) has been established as a non-invasive quick test supporting the diagnosis of asthma in an adequate clinical context. However, the inherent variability in its measurement, as well as the influence of external factors on its results, has made its applicability a challenge. The recommended cutoff points vary between 20 and 50 ppb, depending on patient characteristics, the prevalence of atopy, and other confounding factors such as smoking status or concurrent respiratory conditions.[2–9] The current GEMA guideline recommends a cutoff of 40 ppb, although earlier versions of the guideline suggested values ranging between 30 and 50 ppb.[1] Further studies are needed to explore the cutoff value of FeNO in a clinical context of suspected asthma. The present study aims to evaluate the diagnostic profile of FeNO for asthma in adults referred from primary care and to determine the optimal FeNO cut-off points that balance sensitivity and specificity.

We conducted a prospective, multicentric study in two specialized asthma unit of two hospitals in Southern Spain, and 37 associated primary healthcare centers. The study was approved by the hospital Clinical Research Ethics Committee (approval act 019/2007) and patients signed a written informed consent prior to the inclusion in the study. We included all patients aged over 14 years consecutively referred from primary care to the specialized asthma units between 2009 and 2011 with a symptom history suggestive of asthma. Exclusion criteria included other respiratory diseases (e.g., COPD, bronchiectasis), >10 pack-years smoking history, oral/inhaled corticosteroid or leukotriene antagonist use, and symptoms of acute respiratory infection within four weeks prior to evaluation. Each patient attended three visits at the unit. At the first visit, patients underwent an initial assessment including: clinical variables (symptoms, demographics variables and previous treatments), allergy sensitization-testing (total and specific IgE levels and skin prick tests), hemogram, FeNO measurement and pulmonary functional tests (spirometry with bronchodilator tests, and in cases where the result was negative, methacholine/mannitol tests). During the subsequent two visits (one month and six months after), pulmonary function tests were repeated to confirm diagnosis. The diagnosis of asthma was established at the end of the end of the follow-up based on current recommendations[1] including one of: (1) a positive response bronchodilator test ($\geq$12% and $\geq$200 mL increase in the predicted value for FEV_1 or FVC), (2) a positive mannitol test (15% drop in FEV_1 compared to baseline or an incremental decrease in $FEV_1 \geq 10\%$ between two consecutive doses) or (3) a documented response to corticosteroid therapy, identified as a normalization of the spirometry pattern and clinical improvement after treatment with systemic glucocorticoids (prednisone 40 mg/day or equivalent) or 2–8 weeks of inhaled glucocorticoids (1500–2000 mg/day of fluticasone propionate or equivalent).

We analyzed the differences between asthmatics and non-asthmatics groups, using *t*-test for independent samples for quantitative variables, the Mann–Whitney *U* test for ordinal variables or Wilcoxon test for paired samples. Chi-square analysis was employed for differences in qualitative variables. Analyses of Receiver Operating Characteristics (ROC) curves were conducted to determine the diagnostic accuracy of FeNO. The optimal cut-off value was obtained based on the highest Youden index, identifying the threshold that maximizes sensitivity and specificity. The diagnostic profile of the ROC curve was assessed by calculating the area under the curve (AUC), reported along with its 95% confidence interval (CI) to provide a range of uncertainty for the estimated value. Additionally, The Fagan's Nomogram was use to help in calculating the post-test probability based on the pre-test probability and the likelihood ratio derived from the diagnostic test.

During the study period, 133 patients finally met the inclusion criteria. Of them, 92 were diagnosed with asthma, with 66.3% of the diagnoses made by bronchodilator test, and 33.7% based on a positive bronchoconstriction test. The characteristics of both groups are summarized in Table 1. Significant differences were observed between the groups in smoking habits and FeNO, with a higher percentage of non-smokers and a lower FeNO value in the non-asthmatic group. FeNO values were slightly lower in active smokers asthmatics but with differences not reaching the pre-specified statistical significant threshold (asthmatics active smokers 31.7 ppb vs the rest of the asthmatics 43.0 ppb; $p = 0.129$). Significant differences were also seen in functional parameters, with a higher prebronchodilator FEV_1 in non-asthmatics, a higher FEV_1/FVC and lower reversibility. In non-asthmatics, the final diagnoses were allergic rhinitis in 9 patients (24.39%); postnasal drip of unclear etiology in 20 patients (48%); extended postviral respiratory syndrome in 4 patients (9.8%); vasomotor rhinitis in 2 patients (4.87%); gastroesophageal reflux disease in 4 patients (9.75%); and vocal cord dysfunction in a single patient (2.4%).

Fig. 1 illustrates the ROC curve for FeNO values, demonstrating a significant AUC of 0.806 (95% CI: 0.734–0.879, $p < 0.001$). It additionally demonstrates Fagan's nomogram, showing the post-test probability of being asthmatic (97%) based on the pre-test probability (69.17%) and the positive likelihood ratio[15] of the FeNO test and the distribution of FENO values in both groups. The optimal FeNO cutoff value for asthma diagnosis, based on Youden index, was >22 ppb, showing a sensitivity of 71.7% (95% CI: 61.8–79.9) specificity of 95.1% (95% CI: 83.9–98.7), a positive predictive value

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Table 1
Population Characteristics (Asthmatics and Non-Asthmatics Patients).

	Non-asthmatics ($N=41$)	Asthmatics ($N=92$)	p-Value*
Age (years)	38.1(11.4)	34.6 (11.7)	0.106
Gender (female)	20 (48.8%)	58 (63.0%)	0.384
Smoking habit			**0.025**
Smoker	5 (12.2%)	26 (28.2%)	
Non-smoker	27 (65.8%)	38 (41.3%)	
Ex smoker	9 (21.9%)	28 (30.4%)	
Pack-year index	2.23 (4.8)	3.4 (3.4)	0.141
Body mass index (kg/m^2)	26.4 (4.9)	26.25 (5.3)	0.892
Atopy (yes)	20 (48.8%)	58 (63%)	0.123
Asthma control test	19.03 (4.8)	16.5 (5.6)	**0.030**
FeNO	14.23 (5.3)	39.8 (29.6)	**<0.001**
Eosinophils (cells/μl)	224.85 (123.9)	252.0 (213.9)	0.490
FVC pre-bronchodilator (%)	106.1 (12.7)	106.7 (16.4)	0.816
FVC post-bronchodilator (%)	105.8 (12.5)	108.7 (14.1)	0.790
FEV$_1$ pre-bronchodilator (%)	102.5 (12.5)	88.6(15.5)	**<0.001**
FEV$_1$ post-bronchodilator (%)	105.4 (12.3)	99.8(15.6)	**0.060**
FEV$_1$/FVC pre-bronchodilator (%)	81.6 (4.6)	71.2(10.8)	**<0.001**
FEV$_1$/FVC post-bronchodilator (%)	84.2 (5.2)	77.7 (9.1)	**<0.001**
FEV$_1$ reversibility (%)	3.14 (3.36)	13.8 (9.4)	**<0.001**

BMI: body mass index; ACT: asthma control test, FeNO: exhaled nitric oxide; FVC: forced vital capacity; FEV$_1$: forced expiratory volume in 1 second.
* Calculated by Student's *T*-test or Chi-square test according to the nature of the variable.

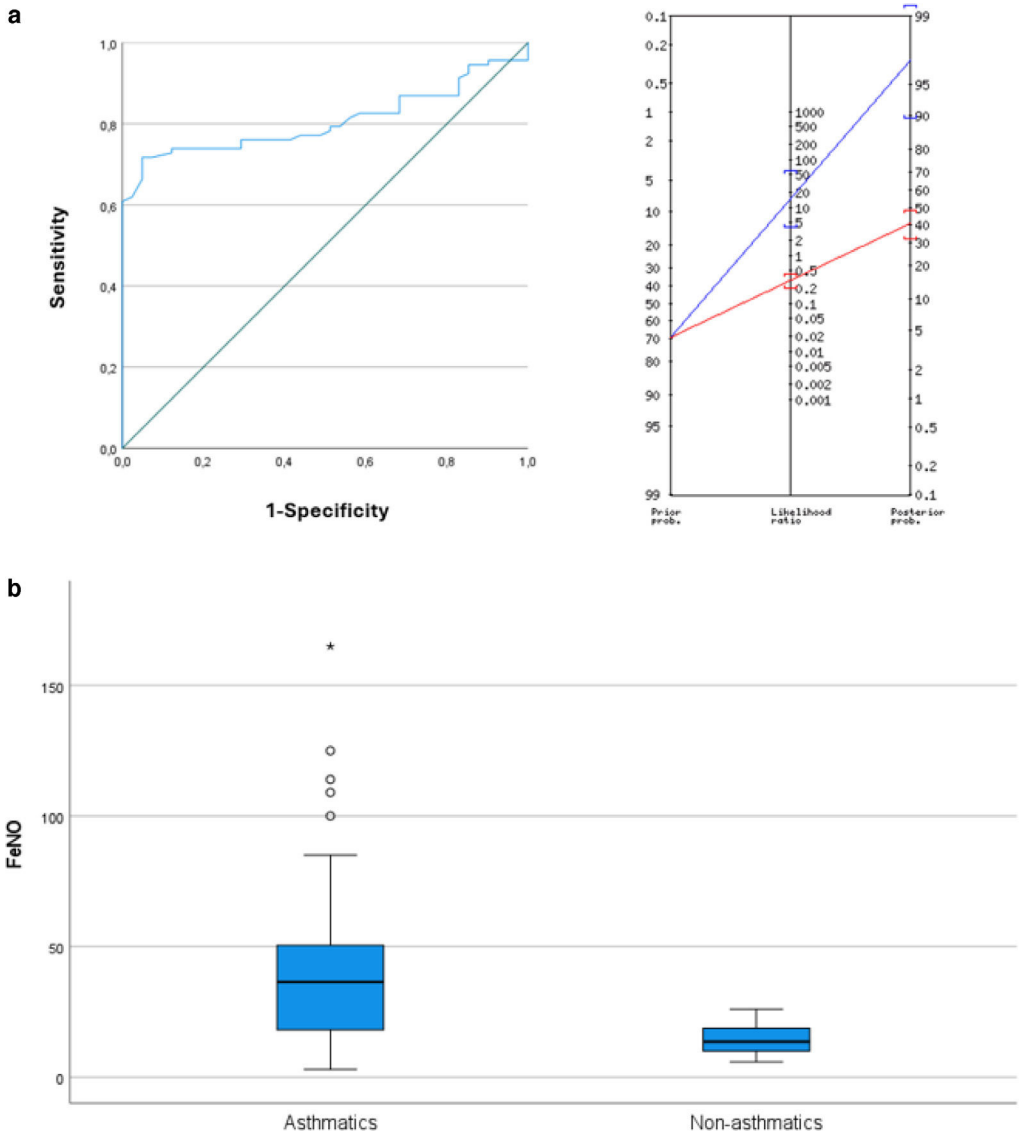

Fig. 1. (a) ROC curve of FeNO measurement for predicting asthma AND Fagan's nomogram. (b) Distribution of FeNO levels in asthmatics and non-asthmatics.

of 97% (95% CI: 89.9–99.2), and a negative predictive value of 60% (95% CI: 47.9–71).

The results of this study exhibit that FeNO is a valuable tool for diagnosing asthma, with an optimal cutoff value of >22 ppb, providing robust diagnostic accuracy. Notably, the high specificity (95.1%) and positive predictive value (97%) of the FeNO test suggests its usefulness in confirming asthma diagnosis in patients with a high pre-test probability. However, the lower negative predictive value (60%) highlights its limited power to exclude asthma. In this regard, the utility of FENO in the diagnosis of asthma is to confirm the disease, as recorded in the current recommendation documents.[1] The potential role of FENO in ruling out asthma is considerably more controversial, as we know that different types of asthma can present with decreased FENO levels.

Our results reveal a FENO cutoff point for asthma diagnosis that is lower than those reported in previous similar studies[10–13] and recommended in guidelines.[1] This discrepancy may be attributed to some methodological and contextual factors. Unlike previous studies that included heterogeneous populations, our study exclusively involved treatment-naïve patients referred from primary care. In particular, high-consumption smokers and patients with relevant environmental exposure were excluded, a population which may show different FENO values. Additionally, our sample may consist of individuals with lower exposure to allergens or pollutants, influenced also by the geographic location, in comparison for example with the study developed by Cordeiro et al.,[12] which was conducted on patients of an allergy clinic,

Our findings align with previous studies that propose lower thresholds in real-world populations, particularly in corticosteroid-naïve patients or those with mild disease severity.[14,15] Furthermore, Schneider et al.,[16] in a systematic review, proposed varying optimal FENO cutoffs depending on pre-test probability, supporting lower thresholds in primary care settings. Guo et al.[17] confirmed FENO's reduced accuracy in smokers and corticosteroid-treated patients, reinforcing the need for context-specific interpretation.

The study's strengths include its multicentric, prospective design and stringent inclusion criteria, ensuring robust data. However, these criteria may limit applicability to broader populations. It is also remarkable that a significant proportion of the population (over 66% of asthma diagnoses) was diagnosed based on a positive bronchodilator test, while the remainder was diagnosed using a bronchoconstriction test, which is significant as it is higher in comparison with other published studies.[14,15,18] The high percentage of diagnoses by the bronchodilator test could be attributed to the inclusion criteria, as every patient should not have received previous corticosteroid treatment. It is also worthy to highlight as a limitation that we used the bronchodilation criteria established at that time, while in 2021 the European Respiratory Society and the American Thoracic Society updated their guidelines, redefining the criteria as an increase in FEV_1 or FVC of $\geq$10%[19] and as it is observed in some studies, the prevalence of bronchodilator responsiveness increase significantly when using the new definition compared with the previous one.[20] Finally, we explored the different behavior of FENO by gender, but we found a similar diagnostic profile (data not shown).

In conclusion, our findings emphasize the clinical utility of FENO as an accessory diagnostic tool for asthma, particularly in patients with a high pre-test probability. Nevertheless, its limited negative predictive value restricts its ability to exclude asthma. Future research should validate these findings in larger and more diverse populations to reconsider the current accepted cutoff values in different clinical contexts.

Artificial Intelligence Involvement

No material has been partially or totally produced with the help of any artificial intelligence software or tool.

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Conflicts of Interest

The authors declare not to have any conflicts of interest that may be considered to influence directly or indirectly the content of the manuscript.

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