

# Comparison of fractional exhaled nitric oxide, spirometry, and Asthma Control Test, in predicting asthma exacerbations: A prospective cohort study

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## ABSTRACT

**Context:** Fractional exhaled nitric oxide (FeNO) is a noninvasive test for airway inflammation in asthma. The usefulness of FeNO in predicting exacerbations is uncertain. **Aims:** The study aims to assess and compare the ability of FeNO, spirometry, and asthma control test (ACT) in predicting future exacerbations of asthma and their correlation with each other. **Settings and Design:** This prospective, cohort study was conducted at the Department of Respiratory Medicine, Kasturba Medical College, Manipal. **Materials and Methods:** Adult asthma patients of age 18–65 years were included. Patients with a smoking history of >10 pack-years and those in whom spirometry was contraindicated were excluded. Patients who consented underwent FeNO and spirometry. The control of asthma was assessed using the ACT questionnaire. We captured the number of exacerbations in the follow-up period of 4 months. **Statistical Analysis Used:** Mann–Whitney test was used to compare the utility of FeNO, spirometry, ACT in predicting exacerbations and Spearman's correlation coefficient was used to ascertain the correlation among them. **Results:** Of 154 study patients, 28% had exacerbations. We found that there was no significant difference in FeNO in patients with and without exacerbations. The median (interquartile range [IQR]) FEV1% in the patients with and without exacerbations were 68 (55–79) and 75 (65–88), respectively ( $P = 0.013$ ). The median (IQR) ACT score in patients with exacerbations was 12 (10–16) which was significantly lower than in those without exacerbation in whom it was 16 (14–18) ( $P = 0.003$ ). There was a negative correlation of ACT with FeNO (Correlation coefficient:  $-0.167$ ,  $P = 0.038$ ). The median (IQR) FeNO level (ppb) was lower in patients who were on inhaled corticosteroid (ICS) than in the other group values being 22 (14–38) and 30 (17–58), respectively ( $P = 0.05$ ). **Conclusions:** In our study, FEV1% and ACT score could predict exacerbations of asthma whereas FeNO could not. FeNO level correlated inversely with ACT score. FeNO level decreased with inhaled corticosteroid usage.

**KEY WORDS:** Asthma, asthma control test, asthma exacerbation, fractional exhaled nitric oxide, inhaled corticosteroid, spirometry

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## INTRODUCTION

Asthma is a chronic inflammatory disorder of the respiratory system, characterized by airway hyper-responsiveness, which in turn leads to recurrent episodes of wheezing, breathlessness, chest tightness and cough, in particular at night or early morning.<sup>[1]</sup> Deaths due to asthma are uncommon but are of serious concern because many of them are preventable. Reducing flare-ups is also vital for a better quality of life.

The immediate objective of asthma treatment is to achieve and maintain control of symptoms. The asthma control test (ACT) scoring, levels of fractional exhaled nitric oxide (FeNO), and spirometry can adequately assess severity and symptom control in asthmatics. FeNO is a reliable, noninvasive and reproducible test for discerning airway inflammation in patients of asthma that correlates with disease activity. The role of FeNO as a predictor of asthma exacerbations is uncertain.<sup>[2]</sup> The data comparing airway inflammation with conventional measures of asthma severity in Indian adult asthmatics is sparse.

The study aimed to assess and compare the ability of FeNO, spirometry, and ACT in predicting future exacerbations of asthma and their correlation with each other.

## MATERIALS AND METHODS

The study population consisted of patients with asthma, aged 18–65 years, from the outpatient and inpatient departments of Respiratory Medicine, Kasturba Medical College, Manipal. Asthma was diagnosed based on GINA guidelines.<sup>[1]</sup> We excluded patients with a smoking history of more than 10 pack-years; those who could not perform spirometry; those in whom spirometry was contraindicated such as hemoptysis and pneumothorax, “recent” myocardial infarction or pulmonary embolism; thoracic, abdominal or cerebral aneurysms; “recent” eye surgery; recent thoracic or abdominal surgery; and pregnancy. The term “recent” was defined as the occurrence of the event within 4 weeks of recruitment. The Institutional Ethics Committee (IEC number - 672/17, Clinical Trial Registry of India (CTRI) number-CTRI/2018/06/014666) approved our prospective cohort study. The study was conducted from June 2018 to July 2019. The written informed consent was obtained from all patients.

We collected the demographic and clinical data of patients such as age, sex, clinical diagnosis, duration of asthma, corticosteroid use, comorbidities, blood parameters such as hemoglobin, total leukocyte count, differential cell counts, and absolute eosinophil count.

All patients underwent FeNO and spirometry. Spirometry and FeNO were performed as per the American Thoracic Society (ATS) guidelines.<sup>[3]</sup> Spirometry was performed to determine forced expiratory volume in 1 s (FEV1),

forced vital capacity (FVC), and FEV1/FVC ratio. FENO measurement was made using a portable chemiluminescence analyzer (BreathFLO, Bedfont, London). The ACT Questionnaire, validated by the ATS, was used to assess the symptom score.<sup>[4]</sup>

We followed the patients for 4 months and captured the details of the worsening of symptoms and unplanned hospitalizations. The data were extracted either from history or by reviewing hospital records of the patient.

## Statistics

Anticipating at least 30% of asthma patients to go for one or more physician visits in 4 months, and assuming a sensitivity of 70% for the tests, with a 95% confidence, a sample size of 154 asthma patients was estimated. The data were analyzed using SPSS software version 25.0 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY, USA: IBM Corp.). Test of normality was done using the Shapiro–Wilk test. Significant values concerning multiple parameters indicated skewed distribution. Thus, Mann–Whitney U test for the binary outcomes was used for the assessment of FeNO, spirometry, ACT in patients with and without exacerbations. Spearman’s correlation coefficient was used to analyze correlations between FeNO, spirometry, ACT, and number of exacerbations.

## RESULTS

Our study population comprised of 154 patients. The mean age of the population was 44 years, ranging from 18 to 65 years. The population size included 154 patients with 67 male (43.5%) and 87 female (56.5%) [Table 1].

Most of the patients were poorly controlled asthma with a mean ACT score of 14.8. 81 (52.6%) patients were on inhaled steroids (ICS) whereas 73 (47.4%) patients were not on ICS [Figure 1]. Fifty-eight (37.7%) patients had allergic rhinitis as comorbidity.

At the end of 4 months of follow-up, 43 (38.7%) patients had exacerbations. When we compared the age of the subjects to FeNO, FEV1%, and ACT score using Spearman’s correlation coefficient ( $r = -0.20$ ,  $-0.30$ , and  $-0.19$ , respectively) we found a significant negative correlation with all the three parameters ( $P < 0.05$ ). On comparison

**Table 1: Baseline data for 154 patients**

Variable	Mean±SD	Median and IQR
Age (years)	44.09±13.13	45.0 (35.0-55.3)
FEV 1 (%)	72.62±17.96	72.0 (60.8-86.0)
FeNO (ppb)	36.29±34.38	25.0 (15.0-44.0)
ACT-SCORE	14.81±2.89	14.0 (12.0-18.0)
Duration of asthma (years)	7.01±7.58	5.0 (2.0-10.0)

IQR: Interquartile range, FEV1: Forced expiratory volume in the 1 s, FVC: Forced vital capacity, FeNO: Fraction of exhaled nitric oxide, ppb: Parts per billion, ACT score: Asthma Control Test score, ICS: Inhaled corticosteroid, SD: Standard deviation

of the gender groups, we found that FeNO was higher in males when compared to females but not statistically significant ( $P = 0.67$ ).

We found that the FeNO levels median (interquartile range [IQR]) were lower in patients with exacerbations (22 [15–61]) compared to patients without exacerbations (25 [15–43]), but this difference was not statistically significant ( $P = 0.7$ ) [Table 2]. We also observed that there was a statistically significant difference in FEV1% values when we compared the patients having exacerbations in whom median (IQR) FEV1% predicted was 68 (55–79) in comparison with those without exacerbations who had a median (IQR) FEV1% predicted of 75 (65–88) ( $P = 0.013$ ). ACT scores in patients with exacerbations were significantly lower, with a median (IQR) of 12 (10–16), while patients without exacerbations had a median (IQR) of 16 (14–18), the difference being statistically significant ( $P = 0.003$ ).

We observed a poor positive correlation of FEV1% with FeNO, which was not statistically significant (correlation coefficient 0.031). There was a poor negative correlation of ACT with FeNO, which was statistically significant (correlation coefficient  $-0.167$ ). The duration of asthma showed no correlation with FeNO, FEV1%, and ACT [Figure 2]. FeNO showed a fair positive correlation with absolute eosinophil count (correlation coefficient 0.247) [Figure 3]. There was no significant correlation between AEC to either FEV1% or ACT score.

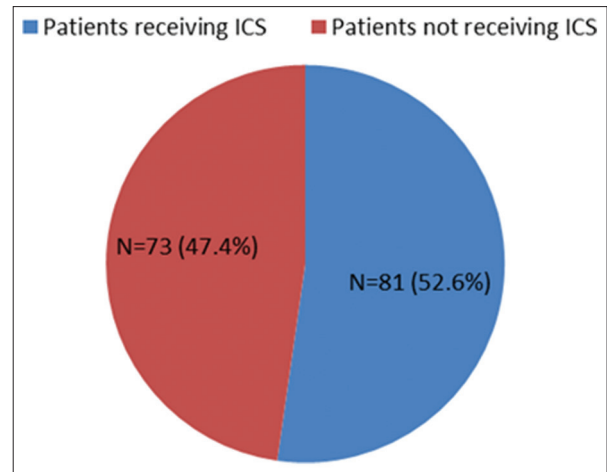
The difference in FeNO, ACT, and FEV1 values in patients with and without allergic rhinitis was not statistically significant.

In our study, we found a statistically significant difference in FeNO, FEV1%, and ACT score in between populations receiving ICS and not on ICS. Levels of FeNO were lower in patients on ICS (median [IQR], 22 [14–38]) when compared to patients who were not on ICS (30 [17–58]) ( $P = 0.050$ ). FEV1% was lower in patients on ICS (median 69, IQR 57–82) in comparison to (median 78, IQR 68–90) those who were not on ICS ( $P = 0.003$ ). The ACT score was lower in the population on ICS [median (IQR), 14 (12–16)] than those who were not on ICS [median (IQR), 16 (14–18)] ( $P < 0.001$ ) [Table 3].

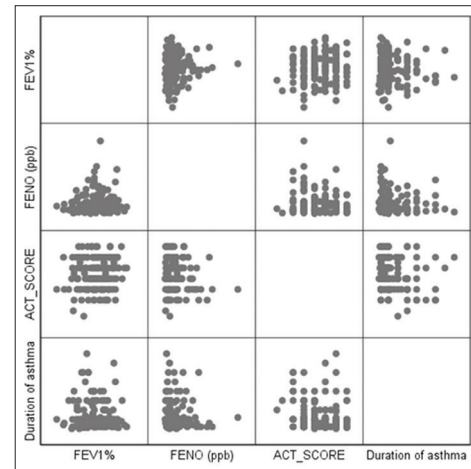
## DISCUSSION

Our study showed that FeNO to be less useful in predicting exacerbations of asthma compared to FEV1% and ACT scores. Lung function and asthma control assessment tests proved independent predictors of asthma exacerbations as per prior studies.<sup>[5-7]</sup>

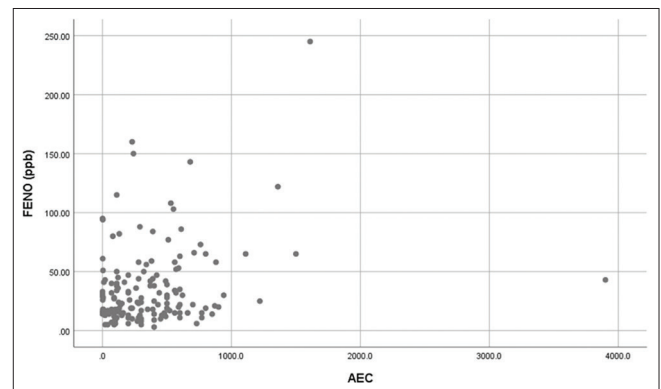
The FeNO level, in our study, did not predict exacerbations of asthma. The result was in concordance with other studies.<sup>[8,9]</sup> Van Vliet *et al.* found that FeNO was not



**Figure 1:** Population distribution with respect to history of treatment with ICS



**Figure 2:** Scatterplot showing the correlations between FeNO, FEV1%, ACT score as measured by Spearman's correlation coefficient. Significant correlation between FeNO and ACT score: Correlation co-efficient = 0.167 ( $P = 0.038$ ). FEV1 = Forced expiratory volume in the first second, FeNO = Fraction of exhaled nitric oxide, ppb = parts per billion, ACT score = Asthma control test score



**Figure 3:** Scatterplot showing correlation between FeNO and AEC. Correlation co-efficient = 0.247 ( $P = 0.002$ ). FeNO = Fraction of exhaled nitric oxide, ppb = parts per billion, AEC = Absolute eosinophil count

**Table 2: Comparison of the variables between the presence and absence of the exacerbation using Mann-Whitney U-test**

	Exacerbation	Count	Median and IQR	Mann-Whitney U	P
FENO (ppb)	Absent	111	25 (15-43)	2291	0.7
	Present	43	22 (15-61)		
FEV1 (%)	Absent	111	75 (65-88)	1768	0.013
	Present	43	68 (55-79)		
ACT score	Absent	111	16 (14-18)	1654.5	0.003
	Present	43	12 (10-16)		

Significant difference  $P < 0.05$ . IQR: Interquartile range, FEV1: Forced expiratory volume in the 1 s, FeNO: Fraction of exhaled nitric oxide, ppb: Parts per billion, ACT score: Asthma control test score

**Table 3: Comparison of fraction of exhaled nitric oxide, forced expiratory volume in the one second, and asthma control test score scores with the use of steroid using Mann-Whitney U-test**

	Count	Median and IQR	Mann-Whitney U	P
FENO (ppb)				
ICS				
No	81	30 (17-58)	2415.5	0.050
Yes	73	22 (14-38)		
FEV1 (%)				
ICS				
No	81	78 (68-90)	2143.5	0.003
Yes	73	69 (57-82)		
ACT score				
ICS				
No	81	16 (14-18)	1943.5	<0.001
Yes	73	14 (12-16)		

Significant difference  $P < 0.05$ . IQR: Interquartile range, FEV1: Forced expiratory volume in the 1 s, FeNO: Fraction of exhaled nitric oxide, ppb: Parts per billion, ACT score: Asthma control test score, ICS: Inhaled corticosteroids

useful either independently or in combination with symptom scores in predicting exacerbations in asthmatic children.<sup>[10]</sup> However, a prospective study of 109 asthma patients over 3 years by Kimura *et al.* demonstrated that FeNO can predict future exacerbations irrespective of the past exacerbation history.<sup>[11]</sup> FeNO has also been shown to predict loss of asthma control, particularly when clubbed with positive bronchodilator reversibility.<sup>[12]</sup>

The utility of a single baseline FeNO is unestablished. Single baseline FeNO level as well as FEV1% were not related to asthma outcomes at the end of 3 months, as per a meta-analysis of seven randomized control trials in children by Fielding *et al.*<sup>[13]</sup>

In this study, ACT score correlated negatively with FeNO, in contrast to a previous study by Menzies *et al.*<sup>[14]</sup> Those patients with poorer control of asthma had higher FeNO levels. The higher FeNO levels could be due to noncompliance of the patient to medications or a need to step up asthma treatment in the patient. FeNO though not a predictor of exacerbations, could be a marker of poor symptom control.

We observed a negative correlation between the percentage of predicted FeNO level and FEV1%, but it was not

statistically significant. This finding is in agreement with the study by Mogensen *et al.*, where they found elevated FeNO and blood eosinophils were associated with poorer lung functions but not increase in asthma exacerbations.<sup>[15]</sup> While FeNO level indicates airway inflammation directly, FEV1 indicates it indirectly. FEV1 and other spirometry measurements are more efforts dependent than FeNO. In a study conducted on asthmatic children, Mappa *et al.* found that FeNO did not correlate with spirometry measurements.<sup>[16]</sup> Another study showed that though FeNO did not correlate with FEV1 or asthma control it is useful in the early diagnosis of asthma.<sup>[17]</sup>

Kavitha *et al.* showed that FeNO negatively correlated with FEV1% and ACT score.<sup>[18]</sup> In addition, FeNO, FEV1 correlated negatively with the duration of asthma. The decline in FEV1 may be due to the progression of the disease and the decrease in airway caliber. The decrease in FeNO maybe because of the long duration of ICS. Perhaps, this can be explained by the non-Th2 inflammation phenotype with more severe asthma and the absence of eosinophilic markers.<sup>[19]</sup>

A study by Shrestha *et al.* showed that IgE correlated well with FeNO and AEC, but the correlation between FeNO and AEC was weak and FeNO was more sensitive as well as specific compared to IgE and AEC to identify asthma and atopy.<sup>[20]</sup> In our study, FeNO correlated well with absolute eosinophil count. Asthma phenotypes are going to be the basis of asthma care in future. FeNO could be a promising marker of the eosinophilic phenotype, due to its noninvasive nature, and simplicity.

FeNO level increased with the advancement of age, according to the present study. The previous studies have shown inconsistency in the variation of FeNO with age. A few studies had shown an increase in FeNO with age.<sup>[21,22]</sup> According to a study from Thailand, FeNO increased up to 11–15 years and then decreased with age, in adults <47 years.<sup>[23]</sup>

The study showed that the FeNO level was higher in male compared to female, but this difference was not statistically significant. This is in agreement with a prior study, which suggests FeNO is higher in male compared to the female population.<sup>[21]</sup> According to a study to set up reference values for FeNO in nonsmoker healthy adults by Olin

*et al.*, age and height were determining factors, but FeNO was independent of gender.<sup>[22]</sup>

Low FeNO level, FEV1%, ACT score were noted in the subset of patients on ICS. Corticosteroids suppress inflammation and consequently reduce the levels of FeNO. This result is in agreement with previous studies that have stated the usefulness of FeNO in predicting steroid responsiveness.<sup>[24]</sup> ATS guideline recommends the use of FeNO in guiding asthma treatment in terms of steroid responsiveness.<sup>[25]</sup>

FeNO was higher in patients with allergic rhinitis, though statistically not significant. This finding is in agreement with the studies by Ciprandi *et al.* and Kumar and Gupta.<sup>[26,27]</sup> An Egyptian study concluded that spirometry was worse when patients had allergic rhinitis with asthma.<sup>[28]</sup> The spirometry values in the above studies showed that FEF 25–75 correlated with the presence of allergic rhinitis more than FEV1. This could explain the discordance between spirometry and allergic rhinitis in our study, as only FEV1% predicted was taken into account.

Our study had certain limitations. A control group was absent. The follow-up period was short, i.e., for 3 months. There was the nonuniformity of treatment of patients, especially corticosteroids, which might have affected the measured values, such as FeNO. Even though we stressed on the inhaler technique and compliance with the given treatment during the follow-up, we could not ascertain it completely and may have a bearing on the outcome. We measured the parameters such as FeNO, FEV1%, and ACT score at the baseline only. A serial recording of FeNO may be required to see if the FeNO level was influenced by exacerbations or vice versa. As the assessment of the three study parameters were not done before the initiation of treatment, this may lead to bias. For example, FeNO could be lesser in patients treated already with corticosteroids.

Larger prospective cohort studies may be needed to ascertain the prognostic value of serial FeNO levels in predicting the loss of asthma control. The cost-effectiveness of serial FeNO measurements also needs to be taken into consideration. We need studies to establish a reference value of FeNO in adult nonsmoker Indian population.

## CONCLUSIONS

In our study, FEV1% and ACT score could predict exacerbations of asthma whereas FeNO could not. FeNO level correlated inversely with ACT score, i.e., symptom control. FeNO level, as well as ACT score, decreased with inhaled corticosteroid usage. There was no significant correlation between FeNO level and airflow limitation. FeNO level linearly correlated with absolute eosinophil count.

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## Conflicts of interest

There are no conflicts of interest.

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