

## RESEARCH ARTICLE

# Diagnostic Utility of Fractional Exhaled Nitric Oxide Findings in Patients of Asthma, COPD and Asthma and COPD Overlap

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## ABSTRACT

**Introduction:** Asthma, COPD and COOP Overlap Syndrome are among the most prevalent chronic disorders affecting the general population. The study was intended to understand the diagnostic utility of Fractional Exhaled Nitric Oxide (FeNO) testing in Asthma, COPD and Asthma COPD Overlap syndrome patients.

**Materials And Methods:** The study was conducted on 100 patients prediagnosed as asthma, COPD or ACOS in the Department of Respiratory Medicine of SRMSIMS, Bareilly. Data was collected using a pretested proforma, which included the demographic details of the patients, presenting complaints and smoking history of the patient. Necessary investigations will be done to rule out other pathologic infections. Then fractional exhaled NO levels were obtained in patients using the portable FeNO device and assessed. Suitable statistical methods were applied after data collection procedure and were analyzed using Microsoft Excel and SPSS version 23.

**Results:** Our study clearly demonstrated the importance of FeNO in establishing the diagnosis of asthma and COPD, as reflected by significant AUC. However, the sensitivity of FeNO depends on several factors like previous history to smoking, exposure to biofuel, etc.

**Conclusion:** Our study demonstrated the importance of FeNO in establishing the diagnosis of asthma and COPD.

**Keywords:** Asthma, Fractional Exhaled Nitric Oxide, Chronic obstructive pulmonary disease

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## INTRODUCTION

Asthma, COPD and COOP Overlap Syndrome are among the most prevalent chronic disorders affecting the general population. According to GINA 2019<sup>1</sup>, asthma is defined as “a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by a history of respiratory symptoms like a wheeze, shortness of breath, chest tightness, and cough that vary over time and in intensity, together with variable expiratory airflow limitation. It is responsible for over 1.5–2 crore patients and at least one in every 10 lives in India. Over 80 percent of asthma deaths, according to the World Health Organization (WHO), occur in low and lower-middle-income countries.<sup>2</sup> Global initiative for chronic obstructive lung disease (GOLD)<sup>3</sup> defines COPD defines chronic obstructive pulmonary disease as a common, preventable, and treatable disease that is characterized by persistent respiratory symptoms and airway limitation that is due to airway and/or alveolar abnormalities, usually caused by significant exposure to noxious particles or gases and influenced by host factors, including abnormal lung development. COPD is currently the 4th most leading cause of death globally but is projected to be 3rd by 2020. More than 3 million people died globally (in 2012) due to COPD, which accounts for 6 of total deaths

Recently, the GOLD 2021 and the Global Initiative for Asthma (GINA) have proposed criteria to assess and diagnose COPD patients with features of asthma, patients having asthma-COPD overlap syndrome (ACOS). Despite the lack of a well-accepted definition, the Global Initiative for Asthma (GINA) identifies a range of features that support a diagnosis of ACO, including<sup>4-6</sup>: Age  $\geq 40$  years; Respiratory symptoms (eg. exertional dyspnea) are persistent, but variability in symptoms may be prominent; Airflow limitation not fully reversible, but with historical variability: Post-broncho-dilator forced expiratory volume in one second/forced vital capacity (FEV/FVC)  $< 0.7$  or lower limit of normal and bronchodilator increase in FEV  $> 12$  percent and 400 mL; History of doctor-diagnosed asthma at some point; History of atopy or allergies; Exposure to a risk factor (e.g.,  $\geq 10$  pack-years tobacco smoking or equivalent indoor/outdoor air pollution.

This study is intended to understand the diagnostic utility of Fractional Exhaled Nitric Oxide (FeNO) testing in Asthma, COPD and asthma COPD Overlap syndrome patients. To investigate the role of Fractional exhaled Nitric Oxide (FeNO) testing and how it may aid it greater accuracy in diagnosing asthma, COPD and asthma chronic obstructive pulmonary disease overlap syndrome (ACOS). To investigate whether FeNO testing can lead to a change in diagnosis. To help develop an evidence-based guideline for the interpretation of FeNO measurements that incorporate evidence accumulated over the past decade.

## MATERIALS AND METHODS

The study was undertaken after obtaining approval from the Hospital Ethics committee and conducted from November 2019 to April 2021, over a period of 18 months in the Department of Respiratory Medicine of SRMSIMS, Bareilly fulfilling the inclusion and exclusion criteria.

### Inclusion Criteria

- Patients > 18 years and diagnosed with any of the below conditions for at least one year.
- Asthma
- COPD and
- Asthma COPD Overlap.
- At least one spirometry in the last year with a post-bronchodilator FEV1/FVC <0.70

### Exclusion Criteria

- Diagnosis of sleep apnea or other chronic respiratory disease
- Bronchiectasis patients

**Type of Study:** Prospective and Observational Study

**Sample Size:** The prevalence of Asthma COPD Overlap (ACO) in previously diagnosed COPD patients is 21.8 (22). Taking absolute error as 7, the minimum sample size is 134.

The sample size for this study = 100

Data was collected using a pretested proforma, which included the demographic details of the patients, presenting complaints and smoking history of the patient; necessary investigations will be done to rule out other pathologic infections. Then fractional exhaled NO levels were obtained in patients using the portable FeNO device and assessed. Suitable statistical methods were applied after the data collection procedure and analyzed using Microsoft Excel and SPSS.

## RESULTS

In our study, total 100 participants were enrolled after ensuring the clinical diagnosis of asthma, ACOS or COPD

for at least 1-year. The males were 60% and the females were 40% (Figure 1).

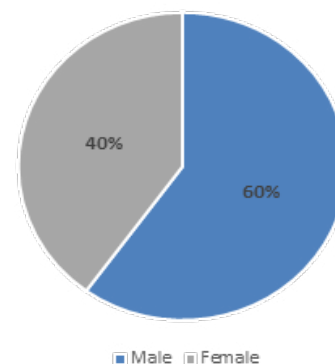
- 47% of participants were diagnosed asthmatic initially, which rose to 48% after FeNO testing. The proportion of COPD decreased after FeNO testing, from 39 to 28% in our study.

The ROC curve plotted for the diagnostic significance of level of FeNO in asthma has shown a significant area under curve of 0.87 ( $p$ -value=0.00). The sensitivity of FeNO at 33.5 was 79.2% and specificity was 82.7%, as the level of FeNO was increased to 50, the specificity rose to 98.1% at the expense of sensitivity which was 58.3% (Figure 2).

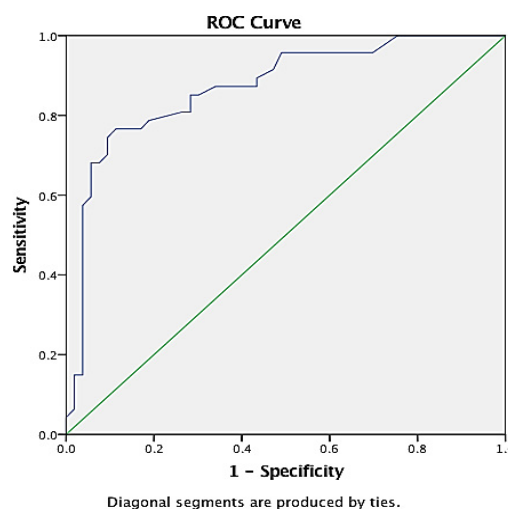
The ROC curve plotted for the diagnosis of COPD has shown a statistically significant area under curve (0.059,  $p$ -value=0.00).

The ROC curve plotted for diagnostic prediction of FeNO level with ACOS diagnosis did not have a significant area undercurve (Figure 3).

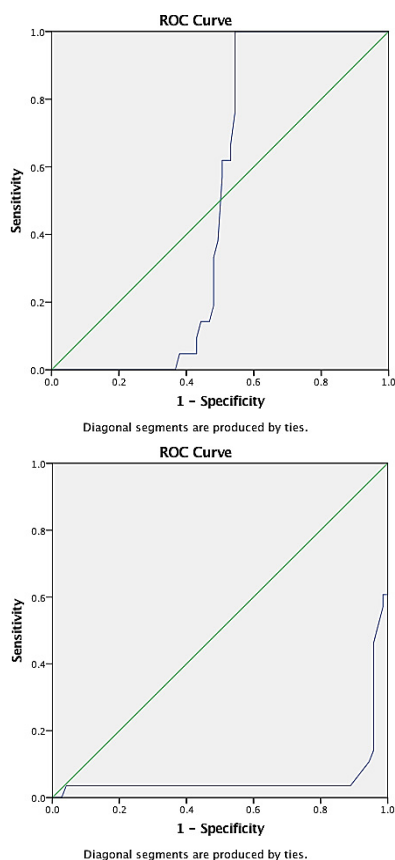
Three-fourths of COPD-diagnosed participants had FeNO level of less than 25, 60% of ACOS-diagnosed participants had FeNO level of 25–50 and 96.6% of the asthmatic had FeNO level of more than 50. Thus, the level



**Figure 1:** Distribution of Males and Females



**Figure 2:** ROC curve showing Asthma prediction by FeNO



**Figure 3:** ROC curve showing ACOS prediction by FeNO

of FeNO was most sensitive for the diagnosis of asthma, followed by COPD and ACOS.

## DISCUSSION

In our study, total 100 participants were enrolled after ensuring the clinical diagnosis of Asthma, ACOS or COPD for at least 1 year. The males were 60% and the females were 40% in our study. Most of the participants belonged to rural areas; half of the males were alcoholics, two-thirds were smokers and one-third were tobacco users. About 50% of the females had exposure to biofuel in this study. Hyperinflation in chest X-ray was seen in about half of the participants and obstruction was seen in four-fifths. In our study, 96.6% of the asthmatic had FeNO level of more than 50, the sensitivity of FeNO at this cut-off was 58.3%, and the specificity was 98.1%. However, the sensitivity of FeNO at 33.5 was 79.2% and the specificity was 82.7%. Three-fourths of COPD-diagnosed participants had FeNO level of less than 25, 60% of ACOS-diagnosed participants had FeNO level of 25–50 in this study.

The significant associated factors with the final diagnosis of asthma and COPD in our study were fever, expectoration, chest pain, rhinitis, diurnal variation, dust or any other allergy, history of smoking, hypertension and biofuel usage.

The findings of our study corroborated with the existing literature.<sup>7-9</sup> The findings of Miskoff JA *et al.*<sup>10</sup> initially had 36% of the patients diagnosed as asthmatics which increased to 47% after FeNO testing, in our study, 47% of participants were diagnosed asthmatic initially which rose to 48% after FeNO testing.<sup>(14)</sup> The proportion of COPD however decreased in both the studies, after FeNO testing, from 24 to 13% in Miskoff JA *et al.*<sup>10</sup> and from 39 to 28% in our study. The AUC for asthma diagnosis was 0.87 which was more than the findings of Heffler *et al.* with AUC of 0.78, the sensitivity and specificity of FENO for detecting asthma, using 36ppb as cut-off point, were 78 and 60% and the positive and negative predictive values were 54 and 82%, respectively, as compared to findings in our study, the sensitivity of FeNO at 33.5 was 79.2% and specificity was 82.7%.

The AUC for diagnosis of asthma has shown to be 0.8 which was like the findings of our study (AUC=0.87). The cut-off for highest sensitivity and specificity of FeNO level was 23 ppb in their study compared to 33.5 ppb. The same could be because of different selection criteria of patients in both studies. In the study by Wang Y *et al.*<sup>11</sup>, 64 ppb was the best cut-off value of FeNO to identify asthma with a sensitivity of 52.0% and specificity of 94.35%, which was very similar to our study finding of sensitivity of 58.3% and specificity of 98.1% at the FeNO cut off of >50 ppb. In the findings of Guo Y *et al.*<sup>12</sup>, the area under the receiver operating curve of FeNO for the diagnosis of ACOS phenotype was 0.815 ( $P < .01$ ), the sensitivity and specificity reached highest when the cut off value was 25.50ppb. However, in our study the AUC for the diagnosis of ACOS was found insignificant, similar to the findings of Goto T *et al.*<sup>13</sup> where the authors failed to discriminate ACOS from COPD by the diagnostic value of FeNO only as supported by the findings of our study as well.

The optimal cut-off for distinguishing asthmatic cough (AC; CPA and CVA) from NAC was 29.2 ppb [area under the curve (AUC) 0.74,  $p < 0.01$ ] in the study by Asano T *et al.*<sup>14</sup>, which was lower than the findings of our study where we found the sensitivity of FeNO at 33.5 was 79.2% and specificity was 82.7% with AUC of 0.87.

Our study clearly demonstrated the importance of FeNO in establishing the diagnosis of asthma and COPD as reflected by significant AUC. However, the sensitivity of FeNO depends on several factors like previous history to smoking, exposure to biofuel etc. Also, patient selection is an important criterion for applying FeNO tests and as suggested by other studies, FeNO as an independent predictor should be used with caution.

This study highlights the significance of FeNO level in the diagnosis of Asthma, ACOS and COPD. Despite

clinical criteria and pulmonary function tests, many patients of asthma and ACOS are misdiagnosed; thus, the specific treatment is missed or delayed. The number of lung diseases is increasing worldwide due to the contributions of air pollution and lifestyle changes in the population worldwide. Thus, it becomes imperative to devise such criteria through sensitive diagnostic tests so that early diagnosis can be done, and treatment thereof can be started. This will in turn facilitate the cost-effectiveness of treatment modalities and reduce the overall burden of disease-related morbidity in the community. Recently, FeNO, as a non-invasive marker of airway inflammation, has attracted wide attention. FeNO is more convenient, rapid, reproducible, and less painful than induced sputum analysis. The NO detected in exhaled air is produced by nitric oxide synthase catalyzing L-arginine in the airway epithelium. A variety of airway inflammations can lead to elevated NO; however, they are mostly dominated by eosinophilic inflammations.

Limitations in our study included that no prior history of steroid-dependent asthma was taken. As the diagnostic efficacy of FeNO is dependent of steroid-dependent status, this parameter should be considered in future studies. Further, this was a single-centric study, so the results of this study could not be generalized to other population settings. Thus, a study with multiple centers and a large sample size should be conducted to validate our findings across different population settings. Only patients with diagnosed asthma, COPD or ACOS were included in our study so the baseline FeNO levels in the normal population cannot be commented upon. The results of this study cannot be applied for Neutrophilic asthma as the diagnostic significance of FeNO lies with eosinophilic asthma only. Also, the treatment history has not been elicited in our study so any comment on the effect of Feno on the treatment regimen or controlled disease status cannot be made.

## CONCLUSION

Our study clearly demonstrated the importance of FeNO in establishing the diagnosis of asthma and COPD as reflected by significant AUC. However, the sensitivity of FeNO depends on several factors like previous history to smoking, exposure to biofuel etc. Also, patient selection is an important criterion for applying FeNO tests; FeNO as an independent predictor should be used cautiously.

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