

ORIGINAL ARTICLE

Importance of Fractional Exhaled Nitric Oxide in the Differentiation of Asthma-COPD Overlap (ACO), Asthma and COPD

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Abstract:

Background: Chronic obstructive pulmonary disease (COPD) and asthma are the most common inflammatory airway diseases. Some individuals share features of both asthma and COPD called asthma-COPD overlap (ACO) syndrome (ACOS). Fractional exhaled nitric oxide (FeNO) is an easy, sensitive, reproducible, and noninvasive marker of eosinophilic airway inflammation. Accordingly, FeNO is extensively used to diagnose and manage asthma. Patients with COPD who share some of the features of asthma have a condition called asthma-COPD overlap syndrome (ACOS).

Aims: To evaluate the importance of fractional exhaled nitric oxide (FeNO) in the differentiation of asthma-COPD overlap (ACO), asthma and COPD.

Materials & Methods: This cross sectional observational study conducted at the Department of Respiratory Medicine in National Institute of Diseases of the Chest and Hospital from January 2019 to December 2019. A total of 117 patients with asthma-COPD overlap (ACO), asthma and COPD were enrolled in this study. Statistical analyses of the results were obtained by using window based computer software devised with Statistical Packages for Social Sciences (SPSS-23).

Results: Out of 117 patients with asthma-COPD overlap (ACO), asthma and COPD. Out of which 50 patients were asthma, 52 were COPD and 15 were asthma-COPD overlap (ACO) group. Age, sex and BMI were not statistically significant when compared Asthma, COPD and ACO group. However, smoker 12(24.0%) patients were smoker in asthma group, 48(92.3%) in COPD group and 13(86.7%) in ACO group, that was statistically significant ($p < 0.05$). Mean FVC, FEV₁, post-bronchodilator FEV₁/FVC and FEF 25-75 were also statistically significant ($p < 0.005$) when compared Asthma, COPD and ACO group. Mean FeNO was found 42.9 ± 18.9 ppb in Asthma group, 12.0 ± 5.4 ppb in COPD group and 25.2 ± 9.3 ppb in ACO group, which indicated that FeNO level was significantly ($p < 0.05$) increased in Asthma group than COPD and ACO group. Based on the receiver-operator characteristic (ROC) curves FeNO level had area under curve 0.560. Receiver-operator characteristic (ROC) was constructed by using FeNO level, which gave a best cut off value ≥ 20.5 ppb, with 60.0% sensitivity and 52.9% specificity for prediction of ACO.

Conclusion: In conclusion, the present study has demonstrated that smoker, FVC, FEV₁, post-bronchodilator FEV₁/FVC, FEF 25-75 and FeNo were statistically significant when compared Asthma, COPD and ACO group. Using ROC best cut off value of FeNO ≥ 20.5 ppb for prediction of ACO.

Keywords: Asthma-COPD Overlap (ACO), Asthma, COPD, Fractional Exhaled Nitric Oxide (FeNO)

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Introduction:

Asthma and COPD are common diseases of airways and lungs and share some common clinical characteristics. Asthma, a chronic disorder of the airways, is associated with two main characteristics: airway hyperresponsiveness (AHR) and airway inflammation. The airflow limitation is reversible.¹ Meanwhile, COPD is a disease characterized by persistent, progressive airflow limitation and is also an inflammatory disease.²

Fractional exhaled nitric oxide (FeNO) is an easy, sensitive, reproducible and noninvasive marker for directly detecting eosinophilic airway inflammation.³ Given the airway inflammation can be assessed through FeNO measurement, the American Thoracic Society clinical practice guideline recommends the use of FeNO to diagnose and monitor asthma.⁴ Some patients with COPD have the features of asthma; FeNo values are elevated in this specific category of patients with COPD, and this condition is called asthma-COPD overlap (ACO).⁵

ACO was proposed by the science committees of both Global Initiative for Asthma (GINA) and Global Initiative for Obstructive Lung Disease (GOLD) in 2015.⁶ However, the exact role of FeNO in patients with ACO remains to be defined. Corticosteroids are known to increase the risk for pneumonia and other diseases in COPD patients, but ACO patients positively respond to treatment with inhaled corticosteroids. FeNO could differentiate ACO from COPD and could offer additional advantages for the management of COPD patients. FeNO measurement is an easy, sensitive, noninvasive and reproducible method for directly detecting airway inflammation. In the present study, we performed a cross sectional-observational study that aimed to evaluate the diagnostic performance of FeNO, which may be able to indicate airway eosinophilic inflammation in patients with COPD and to differentiate ACO from COPD.

Materials and methods

This cross sectional observational study conducted at the Department of Respiratory Medicine of National Institute of the Diseases of the Chest & Hospital (NIDCH), Mohakhali, Dhaka from January 2019 to December 2019.

Inclusion criteria:

Asthma, Asthma-COPD overlap (ACO), and COPD patients defined as per GOLD and GINA guideline who were willing to participate in the study

Exclusion criteria:

- Bronchiectasis
- Cystic fibrosis
- Obliterative bronchiolitis
- Reactive airway dysfunction syndrome
- Used any oral corticosteroid in the previous 4 weeks

Operational definition:**FeNO**

Fractional exhaled breath (FENO) is a quantitative, noninvasive, simple, and safe method of measuring airway inflammation that provides a complementary tool to other ways of assessing airways disease, including asthma.

Asthma

Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of the respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airway limitation.⁶

COPD

COPD is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases.⁶

Asthma-COPD overlap syndrome (ACOS) or Asthma-COPD overlap:

Asthma-COPD overlap syndrome (ACOS) or Asthma-COPD overlap is characterized by persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD. ACO is therefore identified in clinical practice by the features that it shares with both asthma and COPD.

Study procedure

A total of 117 patients with asthma, asthma-COPD overlap (ACO), and COPD attending in outpatient

department of NIDCH were selected as per inclusion & exclusion criteria. Purposive sampling was done in this study. In case, information about patients was obtained after getting consent. Consent from the patient was obtained after discussing with patient about study procedure. Enrolled patients were then evaluated properly by taking history, physical examination and investigations like full blood count and Chest X ray assay. Data were recorded by a standard proforma (History and clinical examination details). The relevant socio-demographic characteristics and history of the smoking were collected by face to face interview using predesigned interview schedule. After completion of interview the patient was examined physically all information and findings were recorded in the preformed proforma. After selection of the patient, spirometry was performed in each case to exclude the restrictive airway diseases. A rapport was built up individually with each patient. All subjects were asked to undergo spirometry in a reproducible way, and the best values were retained. FeNO level was measured according to the American Thoracic Society recommendations. Patients were instructed to inhale NO-free air to total lung capacity and immediately exhale fully into the device at a flow rate of 50 mL/s for 10 seconds. The collected data of each patient was recorded systematically. All data were analyzed by using computer based SPSS -23 (statistical package for social sciences). Data were presented in frequency, percentage and mean and standard deviation as applicable. Chi square test was used for categorical variables. ANOVA test was used for continuous variables. Receiver-operator characteristic (ROC) curve of FeNO level was used for prediction of ACO. P value of less than 0.05 was considered as significant.

Observations and results

This cross sectional observational study was carried out in the Department of Respiratory Medicine, NIDCH, Dhaka from January 2019 to December 2019. One hundred and seventeen (117) patients with asthma, asthma-COPD overlap (ACO), and COPD were included in this study based on inclusion and exclusion criteria. Out of which 50 patients were asthma, 52 were COPD and 15 were asthma-COPD overlap (ACO) group.

In this study half (50.0%) patients belonged to age 51-70 years in asthma group, 33(63.5%) in COPD group and 8(53.3%) in ACO group. The mean age

was found 54.9 ± 15.0 years in asthma group, 60.7 ± 12.6 years in COPD group and 62.3 ± 14.3 years in ACO group. Majority (70.0%) patients were male in asthma group, 42(80.8%) in COPD group and 12(80.0%) in ACO group. Two third (66.0%) patients were BMI $18.5-24.9 \text{ kg/m}^2$ in asthma group, 37(71.2%) in COPD group and 14(93.3%) in ACO group. The mean BMI was found $22.9 \pm 3.6 \text{ kg/m}^2$ in asthma group, $21.5 \pm 3.0 \text{ kg/m}^2$ in COPD group and $22.7 \pm 2.8 \text{ kg/m}^2$ in ACO group. There were no significant different regarding age, sex and BMI among three groups (Table-I). 12(24.0%) patients were smoker in asthma group, 48(92.3%) in COPD group and 13(86.7%) in ACO group. The differences were statistically significant ($p < 0.05$) among three groups (Table-II). Mean FVC was found $2.42 \pm 0.92 \text{ L}$ in asthma group, $1.80 \pm 0.56 \text{ L}$ in COPD group and $2.35 \pm 0.50 \text{ L}$ in ACO group. The mean FEV₁ was found $1.85 \pm 0.77 \text{ L}$ in asthma group, $0.89 \pm 0.37 \text{ L}$ in COPD group and $1.38 \pm 0.26 \text{ L}$ in ACO group. Mean post-bronchodilator FEV₁/FVC was found 83.7 ± 6.9 percent in asthma group, 48.1 ± 10.0 percent in COPD group and 63.6 ± 2.3 percent in ACO group. The differences were statistically significant ($p < 0.05$) among three groups (Table-III). Mean FEF₂₅₋₇₅ was found $2.12 \pm 1.0 \text{ L/sec}$ in asthma group, $0.58 \pm 0.46 \text{ L/sec}$ in COPD group and $1.58 \pm 0.19 \text{ L/sec}$ in ACO group. Mean FeNO was found $42.9 \pm 18.9 \text{ ppb}$ in asthma group, $12.0 \pm 5.4 \text{ ppb}$ in COPD group and $25.2 \pm 9.3 \text{ ppb}$ in ACO group. The differences were statistically significant ($p < 0.05$) among three groups (Table-IV).

Based on the receiver-operating characteristic (ROC) curves FeNO level had area under curve 0.947. Receiver-operating characteristic (ROC) was constructed by using FeNO level, which gave a best cut off value $e^{-21.5 \text{ ppb}}$, with 92.0% sensitivity and 86.6% specificity for prediction of asthma (Table-V & Figure-1). Based on the receiver-operating characteristic (ROC) curves FeNO level had area under curve 0.030. Receiver-operating characteristic (ROC) was constructed by using FeNO level, which gave a best cut off value $e^{-15.5 \text{ ppb}}$, with 30.8% sensitivity and 4.62% specificity for prediction of COPD (Table-VI & Figure-2). Based on the receiver-operating characteristic (ROC) curves FeNO level had area under curve 0.560. Receiver-operating characteristic (ROC) was constructed by using FeNO level, which gave a best cut off value $e^{-20.5 \text{ ppb}}$, with 60.0% sensitivity and 52.9% specificity for prediction of ACO (Table-VII & Figure-3)

Table I
Demographic characteristics of the study subjects (n=117)

Demographic characteristics	Asthma (n=50)		COPD (n=52)		ACO (n=15)		P value
	n	%	n	%	n	%	
Age (years)							
≤30 3	6.0	1	1.9	0	0.0		
31-50	16	32.0	10	19.2	3	20.0	
51-70	25	50.0	33	63.5	8	53.3	
>70	6	12.0	8	15.4	4	26.7	
Mean±SD	54.9	±15.0	60.7	±12.6	62.3	±14.3	0.060 ^{ns}
Range (min-max)	20.0	-85.0	28.0	-90.0	34.0	-86.0	
Sex							
Male	35	70.0	42	80.8	12	80.0	0.413 ^{ns}
Female	15	30.0	10	19.2	3	20.0	
BMI (kg/m ²)							
<18.5	5	10.0	8	15.4	0	0.0	
18.5-24.9	33	66.0	37	71.2	14	93.3	
25.0-29.9	10	20.0	7	13.5	0	0.0	
≥30.0	2	4.0	0	0.0	1	6.7	
Mean±SD	22.9	±3.6	21.5	±3.0	22.7	±2.8	0.079 ^{ns}
Range (min-max)	16.7	-31.0	16.5	-28.9	19.7	-30.8	

ns= not significant; P value reached from ANOVA test; P value reached from chi square test

Table II
Distribution of the study patients according to smoking (n=117)

Smoker	Asthma (n=50)		COPD (n=52)		ACO (n=15)		P value
	n	%	n	%	n	%	
No 38	76.0	4	7.7	2	13.3	0.001 ^s	
Yes 12	24.0	48	92.3	13	86.7		
If yes							
<20 (pack/yr)	10	83.3	12	25.0	3	23.1	
≥20 (pack/yr)	2	16.7	36	75.0	10	76.9	

s= significant; P value reached from chi square test

Table-III
Distribution of the study patients according to FVC, FEV₁ and post-bronchodilator FEV₁/FVC (n=117)

	Asthma(n=50)	COPD(n=52)	ACO(n=15)	P value
	Mean±SD	Mean±SD	Mean±SD	
FVC (L)	2.42±0.92	1.80±0.56	2.35±0.50	0.001 ^s
Range (min-max)	0.76-5.55	0.91-2.93	1.64-2.90	
FEV ₁ (L)	1.85±0.77	0.89±0.37	1.38±0.26	0.001 ^s
Range (min-max)	0.64-4.08	0.40-1.62	1.01-1.70	
Post-bronchodilator FEV ₁ /FVC (%)	83.7±6.9	48.1±10.0	63.6±2.3	0.001 ^s
Range (min-max)	71.6-97.0	33.0-69.4	61.0-67.0	

s= significant; P value reached from ANOVA test

Table IV
Distribution of the study patients according to FEF 25-75 (n=117)

	Asthma(n=50) Mean±SD	COPD(n=52) Mean±SD	ACO(n=15) Mean±SD	P value
FEF 25-75 (L/sec)	2.12±1.0	0.58±0.46	1.58±0.19	0.001 ^s
Range (min-max)	0.35-5.04	0.17-2.23	1.34-1.85	
FeNO (ppb)	42.9±18.9	12.0±5.4	25.2±9.3	0.001 ^s
Range (min-max)	19.0-85.0	3.0-22.0	13.0-41.0	

s= significant; P value reached from ANOVA test

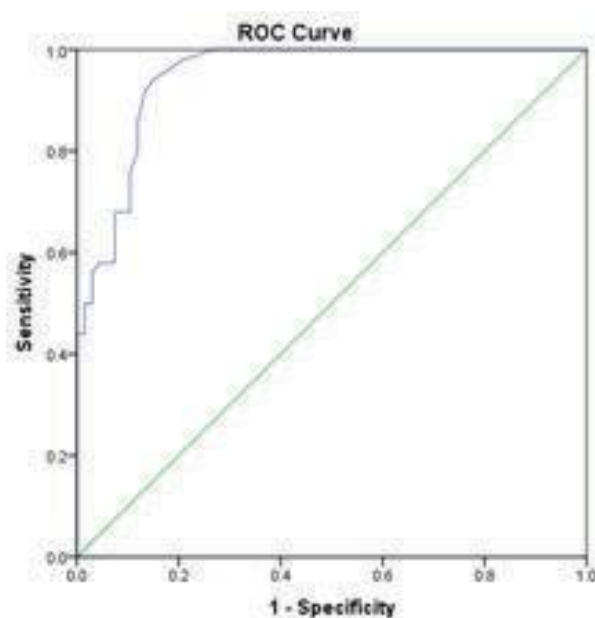


Figure 1: Receiver-operating characteristic curves of FeNO level for prediction of asthma

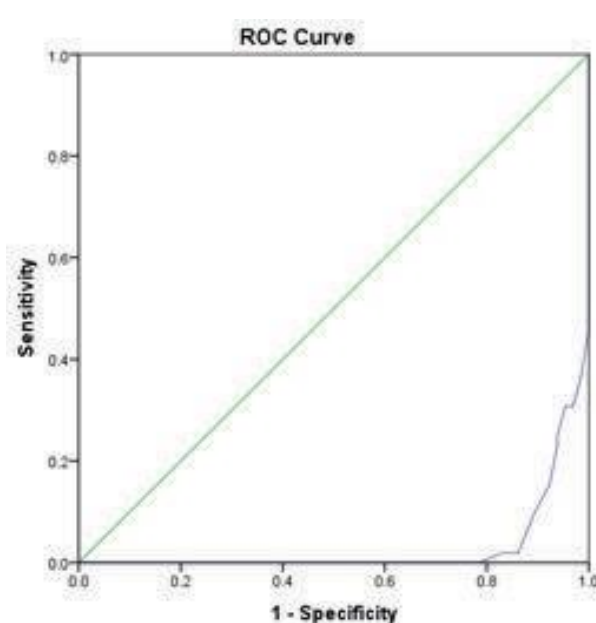


Figure 2: Receiver-operating characteristic curves of FeNO level for prediction of COPD

Table V
Receiver-operating characteristic (ROC) curve of FeNO level for prediction of asthma

	Cut of value	Sensitivity	Specificity	Area under the ROC curve	95% Confidence interval (CI)	
					Lower bound	Upper bound
FeNO level	≥19.5	98.0	79.1	0.947	0.910	0.983
	≥20.5	94.0	85.1			
	≥21.5	92.0	86.6			
	≥22.5	86.0	88.1			
	≥23.5	82.0	88.1			
	≥24.5	80.0	88.1			
	≥25.5	76.0	89.6			

Table VI
Receiver-operating characteristic (ROC) curve of FeNO level for prediction of COPD

	Cut of value	Sensitivity	Specificity	Area under the ROC curve	95% Confidence interval (CI)	
					Lower bound	Upper bound
FeNO level	≥ 13.5	36.5	1.54	0.030	0.005	0.055
	≥ 15.5	30.8	4.62			
	≥ 17.5	23.1	6.15			
	≥ 18.5	15.4	7.69			
	≥ 20.5	1.9	13.85			

Table-VII
Receiver-operating characteristic (ROC) curve of FeNO level for prediction of ACO

	Cut of value	Sensitivity	Specificity	Area under the ROC curve	95% Confidence interval (CI)	
					Lower bound	Upper bound
FeNO level	≥ 16.5	73.3	38.2	0.560	0.445	0.674
	≥ 18.5	66.7	43.1			
	≥ 19.5	60.0	47.1			
	≥ 20.5	60.0	52.9			
	≥ 21.5	53.3	53.9			
	≥ 23.5	53.3	59.8			
	≥ 25.5	46.7	62.7			

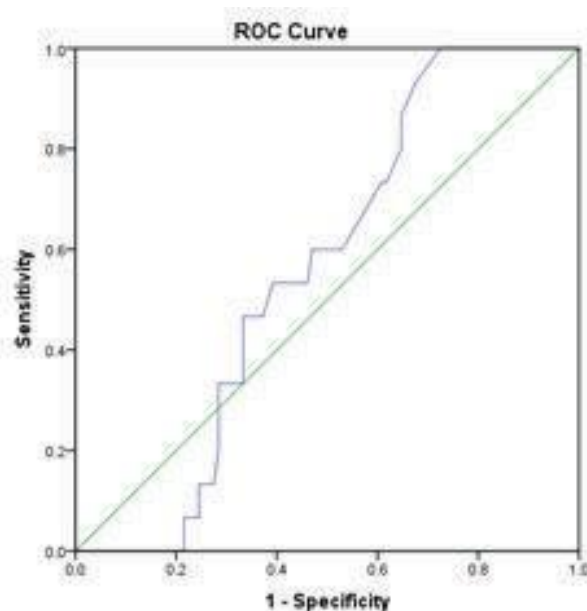


Figure 3: Receiver-operating characteristic curves of FeNO level for prediction of ACO

Discussion:

This cross sectional observational study was carried out with an aim to evaluate the importance of fractional exhaled nitric oxide (FeNO) in the differentiation of asthma-COPD overlap (ACO), asthma and COPD. A total of 117 patients with asthma-COPD overlap (ACO), asthma and COPD were attending in the Department of Respiratory Medicine in National Institute of Diseases of the Chest and Hospital (NIDCH), Mohakhali, Dhaka during the period from January 2019 to December 2019 were included in this study. Asthma, Asthma-COPD overlap (ACO), and COPD patients defined as per GOLD and GINA guideline were enrolled in this study.

In this study it was observed that half (50.0%) patients belonged to age 51-70 years in asthma group, 33 (63.5%) in COPD group and 8(53.3%) in ACO group. The mean age was found 54.9 ± 15.0 years in asthma group, 60.7 ± 12.6 years in COPD

group and 62.3 ± 14.3 years in ACO group. The mean age was not statistically significant ($p > 0.05$) among three groups. In a study of Chen et al.⁷ found that the mean age was 41.92 ± 15.23 years in asthma group, 63.52 ± 9.58 years in COPD group and 63.17 ± 9.17 years in ACOS group. Shi et al.⁸ reported that the mean age was 62.2 ± 5.9 years in asthma group, 65.4 ± 7.0 years in COPD group and 64.8 ± 6.5 years in ACO group, the difference was not statistically significant among three groups. Takayama et al.⁹ demonstrated that the mean age was 72.3 ± 9.8 years in COPD group and 72.3 ± 7.8 years in ACO group, the difference was not statistically significant between two groups. Another study conducted by Colak et al.¹⁰ documented that mean age was 60 years, 68 years and 68 years in asthma, COPD and ACO group respectively. The reason for the difference of age at presentation in various regions of the world may be due to geographic/ ethnic influence.

In this present study it was observed that majority (70.0%) patients were male in asthma group, 42(80.8%) in COPD group and 12(80.0%) in ACO group. Female was 15(30.0%), 10(19.2%) and 3(20.0%) in asthma, COPD and ACO group respectively. The differences were not statistically significant ($p > 0.05$) among three groups. Almost similar study observed by Shi et al.⁸ which showed that male was 11(68.8%) in asthma group, 21(84.0%) in COPD group and 13(68.4%) in ACO group. The differences were not statistically significant among three groups. Chen et al.⁷ consisted that male was found 215(43.0%) in asthma group, 109(82.6%) in COPD group and 37(64.9%) in ACOS group. Female was 285(57.0%), 23(17.4%) and 20(35.1%) in asthma, COPD and ACOS group respectively. Takayama et al.⁹ in their study found that the male was 54(83.1%) in COPD group and 42(75.0%) in ACO group. Female was 11(16.9%) and 14(25.0%) in COPD and ACO group respectively. The differences were not statistically significant ($p > 0.05$) between two groups. Another study conducted by Colak et al.¹⁰ where they observed that male patients was 142(32.0%) in asthma group, 220(54.0%) in COPD group and 58(42.0%) in ACO group. This difference across various studies may be due to different demographic and geographic distribution of the population.

In this study it was observed that 12(240%) patients were smoker in asthma group, 48(92.3%) in COPD

group and 13(86.7%) in ACO group. The differences were statistically significant ($p < 0.05$) among three groups. In a study of Chen et al.⁷ which showed that smoking history was 129(25.80%) in asthma group, 98(74.24%) in COPD and 23(40.35%) in ACOS patients. Takayama et al.⁹ documented that current smoker was 14(21.5%) in COPD group and 12(21.4%) in ACO group. Ex-smoker was 48(73.9%) and 40(71.4%) in COPD and ACO group respectively. Mean pack-year was 56.0 ± 31.6 in COPD group and 46.4 ± 30.0 in ACO group. The mean pack-year was statistically significant between two groups. Shi et al. (2018) have found that there were more smokers in the ACO group (57.9%) than in the Asthma group (25.0%, $p = 0.037$). Another study documented by Colak et al.¹⁰ where they observed smoker was 55(12.0%), 100(25.0%) and 40(29.0%) in asthma, COPD and ACO group respectively. This difference across various studies may be due to different demographic and geographic distribution of the population.

Our study showed that two third (66.0%) patients were BMI 18.5 - 24.9 kg/m² in asthma group, 37(71.2%) in COPD group and 14(93.3%) in ACO group. The mean BMI was found 22.9 ± 3.6 kg/m² in asthma group, 21.5 ± 3.0 kg/m² in COPD group and 22.7 ± 2.8 kg/m² in ACO group. The mean BMI were not statistically significant ($p > 0.05$) among three groups. Similarly, Shi et al.⁸ had found that mean BMI was 24.0 ± 2.0 kg/m² in asthma group, 23.0 ± 3.7 kg/m² in COPD group and 22.9 ± 1.9 kg/m² in ACO group. The differences were not statistically significant ($p > 0.05$) among three groups. Takayama et al.⁹ reported that the mean BMI was 23.0 ± 3.7 kg/m² in COPD group and 22.6 ± 5.6 kg/m² in ACO group, The mean BMI were not statistically significant ($p > 0.05$) between two groups. Colak et al.¹⁰ also documented that mean BMI was 25 kg/m² in asthma group, 25 kg/m² in COPD group and 26 kg/m² in ACO group. This difference across various studies may be due to different demographic and geographic distribution of the population.

In this study it was observed that mean FVC was found 2.42 ± 0.92 L in asthma group, 1.80 ± 0.56 L in COPD group and 2.35 ± 0.50 L in ACO group. The mean FEV₁ was found 1.85 ± 0.77 L in asthma group, 0.89 ± 0.37 L in COPD group and 1.38 ± 0.26 L in ACO group. The differences were statistically

significant ($p<0.05$) among three groups. In a study of Shi et al.⁸ which showed mean FVC was 3.49 ± 0.51 L in asthma group, 2.57 ± 0.76 L in COPD group and 5.50 ± 0.50 L in ACO group. The mean FEV₁ was 2.59 ± 0.37 L, 1.47 ± 0.56 L and 1.39 ± 0.35 L in asthma, COPD and ACO group respectively. The differences were statistically significant ($p<0.05$) among three groups. Takayama et al.⁹ in their study found that mean FVC was 3.15 ± 0.80 L in COPD group and 3.04 ± 0.77 L in ACO group. The differences were not statistically significant between two groups. The mean FEV₁ was 1.72 ± 0.56 L in COPD group and 1.55 ± 0.51 L in ACO group. The differences were not statistically significant ($p>0.05$) between two groups. Another study conducted by Chen et al.⁷ which consisted that mean FVC was 96.99 ± 15.59 % predicted in asthma group, 75.80 ± 17.73 % predicted in COPD group and 77.42 ± 17.56 % predicted in ACOS group. Mean FEV₁ was 88.49 ± 19.38 % predicted in asthma group, 50.81 ± 19.30 % predicted in COPD group and 51.01 ± 18.64 % in predicted ACOS group.

In my study showed that mean post-bronchodilator FEV₁/FVC was found 83.7 ± 6.9 percent in asthma group, 48.1 ± 10.0 percent in COPD group and 63.6 ± 2.3 percent in ACO group. The differences were statistically significant ($p<0.05$) among three groups. In a study of Chen et al.⁷ demonstrated that mean post-bronchodilator FEV₁/FVC was 76.89 ± 11.37 % in asthma group, 51.44 ± 12.37 % in COPD group and 51.88 ± 11.70 % in ACOS group. Another study documented by Shi et al.⁸ where they found mean FEV₁/FVC was 74.37 ± 2.25 % in asthma group, 53.65 ± 10.93 % in COPD group and 55.39 ± 6.28 % in ACO group. The differences were statistically significant ($p<0.05$) among three groups.

Our study showed that mean FEF 25-75 was found 2.12 ± 1.0 L/sec in asthma group, 0.58 ± 0.46 L/sec in COPD group and 1.58 ± 0.19 L/sec in ACO group. The differences were statistically significant ($p<0.05$) among three groups. In a study of Donohue et al.¹¹ where they showed mean FEF 25-75% was 0.759 ± 0.6898 L/Sec with range from 0.12 to 3.87 L/sec.

In this study it was observed that mean FeNO was found 42.9 ± 18.9 ppb in asthma group, 12.0 ± 5.4 ppb in COPD group and 25.2 ± 9.3 ppb in ACO group. The differences were statistically significant

($p<0.05$) among three groups. Almost similar study conducted by Miskoff et al.¹² which showed that the mean FeNO (ppb) level in patients with an initial diagnosis of asthma, COPD, ACOS, and without a diagnosis was 40.5 (ppb), 19.48 (ppb), 28.19 (ppb), and 12.38 (ppb), respectively. Takayama et al.⁹ in their study found that the FeNO levels were higher in patients with ACO than in patients with COPD (median 24.5 ppb [14.0–39.5 ppb] vs 16.0 ppb [12.0–20.0 ppb], respectively; $P<0.01$). Shi et al.⁸ also observed their study that the FeNO levels of ACO (37.7 ± 16.5 ppb) and asthma group (36.3 ± 17.7 ppb) were higher in the COPD (21.9 ± 10.3 ppb), while there was no significant difference between ACO and asthma groups ($p=0.833$). All subjects in ACO group had FeNO levels of >20 ppb, except for two patients; these patients had FeNO level of 15 and 18 ppb. 10 (52.6%) of total 19 in ACO group had FeNO levels of >35 ppb. Furthermore, the proportion of subjects with an elevated FeNO level also had significant differences among the three groups ($p<0.001$). Pillai¹³ reported that mean FeNO in ACO group and COPD was 40.13 ± 17.2 ppb and 12.35 ± 4.19 ppb ($p<0.001$). Donohue et al.¹¹ consisted that the mean FeNO level for all patients was 15.3 ± 17.2 parts per billion (ppb).

In this study it was observed that based on the receiver-operating characteristic (ROC) curves FeNO level had area under curve 0.560, 0.030 and 0.947 for prediction of ACO, COPD and asthma respectively. Receiver-operating characteristic (ROC) was constructed by using FeNO level, which gave a best cut off value $e^{-20.5}$ ppb, with 60.0% sensitivity and 52.9% specificity for prediction of ACO. Receiver-operating characteristic (ROC) was constructed by using FeNO level, which gave a best cut off value $e^{-15.5}$ ppb, with 30.8% sensitivity and 4.62% specificity for prediction of COPD. Receiver-operator characteristic (ROC) was constructed by using FeNO level, which gave a best cut off value $e^{-21.5}$ ppb, with 92.0% sensitivity and 86.6% specificity for prediction of asthma. In a study of Chen et al.⁷ where they constructed ROC curve defines the optimal cutoff value for FeNO level and was used to differentiate ACOS from COPD. The ROC AUC was estimated to be 0.783 for FeNO. The optimal diagnostic cutoff point was 22.5 ppb (with 70% sensitivity and 75% specificity). FeNO is a good predictor for differentiating ACOS from COPD, with an ROC AUC of 0.783. Taking

22.5 ppb as a cut-off point to diagnose ACOS, FeNO measurement indicated a sensitivity of 70% and a specificity of 75%, which agreed with previous studies. Donohue et al.¹¹ (2014) showed an FeNO level of 20 ppb in COPD patients with a previous diagnosis of asthma. Some authors have observed that patients with a cutoff point of 35 ppb can be classified as ACOS, whether or not they have allergic rhinitis.¹⁴ Corticosteroids are known to increase the risk for pneumonia and other diseases in COPD patients¹⁵, but ACOS patients positively respond to treatment with inhaled corticosteroids. Given that FeNO could differentiate ACOS from COPD, FeNO could offer additional advantages for the management of COPD patients. Takayama et al.⁹ reported that ROC curve analysis demonstrated that 21.0 ppb was the best diagnostic cutoff value of FeNO for differentiating ACO from COPD (AUC: 0.671). The sensitivity and specificity at 21.0 ppb for the diagnosis of ACO were 62.5% and 75.4%, respectively. Among patients naïve to ICS, the AUC for FeNO was calculated to be 0.726, and the optimal diagnostic cut-off level was 25.0 ppb, with 60.6% sensitivity and 87.7% specificity for differentiating ACO from COPD. Chen et al.⁶ reported that the best diagnostic cutoff level of FeNO was 22.5 ppb, with 70.2% sensitivity and 75.0% specificity for differentiating ACO from COPD. Four studies showed that FeNO can be useful to differentiate ACO(S) from COPD and introduced optimal cut-off values of 19, 22.5, 23, and 29 ppb with a sensitivity of 68, 70, 73, 80%, and specificity of 75, 75, 68.2, and 73%, respectively. The area under the curve (AUC) for the cut-off 19, 22.5, 23 and 29 ppb was 0.79, 0.78, 0.74, and 0.85, respectively.^{7,16,17,18} This combination of cutoff values, which showed such high specificity, could be useful for preventing the inappropriate use of ICS in patients without an asthmatic component.

Conclusion:

In conclusion, the present study has demonstrated that smoker, FVC, FEV₁, post-bronchodilator FEV₁/FVC, FEF 25-75 and FeNo were statistically significant when compared asthma, COPD and ACO group. Using ROC best cut off value of FeNO e"20.5 ppb for prediction of ACO. Fractional exhaled nitric oxide (FeNO) is a simple, reproducible, and a noninvasive marker of inflammation which may be used as one piece of data to help the clinician

better assess the patients true underlying pulmonary disorder and potentially change the treatment plan. Measurement of FeNO provides useful information to evaluate the airway calibre and responsiveness, and may indicate the management of patients with asthma, COPD and ACO. Although the primary purpose of this study was to help more accurately diagnose the patient, the true value of FeNO may be in regards to treatment. Therefore, further studies are needed to better understand FeNO and its applicability across the clinical spectrum. Furthermore, we simply focused the initial FeNO levels, and didn't follow-up serial FeNO levels regularly. It would be of interest to evaluate the role of FeNO monitoring the treatments of older patients with ACO.

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