PREVALENCE AND CLINICAL CHARACTERISTICS OF ACO IN A TERTIARY CARE CENTRE

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ABSTRACT

BACKGROUND:

Asthma –COPD overlap is characterized by persistent airflow limitation with several features usually associated with COPD. It is identified in clinical practice by the features it shares with both asthma and COPD. A stepwise approach to diagnosis is advised, with recognition of the presence of chronic airway disease, syndromic categorization as characteristic asthma, characteristic COPD or ACO, confirmation of chronic airflow limitation by spirometry and, if necessary, referral for specialized investigations. The aim of the study was to determine the prevalence and to study various clinical characteristics of the patients with ACO.

METHODS:

This was a prospective observational study in 79 patients with chronic airflow obstruction. The patients were categorized as asthma, COPD or ACO as per the GINA guidelines. Prevalence of ACO, various clinical characteristics, genetic, environmental factors and comorbidities associated with ACO were analysed.

RESULTS:

The prevalence of ACO in my study population was 17.7%. The patients with ACO belonged to middle age group (40-70 yrs), mostly females (71%), with 14% having a family history of chronic airflow obstruction, more from the previously diagnosed asthma group, 21% and 64% had exposure to smoking and biomass fuel exposure respectively, 7% and 14% had diabetes and hypertension respectively, 28% had pulmonary hypertension, 7% had a significant absolute eosinophil count.

CONCLUSION:

ACO is a disease entity that is often missed which leads to suboptimal therapy and frequent exacerbations. Keen clinical judgement and investigations on patients with chronic airflow obstruction helps obviate such problems.

KEYWORDS: Asthma, COPD, ACO, chronic airflow obstruction

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INTRODUCTION:

"ACO is a heterogeneous condition seen in patients with persistent airflow limitation and also having clinical and inflammatory features of both asthma and COPD". Significant smoking or other exposure to noxious particles and gases precede development of ACO. It may be difficult to differentiate asthma and COPD in clinical practice, particularly among old patients, smokers and reformed smokers, as these may overlap. Patients with ACO have recurrent exacerbations, decline in the quality of life and lung function with greater use of healthcare resources. Global diagnostic criteria for ACO are inconclusive [1]. A subset of COPD patients who have variable symptoms and significant bronchodilator reversibility and a subset of diagnosed asthma patients exposed to risk factors like tobacco smoke, indoor or outdoor air pollution, with persistent expiratory airflow limitation with or without post bronchodilator reversibility can be considered as ACO. If the diagnosis is uncertain, referral for special investigations and treatment should be considered as compared to those with asthma or COPD alone, the patients with ACO has a bad prognosis. Prevalence rates in epidemiological studies to date shows significant variations ranging from 15% to 55%, primarily due to the various inclusion criteria utilised by researchers as there is no strong

evidence to define this population. In 2014, the GINA committee published a consensus statement for the first time on the diagnosis of chronic airflow limitation disorders such as typical asthma, typical COPD, and ACOS. Since it is not a syndrome, the word ACOS was subsequently removed and replaced with ACO in 2017. The GINA guideline offers a helpful protocol to promote consistency among doctors for identifying and treating patients with overlap through a stepwise syndromic approach that considers the patient's history, clinical examination, chest X-ray, and spirometry[2]. Identifying the frequency and demography of ACO is important since it allows for better therapeutic approach to be maintained because the disease is more severe and results in a bigger burden for the patient and the economy.

This study aimed to explore the prevalence and various clinical characteristics , contribution of genetic and environmental factors along with association of comorbidities in ACO among asthma and COPD patients using the stepwise approach proposed by GINA.

MATERIALS AND METHODS:

This was a prospective observational study over a 2-year period from September 2020 to September 2022. 79 Patients attending the OPD and admitted in the wards of Respiratory medicine department of Dr. D Y Patil medical college, Pimpri, Pune with features of chronic airflow obstruction or previous doctor diagnosed cases of asthma and COPD were enrolled. Informed consent was obtained. The study population were divided into pre-study asthma and pre-study COPD groups based on the history and previous spirometry reports. Using the stepwise syndromic approach as per the GINA guidelines [2], they were divided as asthma, COPD, or ACO. Patients who had same number of features (3 or more of each) favoring asthma and COPD as shown in Table 1 were diagnosed to have ACO. Spirometry was performed as per the ATS guidelines to confirm the presence of persistent expiratory airflow limitation (post bronchodilator FEV1/FVC <0.7) and reversible obstruction. All the three categories of patients were assessed for clinical characteristics like

1. Age
2. Sex
3. BMI
4. Presence of risk factors like smoking and biomass fuel exposure
5. Absolute eosinophil count

6. Features of OSA like excessive daytime somnolence, witnessed apnea spells, snoring, early morning headache
7. Features of DPLD like skin rash, photosensitivity, joint pain, raynaud's phenomenon
8. Presence of diabetes mellitus, systemic hypertension, Pulmonary hypertension and pulmonary tuberculosis.

Data entry was done in Microsoft excel 2018 and the analysis was done using SPSS version 22. Non parametric test were used for bivariate analysis with Chisquare and Fisher exact test.

P value< 0.05 was considered as statistically significant.

Table 1: syndromic approach for the diagnosis of Asthma- COPD overlap [2]

FEATURE	ASTHMA	COPD
Age of onset	< 20 years	> 40 years
Pattern of respiratory symptoms	1) Variation of symptoms over minutes, hours, or days 2) Symptoms worsen during the night or early morning 3) Symptoms triggered by exercise, emotions including laughter, dust, and exposure to allergens	1) Persistence of symptoms despite treatment 2) Good and bad days , but always daily symptoms and exertional dyspnoea 3) Chronic cough and sputum preceded the onset of dyspnoea, unrelated to triggers
Lung function	Record of reversibility/ variable airflow limitation	Record of persistent airflow limitation (postbronchodilator

	(spirometry, peak flow)	FEV1/FVC <0.7)
Lung function between symptoms	Normal	Abnormal
Past history and family history	Previous doctor diagnosed asthma Family history of asthma and other allergic conditions	Previous doctor diagnosis of COPD Heavy exposure to a risk factor: tobacco smoke and biomass fuels
Time course	No worsening of symptoms over time. Seasonal variation of symptoms present or may vary from year to year Symptoms may improve spontaneously or may have immediate response to BD or to ICS over weeks	Slow worsening of symptoms over time (progressive over years) Only limited relief with rapid acting bronchodilators
Chest radiograph	Normal	Severe hyperinflation

FEV1 /FVC: Forced expiratory volume in 1 s/forced vital capacity, COPD: Chronic obstructive pulmonary disease, ICS: Inhaled corticosteroids, BD: Bronchodilator

OBSERVATIONS AND RESULTS:

Out of the 79 patients with chronic airway obstruction in our study, 17.7% was the proportion of people with ACO of which 18% were from the asthma group and 17% were from the COPD group.

Figure1: Proportion of Confirmed diagnosis

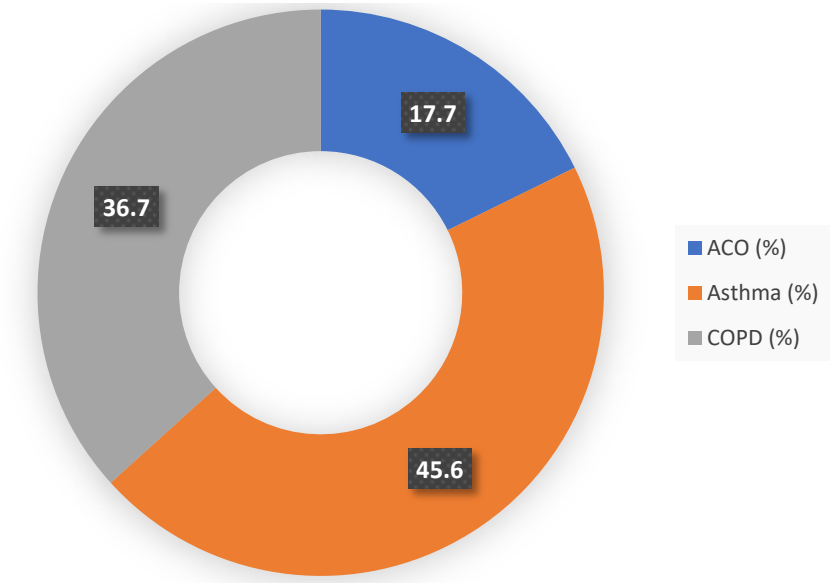
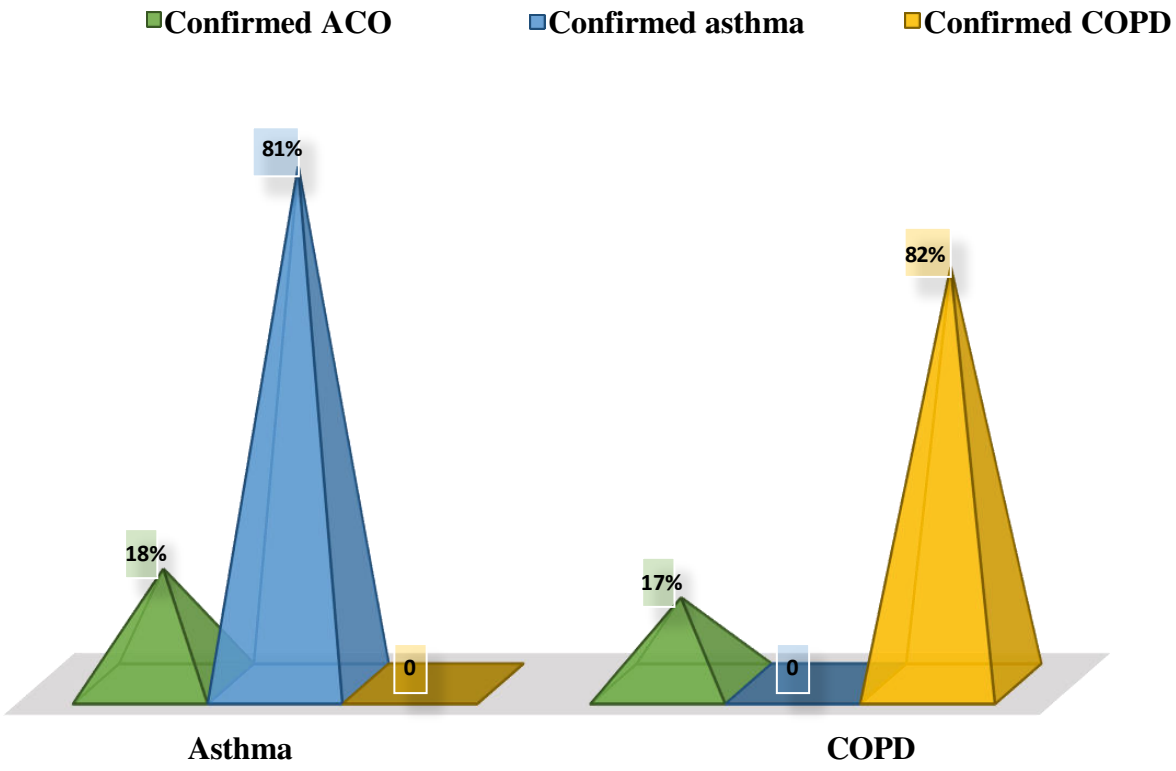


Figure 2: Comparison of pre study and confirmed diagnosis



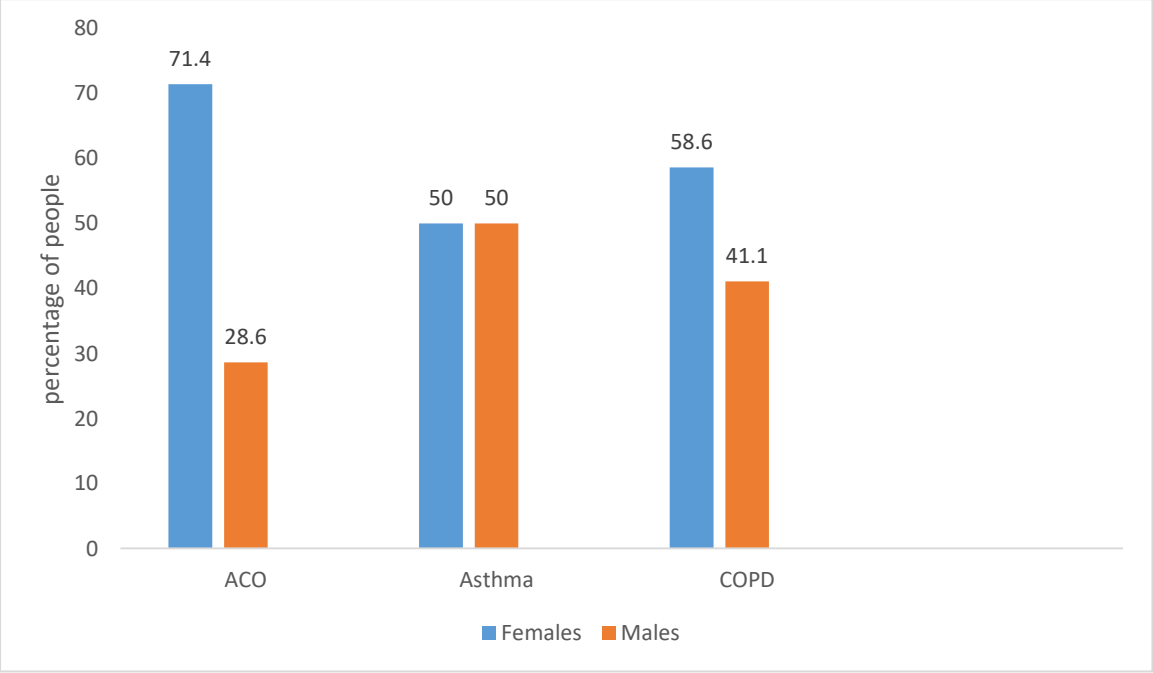
The age distribution showed middle-aged patients (>40 years) were more with ACO, younger patients with asthma and older patients with COPD, this was statistically significant

(p value <0.001) (table 1) . The gender comparison showed no difference between the number of males and females among the patients with ACO.

Table 1: Age distribution amongst the people with asthma, COPD and ACO

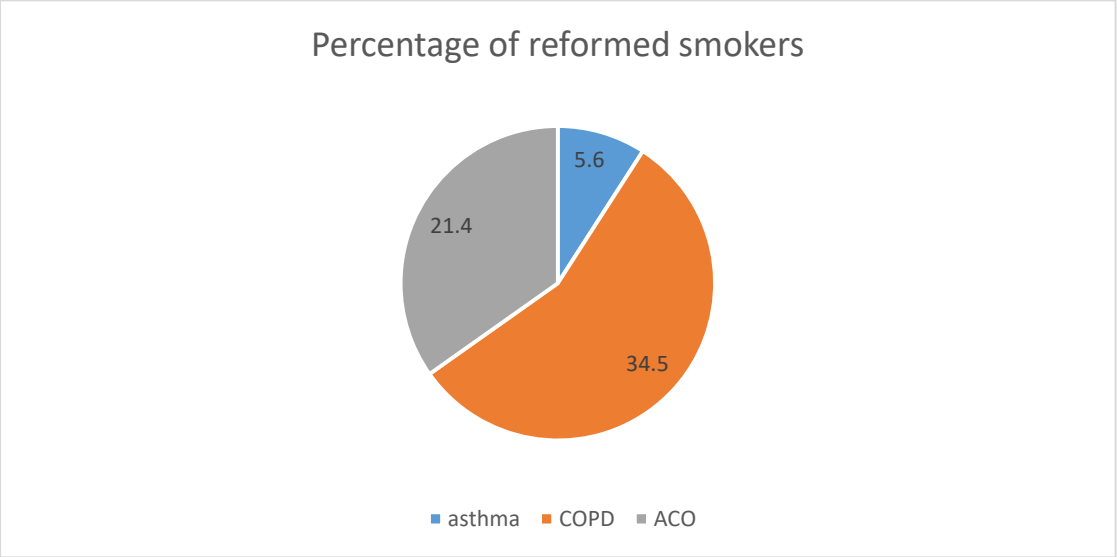
Age	Confirmed Diagnosis		
	ACO n (%)	Asthma n (%)	COPD n (%)
< 20 years	0 (0.0)	2 (5.6)	0 (0.0)
21 to 30 years	0 (0.0)	15 (41.7)	0 (0.0)
31 to 40 years	0 (0.0)	12 (33.3)	0 (0.0)
41 to 50 years	5 (35.7)	4 (11.1)	4 (13.8)
51 to 60 years	4 (28.6)	0 (0.0)	12 (41.4)
61 to 70 years	5 (35.7)	3 (8.3)	6 (20.7)
71 to 80 years	0 (0.0)	0 (0.0)	5 (17.2)
> 80 years	0 (0.0)	0 (0.0)	2 (6.9)

Figure 3: The percentage of males and females amongst the three groups



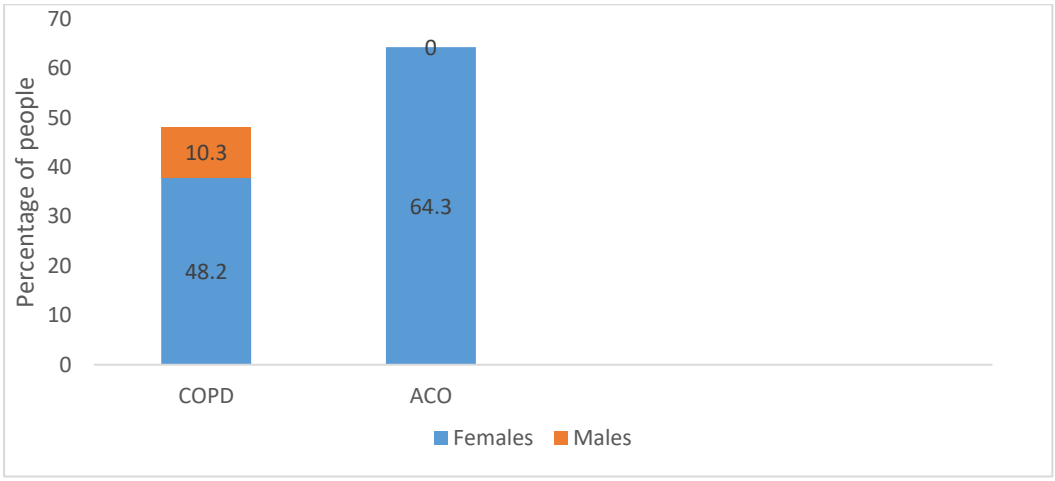
The smoking status amongst the subjects in our study showed that, among the reformed smokers, 21.4% patients had ACO, 5.6% patients had asthma and 34.5% patients had COPD. The smoking index showed 200 to 400 indices in ACO patients, less than 200 in asthma patients and 400 to 600 in COPD patients (figure 3, table 2).

Figure 4: Diagram depicting the percentage of reformed smokers among the three groups.



Amongst the patients with biomass fuel exposure, 9 (64.3%) patients had ACO, none had asthma and 14 (48.2%) patients had COPD and females were having more exposure to it when compared to males, 71.4% and 58.6% of the patients diagnosed to have ACO and COPD respectively were females (figure 4).

Figure 5: Diagram depicting the percentage of people exposed to biomass fuel among the patients

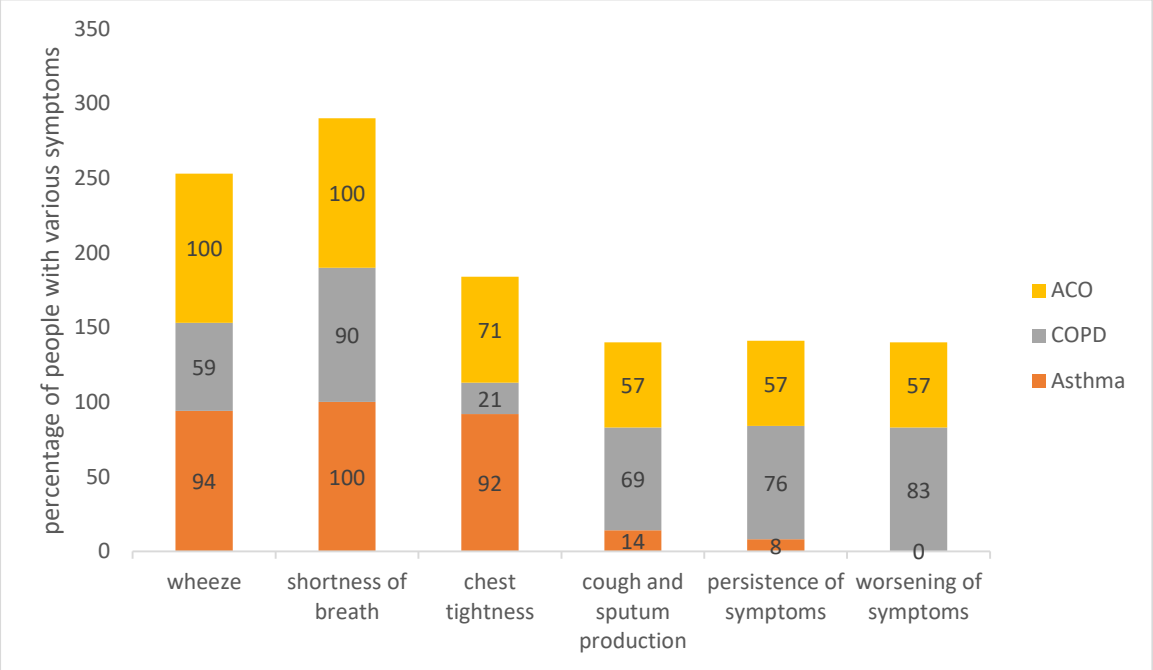


The correlation between family history of obstructive airway diseases to asthma, COPD and ACO showed, 2 (14%) patients diagnosed as ACO , 15 (41%) asthma patients and 2 (6.8%)

COPD patients had a positive family history, this difference was statistically significant (p value 0.003) (table 2).

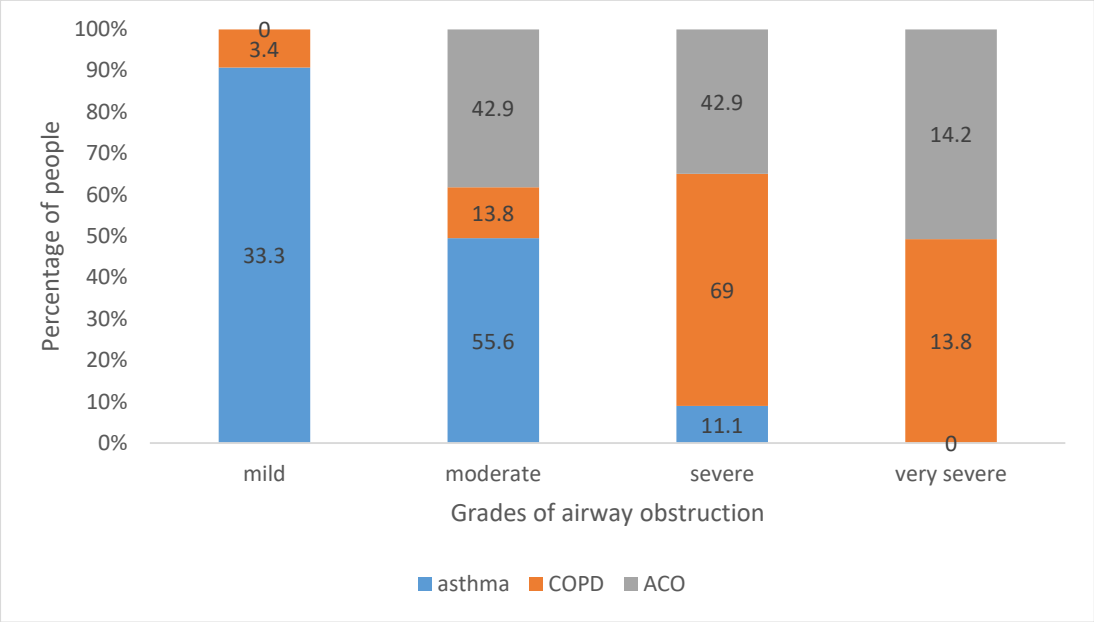
A significant statistical association (p value <0.001) between symptoms and confirmed diagnosis of asthma, COPD and ACO was seen in our study. All patients with ACO in this study had history of breathlessness and wheeze, 71.4% had chest tightness, 57.1% had persistence of symptoms despite treatment and had worsening of symptoms with persistent cough and expectoration. This showed an overlap of symptoms of asthma and COPD (figure 5).

Figure 6: Diagram depicting the percentage of people with various symptoms among the three groups



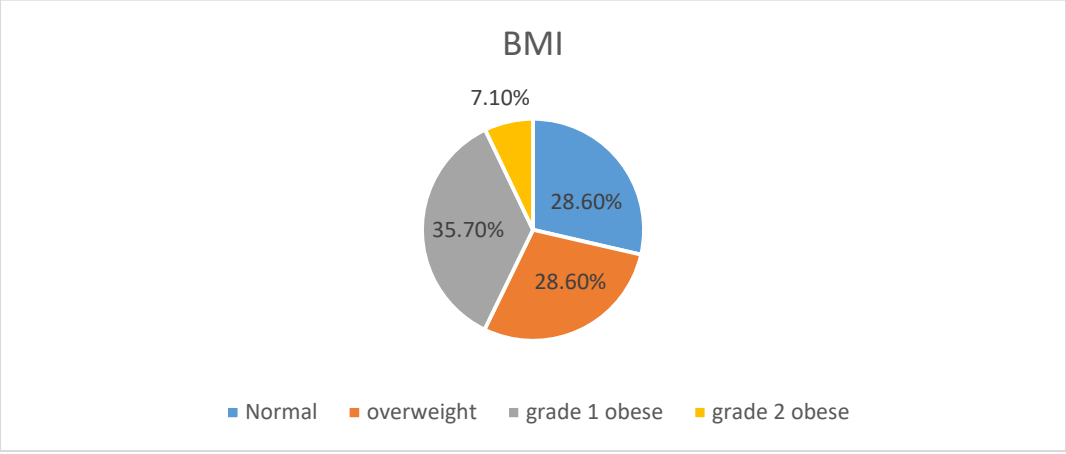
Majority of patients with ACO belonged to moderate and severe grades of obstruction. 6 (42.9%) patients had moderate and severe obstruction each and 2 (14.2%) patients had very severe obstruction. ACO and COPD group had more degrees of obstruction compared to asthma group that was statistically significant (p value <0.001) (figure 6).

Figure 7: Diagram depicting the percentage of people with various grades of airway obstruction among the three groups



The BMI and confirmed diagnosis of chronic airflow obstruction showed similar distribution amongst all the groups, there was no statistical difference (p value 0.114) among them. The patients with ACO belonged to the categories of obese grade1 (35.7%), overweight (28.6%), normal (28.6%), obese grade 2 (7.1%).

Figure 8: Distribution of BMI among patients with ACO



8 patients (27.6%) with COPD, 1 patient with asthma & 2 patients with ACO had systemic hypertension which was statistically significant. No significant association was seen between the diagnosis and with other comorbidities like diabetes, OSA, DPLD or with presence of active PTB. 4 (28.6%) patients with ACO and 14 (48.3%) patients with COPD had pulmonary hypertension which was statistically significant (table 2).

Though significant peripheral blood eosinophilia is commonly seen in eosinophilic asthma and ACO when compared to COPD, No significant association was found with absolute eosinophil count and final diagnosis among our study population (table 2).

Table 2: The correlation between various variables to ACO, asthma and COPD

VARIABLES	ACO	ASTHMA	COPD
Age	< 40 yrs – 0% > 40 yrs – 100%	< 40 yrs – 80.6% > 40 yrs – 19.4%	< 40 yrs – 0% > 40 yrs – 100%
Gender	Females – 71.4% Males – 28.6%	Females – 50% Males – 50%	Females – 58.6% Males – 41.4%
Positive family history	Present in 14.3%	Present in 41.4%	Present in 6.9%
Persistent symptoms	57.1%	8.3%	75.9%
Worsening of symptoms	57.1%	0%	82.8%
FEV1/FVC	<0.7 – 100% >0.7 – 0%	<0.7 – 68.8% >0.7 – 36.2%	<0.7 – 100% >0.7 – 0%
Grades of obstruction	Mild – 0% Moderate- 42.9% Severe – 42.9% Very severe – 14.2%	Mild – 33.3% Moderate- 55.6% Severe – 11.1% Very severe – 0%	Mild – 3.4% Moderate- 13.8% Severe – 69% Very severe – 13.8%
Smoking status (Reformed smokers)	21.4%	5.6%	34.5%
Smoking index	NA – 78.6% <200 – NIL 200-400 – 21.4% 400-600 - NIL	NA – 94.4% <200 – 5.6% 200-400 – NIL 400-600 - NIL	NA – 65.5% <200 – 3.4% 200-400 – 10.3% 400-600 – 20.7%
Biomass fuel exposure	Females- 64.3% Males- 0%	Females- 0% Males- 0%	Females- 37.9% Males- 10.3%
Diabetes mellitus	7.1%	2.8%	10.3%

Systemic hypertension	14.3%	2.8%	27.6%
Pulmonary hypertension	28.6%	0%	48.3%
Absolute eosinophil count (>300)	7.1%	5.6%	3.4%

DISCUSSION:

In our hospital based prospective observational study in 79 patients with chronic airflow obstruction conducted in a span of 2 years, which aimed to determine the prevalence and clinical characteristics of the patients with Asthma-Chronic obstructive pulmonary disease overlap (ACO), asthma was observed in 36 patients (45.6%), COPD in 29 patients (36.7%) and ACO in 14 patients (17.7%) according to the widely accepted GINA-GOLD guidelines. The prevalence rate of ACO according to the joint report of GINA and GOLD on ACO was between 15-55%[2]. A systematic review of literatures on ACO in 2015 by Alshabanat et al in which 19 studies were included, pooled prevalence of ACO in COPD patients was 27% and 28% respectively in population and hospital based studies[3]. In our study, 18% of the pre study asthma patients and 17% of the pre study COPD patients were diagnosed to have ACO. In a study by Hosseini M et al, ACO was seen in 2% of the general population, 29.6% of asthmatics and 26.5% of those patients with COPD[4]. Prevalence of ACO in patients with obstructive lung diseases was found to be 14% in a study by Henriksen et al [5] and in a study by Kiljander et al [6] , the prevalence of ACO among asthmatics was 27.4%.

The age distribution showed the middle-aged (>40 years) patients were more with ACO, younger patients with asthma and older patients with COPD, this was statistically significant (p value <0.001). The gender comparison showed there was no difference between the number of males and females among these different diagnosis (p value 0.379). This was similar to the results obtained in the study conducted by Suchit Kumbhare et al on 2015, the prevalence of ACO and COPD increased with age, an increase was noticed in COPD prevalence after 65 years of age. Asthma was found to be more in younger age group. The ACOS group had more proportion of women (71.4%) than the other two groups [7].

The correlation between family history of airway obstructive airway diseases to various disorders like asthma, COPD and ACO showed that 2 (14%) patients diagnosed as ACO, 15 (41%) asthma patients and 2 (6.8%) COPD patients had a positive family history, this

difference was statistically significant (p value 0.003). A consistent risk factor for asthma used to be family history of the same in immediate family members. Family history of asthma and childhood respiratory infections were the most frequent in subjects with asthma or ACOS ($p<0.001$)[8].

A significant statistical association (p value <0.001) between symptoms and confirmed diagnosis of asthma, COPD and ACO was seen in our study. All patients with ACO in this study had history of breathlessness and wheeze, 71.4% had chest tightness, 57.1% had persistence of symptoms despite treatment and had worsening of symptoms with persistent cough and expectoration. This showed an overlap of symptoms of asthma and COPD. It is similar to the findings by Ayub et al [9] where the wheezers were more in the ACO group compared to the non ACO group. Henriksen et al [5] has reported that the subgroup with ACO had the maximum frequency of respiratory symptoms compared to asthma or COPD alone. There was a two fold rise in the incidence of allergic rhinitis among patients with ACO and also in the presence of cough, wheeze and medication use.

Majority of patients with ACO belonged to moderate and severe grades of obstruction. 6 (42.9%) patients had moderate and severe obstruction each and 2 (14.2%) patients had very severe obstruction. ACO and COPD group had more degrees of obstruction compared to asthma group that was statistically significant (p value <0.001). Henriksen et al [5] in his study has observed the mean FEV1 pre and post bronchodilation was lower in the ACO group. This implied severe grades of obstruction when compared to the asthma alone or COPD alone groups. Most of the studies showing the FEV1 and the FEV1 decline have shown a low FEV1 in ACO than in asthma patients , but similar values as that of ACO are seen in patients with COPD[10].

The smoking status amongst the subjects in our study showed that, among the reformed smokers, 3 (21.4%) patients had ACO, 2 (5.6%) patients had asthma and 10 (34.5%) patients had COPD; this difference was statistically significant (p value 0.012). The smoking index showed 200 to 400 indices in ACO patients, less than 200 in asthma patients and 400 to 600 in COPD patients which was statistically significant (p value 0.004) . Amongst the patients with biomass fuel exposure, 9 (64.3%) patients had ACO, none had asthma and 14 (48.2%) patients had COPD, this difference was statistically significant (p value <0.001). The stratification of biomass fuel exposure showed that females are having more exposure to it when compared to males and there are more ACO and COPD among females. 71.4% and

58.6% of the patients diagnosed to have ACO and COPD respectively were females. In a study by Golpe R et al, the prevalence of smoking among diagnosed ACO patients was less than that of COPD. However the prevalence of biomass fuel exposure was high in people with ACO [11] which is similar to the results we got in this study. Renthlei Lalfakzuala et al [12] showed the number of smokers having ACO was highest (51.4%), followed by ex smokers and then non smokers. Studies by Henriksen et al [5] and Baarnes et al [13] have also shown a higher incidence of ACO amongst smokers.

The BMI and confirmed diagnosis of chronic airflow obstruction showed similar distribution amongst all the groups, there was no statistical difference (p value 0.114) among them. The patients with ACO belonged to the categories of obese grade1 (35.7%), overweight (28.6%), normal (28.6%), obese grade 2 (7.1%). In the study conducted by Renthlie et al,[12] patients with ACO had a BMI of normal range, but few studies showed incidence of ACO in patients with higher BMI [5,6]. In a study by Kumbhare S et al, the ACO group had a greater prevalence of obese and morbidly obese participants than all the groups [7].

The presence of comorbidities in asthma, COPD and ACO patients showed that only one patient with ACO and asthma had diabetes. 3 patients with COPD had diabetes. This was not found to be statistically significant (p value 0.456). 8 (27.6%) patients with COPD, 1 patient with asthma & 2 patients with ACO had systemic hypertension and this was statistically significant (p value 0.016). In a study named Chronic Obstructive Pulmonary Disease and Asthma- Patient characteristics and health impairment by Pleasants, Ohar and Croft et al, age adjusted prevalence of overlap syndrome was significantly higher in persons with obesity, coronary heart disease, stroke, diabetes, arthritis or high blood pressure than persons without the respective co-morbid condition [14]. The respondents with ACOS has a higher prevalence of at least one comorbidity (90.2%) than the group with COPD alone (84%), asthma alone (71.4%), or control subjects (58.4%; P <0.0001) [7]. In a study by Ayub et al there was no significant difference in comorbid illnesses like diabetes mellitus, sleep apnea or history of tuberculosis between the ACO and non ACO groups [9].

The presence of features of OSA, DPLD were assessed in patients with ACO, asthma and COPD, no significant association was found. 4 (28.6%) patients with ACO and 14 (48.3%) patients with COPD had pulmonary hypertension, which was statistically significant (p value <0.001). Similar results were obtained in the study by Ayub et al [9], where pulmonary hypertension was found to be significantly more in the non-ACO COPD group. They were

attributing this to the greater duration of hypoxia which led into pulmonary vascular remodelling in patients with non reversible airway obstruction.

Significant peripheral blood eosinophilia is commonly seen in eosinophilic asthma. This was commonly seen in asthma and ACO when compared to COPD. But, there was no significant difference (p value 0.414) amongst our study population. Mean blood eosinophil count was significantly high is patients with ACO in the study by kobayashi et al.[15] Kitaguchi et al has observed raised sputum and blood eosinophil counts in COPD patients having asthma symptoms [16]. No significant difference in blood eosinophil count was seen in ACO and non ACO groups in a study by Ayub et al [9].

CONCLUSION:

Although there is disagreement on the recognition and definition of ACO as an entity with separate pathophysiological characteristics, the definitions of asthma and COPD is leaving back a subgroup of patients with overlap features of both which usually has a different phenotype in terms of presentation and clinical course. Correct identification of this subgroup helps in better targeted therapy and a better clinical course of the disease, hence this subgroup of patients deserve more attention in terms of identification and individualized management.

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