Assessment of prevalence and characteristics of asthma-COPD overlap among patients with chronic airflow obstruction

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Abstract

Given the paucity of research on asthma-chronic obstructive pulmonary disease (COPD) overlap (ACO) and the high prevalence of co-morbidities and healthcare utilization associated with it, the current study looked at the prevalence of ACO and its clinico-radiological phenotype in patients with chronic airflow obstruction. The study was conducted at a tertiary care hospital in North India. Patients over 40 with COPD or asthma were screened for inclusion in the ACO, asthma, and COPD groups. The ACO and COPD groups were further investigated. The clinical characteristics, lung functions, health-related quality of life, and radiological features of both groups were investigated and compared. ACO was discovered in 16.3% of patients with chronic airflow obstruction (asthma and COPD). The most commonly observed symptoms at presentation in the evaluated ACO patients (n=77) were shortness of breath, wheezing, cough, and expectoration (mean age at presentation: 57.9; mean duration of illness: 8.62 years). Exacerbation rates in ACO patients were significantly higher than in COPD patients ($p<0.001$). The ACO group had a significantly greater mean change in FEV_1 post-bronchodilator in millilitres (ml) and percentage (379.61 ml and 37.72%) than the COPD group ($p<0.001$). The proportion of patients with emphysema was lower in the ACO group than in the COPD group ($p<0.001$). The ACO and COPD groups did not differ significantly in major airway wall thickness ($p=0.3$), but the COPD group had a significantly higher proportion of patients with vascular attenuation and distortion ($p<0.001$). Patients with COPD had a higher degree of hyperinflation, according to high resolution computed tomography (HRCT) indices. This study found that patients with ACO have a distinct phenotype in terms of clinical presentation and HRCT features. More research on the radiological features of ACO is required to identify the anatomical abnormalities involved in the disease's pathogenesis and to validate the radiological features of ACO.

Introduction

Asthma and chronic obstructive pulmonary disease (COPD) are two common chronic airway diseases that have a significant impact on patients' health and quality of life [1,2]. COPD prevalence varies greatly across populations and countries, depending on the diagnostic criteria used and the age group studied. In India, the reported prevalence of COPD ranges from 1.2% to 22% [2,3]. Asthma affects people of all ages, with a 2.05% prevalence among

Indians over the age of 15 and a global prevalence ranging from 1 to 21% in adults [4-6]. In uncontrolled states, these chronic airway diseases cause significant morbidity, healthcare utilization, and decreased productivity in patients [7,8].

It has recently been discovered that typical asthma and COPD symptoms can coexist in the same patient, indicating a novel phenotype of airway disease known as asthma-COPD overlap (ACO) [9,10]. Given its higher healthcare utilization and the difficulties encountered in the diagnostic process, identifying and evaluating this overlap is critical [11,12]. The clinical characteristics of this overlap, however, have not been fully documented, and it may be associated with a variety of heterogeneous phenotypes with diverse underlying mechanisms. Furthermore, having both asthma and COPD is frequently an exclusion criterion for participation in studies investigating either disease [13]. Because this large group of patients has been systematically excluded from clinical studies, there is little scientific data on their diagnosis, treatment, and prognosis. The current study examined the prevalence of ACO and its clinico-radiological characteristics in patients with chronic airflow obstruction in North India. Furthermore, the clinical and radiological characteristics of the ACO group of patients were compared to those of the COPD group.

Materials and Methods

The study was conducted at the Department of Respiratory Medicine and Radio-Diagnosis, at a tertiary care hospital in North India. The study was initiated after approval from the Institutional Ethics Committee. The primary objective of the current study was to calculate the prevalence of ACO among patients with chronic airflow obstruction (asthma, COPD) aged more than 40 years. The secondary objective was to study and compare the clinical features, lung functions, and radiological features of the ACO group with age-matched COPD subjects.

During the study period of one year, physician-suspected COPD or asthma patients aged more than 40 years presenting at the outpatient unit were identified and screened for inclusion in the study. Patients with respiratory disorders other than asthma and COPD, pregnant females, and those with other concomitant diseases or disorders were excluded from this study. Using the syndromic diagnosis of asthma, COPD and ACO published by a joint project of GINA and GOLD in 2017 these patients were categorized into asthma, ACO and COPD groups [14]. The attached supplementary file carries the details of this syndromic diagnosis.

The COPD group included patients with three or more COPD characteristics and an FEV_1/FVC ratio of less than 0.7 post-bronchodilator. Similarly, the diagnosis of asthma required three or more asthma characteristics and evidence of reversible airflow limitation characterised by a post-bronchodilator increase in FEV_1 >12% and 200 ml from baseline. The ACO group included patients with a similar number of asthma and COPD features, as well as markedly reversible airflow limitation (post-bronchodilator) or other proof of variable airflow limitation, and FEV_1/FVC<0.7 post-bronchodilation. Markedly reversible airflow limitation is said to be present when post-bronchodilator increase in FEV_1 >12% and 400 ml from baseline is observed. A post-bronchodilator increase in FEV_1 >12% and 200 ml from baseline was also considered compatible with diagnosis of ACO in subjects with low FEV_1 and similar number of both asthma and COPD features.

Detailed methodology

Patients with ACO and COPD were evaluated in detail (history and physical examination). The number of exacerbations (defined as events when subjects experienced increased respiratory symptoms requiring antibiotics, steroids, or presentation to a physician or hospital) in the one year before the presentation was recorded. The enrolled patients then underwent spirometry and high-resolution computed tomography (HRCT) of the chest. Health-related quality of life in both ACO and COPD groups was determined by using COPD Assessment Test (CAT) score[15] and Clinical COPD Questionnaire (CCQ) [16].

Spirometry

After withholding the short-acting bronchodilators for 6 hours or more, long-acting bronchodilators for 12 hours or more and sustained-release theophylline for 24 h, the spirometry was performed using RMS Helios 702 spirometer before and 15-20 min after a bronchodilator (400 µg salbutamol). Spirometry indices [forced vital capacity (FVC), forced expiratory volume in 1st sec (FEV_1), the ratio of FEV_1 to FVC (FEV_1/FVC), and bronchodilator reversibility] were assessed using the best out of three technically satisfactory acceptable performances as per recommendations of American Thoracic Society [17].

High-resolution computed tomography

The scans were obtained using Siemens Somatom plus 4 volume zoom (Siemens, Erlangen, Germany) Spiral CT scanner. Scanning was performed at a field of view large enough to encompass the patient in the supine position. The images were obtained in deep inspiration and expiration using a thin-section (1-mm collimation) technique at 120 kVp and 90 mA. Subsequently, the images were reconstructed using a high spatial frequency algorithm. The supplementary file details the HRCT parameters studied, and definitions used.

Statistical analysis

IBM SPSS Statistics was used for statistical analysis. Categorical data were presented as percentages (%) and frequency distribution tables were prepared. Quantitative data were presented as mean and standard deviation. For the comparison of quantitative data between ACO and COPD groups, the independent Student's *t*-test, Chi-square test and Wilcoxon-Mann-Whitney U test were employed. All tests were performed at a 5% level of significance indicating that an association was significant if the p-value was less than 0.05 ($p<0.05$).

Results

A total of 503 subjects were screened for the study, out of these 82 had ACO, 273 had COPD, and 148 had asthma. Hence, among the patients aged more than 40 years with chronic airway obstruction, the prevalence of ACO was 16.3%.

Clinical characteristics of ACO patient

Of 77 subjects with ACO who volunteered for further study, 53 (68.8%) were male and the rest 24 were female. The mean age at presentation was 57.9±8.9 years and the mean duration of illness at presentation was 8.62±8.17 years. All subjects had shortness of breath at the presentation. Most patients showed intermittent (64.9%) pattern of symptoms. The perennial or persistent pattern

of symptoms was observed in 27 (35.1%) patients. The symptoms were progressive in the majority (77.9%) of patients. The baseline characteristics of the study population have been illustrated and compared in Table 1. The ACO group had a significantly more proportion of females in their group compared to the COPD group. The pattern of symptoms also differed significantly among the two groups with the ACO group having more patients with intermittent and progressive symptoms while the COPD group had more patients with persistent and progressive symptoms. Seasonal or diurnal variability in the symptoms and the presence of a trigger factor for the symptoms were observed in a significantly higher number of ACO patients (p<0.001). A positive family history of atopic disease (asthma, allergic rhinitis, atopic dermatitis) was present in a significantly higher number of ACO patients compared to COPD patients (p=0.016). The COPD group of patients had significantly more pack-years of smoking (p<0.001), as shown in Table 1.

Health status

The mean CAT and CCQ scores in patients with ACO were 10.8 and 15.3 respectively. The mean CCQ score among the ACO patients was significantly higher than that observed in COPD patients (p=0.03) representing a relatively lower health status. However, there was no significant difference in CAT scores of both the groups (p=0.07). The mean number of exacerbations observed in ACO group were 2.1±1.1 while that in the COPD group were 1.5±0.7. The exacerbation rate observed among ACO patients was significantly higher than in COPD patients (p<0.001). These findings have been depicted in Table 2.

Spirometry findings

The mean change in FEV1 observed after bronchodilator was significantly larger among ACO patients compared to the COPD group (p<0.001). No significant difference was observed among the two groups in the rest of the lung function parameters as shown in Table 3. More than half of ACO patients (51.9%) had a post-bronchodilator increase in FEV_1 of more than 400 ml and 12%, rest had a change within the range 200ml to 400ml and more than 12%.

HRCT findings

In the ACO group, emphysema was observed in 45.5% of patients while 87% of patients in the COPD group had emphysema (p<0.001; Table 4). Panacinar emphysema was not seen at all in the ACO group, while in the COPD group, 4 patients (5.2%) had panacinar emphysema. Centriacinar emphysema was observed in 26% and 57.1% of patients in the ACO and COPD groups respectively (p<0.001) while paraseptal emphysema was present in 32.5% of patients in the ACO group and 64.9% in COPD group (p<0.001). Mosaic attenuation pattern was present in 7 cases (9.1%) in the ACO group and 26 cases (33.8%) in the COPD group. The involvement of different lobes of the lungs in ACO and COPD groups is depicted in Figure 1. The ACO and COPD group did not differ significantly in major airway wall thickness (p= 0.3) while the COPD group had a significantly higher proportion of vascular attenuation and distortion (p<0.001).

Table 1. Comparison of baseline characteristics of patients with ACO and COPD.

Characteristic	ACO (n=77), (%)	COPD (n=77), (%)	p-value
Age (years)	57.97±8.86	57.86±8.38	0.94*
Male gender	53 (68.8)	73 (94.8)	<0.001#
Rural residence	64 (83.1)	69 (89.6)	0.240#
BMI (kg/m^2)	22.73±2.92	22.04±4.81	0.288*
Duration of illness (years)	8.62±8.17	8.49±5.28	0.250$
Dyspnea	77 (100.0)	77 (100.0)	1.0#
Cough	35 (45.5)	52 (66.2)	0.009#
Sputum	33 (42.9)	48 (62.3)	0.015#
Wheeze	14 (18.2)	24 (31.2)	0.062#
Pattern of symptoms			
Persistent	27 (35.1)	66 (85.7)	<0.001#
Progressive	60 (77.9)	71 (92.2)	0.013#
Seasonal variability	75 (97.4)	42 (54.5)	<0.001#
Diurnal variability	74 (96.1)	26 (33.8)	<0.001#
Triggering factor	54 (70.1)	11 (14.3)	<0.001#
Family history of atopic disease	10 (13.0)	02 (2.6)	0.016#
Pack years	16.97±19.32	29.87±13.96	<0.001$

ACO, asthma chronic obstructive pulmonary disease overlap; COPD, chronic obstructive pulmonary disease; BMI, body mass index; *independent Student's t-test; #Chi-square test; $Wilcoxon-Mann-Whitney U test.

Table 2. Comparison of exacerbation rate, COPD assessment test (CAT), and clinical COPD questionnaire (CCQ) scores among patients with ACO and COPD.

Characteristic	ACO (n=77)	COPD (n=77)	p value
Mean number of exacerbations (±SD)	2.08±1.13	1.52±0.72	0.001*
CAT score (mean±SD)	10.77±4.06	9.78±2.61	0.07*
CCQ score (mean±SD)	15.35±5.73	13.40±4.96	0.03*

COPD, chronic obstructive pulmonary disease; CCQ, clinical chronic obstructive pulmonary disease questionnaire; *independent Student's *t*-test; ACO, asthma chronic obstructive pulmonary disease overlap.

Table 3. Comparison of lung function parameters of ACO and COPD patients.

Characteristic (mean±SD)	ACO (n=77)	COPD (n=77)	p value
Post BD FEV_1 (ml)	1.47±0.44	1.37±0.59	0.246*
Post BD FEV_1 (% of predicted)	60.51±18.78	56.06±22.47	0.185*
Change in FEV_1 post bronchodilation (ml)	379.61±123.55	76.62±63.73	<0.001$
Percent change in FEV_1 post bronchodilation	37.72±16.28	6.98±7.29	<0.001$
Post BD FVC	2.68±0.63	2.59±0.85	0.489*
Post BD FEV_1/FVC	0.55±0.10	0.52±0.09	0.059*

COPD, chronic obstructive pulmonary disease; ACO, asthma chronic obstructive pulmonary disease overlap; BD, bronchodilator; COPD, chronic obstructive pulmonary disease; FEV, forced expiratory volume; FVC, forced vital capacity; * independent Student's *t*-test; $Wilcoxon-Mann-Whitney U test.

Table 4. Comparison between ACO and COPD group based on HRCT findings.

Findings on HRCT	ACO (n=77), (%)	COPD (n=77), (%)	p value
Emphysema	35 (45.5)	67 (87.0)	<0.001#
Panacinar	0 (0.0)	4 (5.2)	0.043#
Centriacinar	20 (26.0)	44 (57.1)	0.001#
Paraseptal	25 (32.5)	50 (64.9)	0.001#
No emphysema	42 (54.5)	10 (13.0)	0.001#
Mosaic attenuation pattern	7 (9.1)	26 (33.8)	0.001#
Chronic bronchitic changes			
Major airway wall mean thickness (in mm)	1.88±0.39	1.82±0.38	0.328*
Visibility of small airway	77 (100)	71 (92.2)	0.012#
Pulmonary vasculature			
Vascular attenuation	25 (32.5)	47 (61.0)	<0.001#
Vascular distortion	24 (31.2)	47 (61.0)	<0.001#
Features of hyperinflation			
Mean tracheal index	0.90±0.15	0.90±0.22	0.918*
Tracheal index <0.67	2 (2.6)	14 (18.2)	0.002#
Mean Sterno aortic distance at carinal level (in mm)	24.84±8.38	31.10±10.48	<0.001*
Mean thoracic cage ratio (AP/transverse] diameter			
At tracheal carina	0.65±0.07	0.69±0.07	0.001*
At 5 cm blow carina	0.78±0.08	0.82±0.08	<0.001*
Mean thoracic cross-sectional area at 1 cm below the top of the aortic arch (mm^2)	23231.09±4227.62	26261.61±3434.75	<0.001#

ACO, asthma chronic obstructive pulmonary disease overlap; COPD, chronic obstructive pulmonary disease; HRCT, high-resolution computed tomography; *independent Student's *t*-test; #Chi-square test; AP, anterio-posterior.

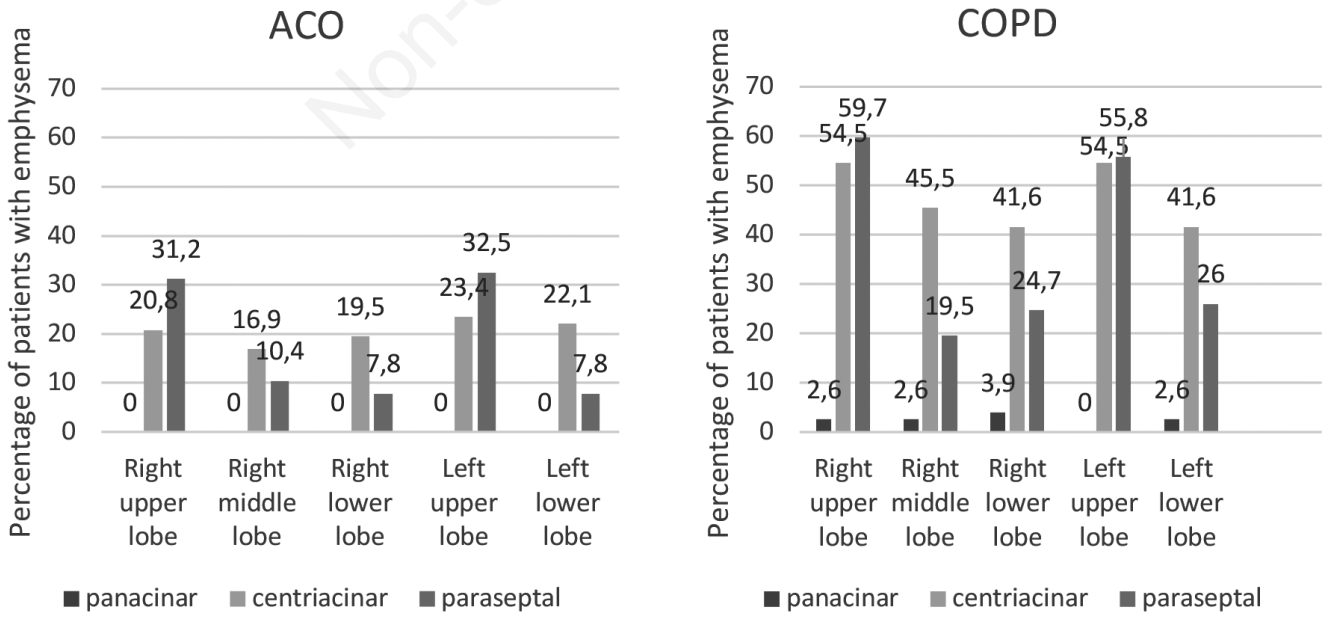

Figure 1. Histograms comparing emphysematous involvement of lung lobes among ACO and COPD groups.

Both the groups differed significantly in the mean Sterno-aortic distance at the carinal level ($p<0.001$), mean thoracic cage ratio ($p<0.05$), and mean thoracic cross-sectional area at 1 cm below the top of the aortic arch ($p<0.001$) suggesting a relatively higher degree of lung hyperinflation in patients with COPD (Table 4).

Discussion

The current study looked at the clinical phenotype and prevalence of ACO among patients with chronic airflow obstruction. ACO was found in 16.3% of patients with chronic airflow obstruction, which is comparable to the prevalence reported in the literature (15-25%) [9,18]. Since different criteria have been employed across studies evaluating different demographic groups (patients with COPD, patients with airway obstruction, the general population, different age groups), the reported prevalence of ACO differs from study to study [19]. Furthermore, this is one of the initial Indian studies using a syndromic approach to chronic airway diseases. The majority of other studies have looked at the prevalence of ACO in either asthma or COPD patients. There is a single study (a nationwide hospital discharge registry data from Finland) on the prevalence of ACO in patients with chronic airflow obstruction [18]. This study identified patients >34 years of age with a diagnosis of COPD or asthma (from 2000-to 2009) and estimated the prevalence of ACO to be 16.1% in patients with primary or secondary diagnoses of COPD or asthma in Finland.

In the current study, all patients with ACO presented with shortness of breath. The observed prevalence of wheeze, cough, and expectoration was less than that was observed in previous studies, possibly due to inconsistency in the reporting of the symptoms because of regional or environmental impact [1,12,20]. Most of the patients with ACO in our study showed intermittent (64.9%) and progressive (76.6%) pattern of symptoms while 96.1% of patients had seasonal and diurnal variability. This pattern of symptoms is expected from the ACO population as they exhibit features of both asthma and COPD.

ACO patients had significantly higher CCQ scores compared to COPD patients in our study. This points toward higher symptom frequency, severity and lower health status in ACO patients than in COPD patients. Kauppi *et al.* [21] and Corlateanu *et al.* [22] evaluated the health-related quality of life in patients with chronic airway obstruction and different phenotypes of COPD respectively. According to these studies, patients with ACO had worse health-related quality of life (HRQoL) than asthma patients, whereas frequent exacerbator COPD patients had more severe deterioration of HRQoL and worse lung function than patients with ACO. Furthermore, ACO patients had a significantly higher exacerbation rate than COPD patients which is in accordance with the observations of Hardin *et al.* [11], Miravitlles *et al.* [20] and Menezes *et al.* [12].

All ACO patients had a post-bronchodilator increase in FEV_1 of more than 200 ml and 12%, while more than half (51.9%) had a post-bronchodilator increase in FEV_1 of more than 400 ml and 12%. These values of post-bronchodilator change in spirometry parameters were expected in the ACO group as it is required for its diagnosis in the syndromic approach to chronic airway diseases [14]. The increase in FEV_1 postbronchodilator was significantly larger than that observed in COPD patients, as patients with ACO show marked postbronchodilator reversibility ($p<0.001$).

We discovered that COPD patients had a higher prevalence and extent of emphysema on HRCT than ACO patients. This is consistent with previous research comparing ACO and COPD [23,24]. The COPD group had significantly higher parameters of lung hyperinflation, vascular attenuation, and vascular distortion than the ACO group. The parameters of lung hyperinflation described in our study had not previously been studied in the ACO population. Major airway wall thickness, a chronic bronchitis indicator, was higher in ACO patients but not statistically significant. Suzuki *et al.* [25] discovered that airway wall thickness was significantly higher in ACO than in COPD, and that it decreased after treatment with budesonide/formoterol. However, the subjects in this study were much older than those in the current study. In their study on the COPD gene cohort, Cosentino *et al.* [23] discovered that patients with ACO had more airway disease, as evidenced by a greater segmental wall area and thickness when compared to COPD patients. Despite the fact that the ACO patients in this study were significantly younger than the COPD patients. Another recent study on the Egyptian population found that patients with asthma had significantly greater airway wall thickness compared to the ACO and COPD groups ($p<0.001$) [26]. The study, however, did not provide data on the comparison of this variable in the ACO and COPD groups. Overall, the current study provides higher-quality comparative data on this parameter for the ACO and COPD groups.

This prospective study provides insight into the clinical phenotype and characteristics of ACO patients. Given the scarcity of Indian studies on the topic, this is an important contribution to the literature. However, there are some limitations. For example, because the study was conducted at a tertiary care institution, the possibility of referral bias cannot be ruled out. Another significant limitation of the current study is the lack of gender matching in the two comparative groups. Furthermore, the study did not compare ACO patients to those who only had asthma.

Conclusions

Many patients who have asthma or COPD have symptoms from both diseases. The use of a syndromic approach to chronic airway diseases may result in the diagnosis of ACO in many patients who were previously treated for COPD or asthma. According to the findings of this study, patients with ACO have a distinct phenotype in terms of clinical presentation and HRCT features. HRCT features may aid in distinguishing ACO patients from COPD and asthma patients and may be included in future ACO diagnostic guidelines.

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