Predictors of asthma-chronic obstructive pulmonary disease overlap syndrome in patients with chronic obstructive pulmonary disease from a tertiary care center in India

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ABSTRACT

Background: There is dearth of literature on asthma-chronic obstructive pulmonary disease overlap syndrome (ACOS) in India. The aim was to compare clinical characteristics between patients with ACOS and non-ACOS COPD and to identify clinical predictors of ACOS in patients with COPD. Methods: We conducted a retrospective study by reviewing data collected from patients performing spirometry at our hospital. Those with postbronchodilator FEV$_1$/FVC <70% were included in the study. Among them, those with significant reversibility (change in FEV$_1$ or FVC by 12% and 200 ml postbronchodilator) were diagnosed with ACOS and the rest were considered to have non-ACOS COPD. Data on the 2 groups were compared and statistical analysis was performed. Results: Out of a total of 324 patients, 100 of them had postbronchodilator FEV$_1$/FVC <70%. Of them, 45 and 55 were diagnosed with ACOS and non-ACOS COPD, respectively. Patients with ACOS had significantly higher postbronchodilator FVC volumes and FVC % predicted values ($P < 0.05$), had higher reported wheeze ($P = 0.02$) and ankle edema ($P < 0.05$), were more likely to be smokers ($P = 0.01$) with lower smoking index ($P = 0.03$), and had frequent (≥2) ER visits ($P = 0.04$). However, very frequent (≥3 per year) hospital admissions ($P < 0.01$) with higher rates of invasive mechanical ventilation ($P = 0.02$), and pulmonary hypertension diagnosed by two-dimensional echocardiography ($P < 0.01$) were significantly higher in the non-ACOS group. The two groups did not differ with respect to history of atopy, family history of wheeze, compliance to inhaler therapy, or blood absolute eosinophil counts. Conclusion: Our study highlights how the ACOS phenotype may clinically differ from their counterparts elsewhere, making it a clinical challenge to identify them in India.

KEY WORDS: Asthma chronic obstructive pulmonary disease overlap syndrome, chronic obstructive pulmonary disease, significant post bronchodilator reversibility

INTRODUCTION

Asthma and chronic obstructive pulmonary disease (COPD) are chronic respiratory diseases involving the major and small airways and manifest with wheeze, shortness of breath, chest tightness, and cough. Asthma is characterized by chronic airway inflammation and airway hyper-responsiveness to a variety of stimuli with symptoms varying over time and intensity associated with variable expiratory flow limitation. COPD is characterized by persistent airflow limitation that is usually progressive and is associated with a chronic inflammatory response in the airways to noxious particles and gases.$^{[1,2]}$

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COPD is a major cause of death and disability throughout the world. According to the WHO estimates, 65 million people have moderate-to-severe COPD.\cite{3,4} The Indian study on epidemiology of asthma, respiratory symptoms, and chronic bronchitis questionnaire-based study on chronic bronchitis reported an overall prevalence of 3.49%\cite{3} Considering the high prevalence, a lot of importance is given to diagnosing and treating these patients. Research has revealed that COPD encompasses various phenotypes and that clinical presentation and response to therapy varies in different patients. Authors have identified subsets within patients with COPD: predominantly emphysema on imaging, chronic bronchitis with increased sputum production, and nonexacerbators and frequent exacerbators.\cite{2,3,4}

In this regard, a subset of patients with COPD with clinical implications has been identified: in addition to having chronic airflow limitation (postbronchodilator forced expired volume in 1 second/forced vital capacity, $\text{FEV}_1/\text{FVC} < 70\%$), they also demonstrate variability in symptoms along with significant postbronchodilator reversibility. These patients had clinical features of both asthma and COPD and hence were diagnosed to have asthma COPD overlap syndrome (ACOS).\cite{7}

There is little data on ACOS from India. We reviewed routine data collected from patients undergoing spirometry at our centre and tried to identify this subset of COPD patients as well as identify predictors of this group of patients.

**METHODS**

This retrospective descriptive study was conducted at the Department of Pulmonary Medicine at Sri Ramachandra Medical College and Research Institute between January 2017 and March 2017. Approval was obtained from the Ethics Committee of our university. Our university hospital is a large tertiary referral centre for the city of Chennai in the state of Tamil Nadu in India. Spirometry was performed as a routine investigation for patients who presented to our outpatient services with dyspnea, wheeze, or chest tightness. Before spirometry, a detailed clinical history (including symptoms of atopy, dyspnea, wheeze, cough, sputum and ankle edema, family history of wheeze, history of tuberculosis, comorbidities such as diabetes mellitus, systemic hypertension and obstructive sleep apnea, smoking history, occupation in the farming industry, inhaled medication use, use of home nebulisers and home oxygen and hospital visits, including number of emergency room (ER) visits, hospitalization, and requirement for noninvasive or invasive mechanical ventilation [IMV]) was obtained, and clinical examination findings were recorded. Patients who had a postbronchodilator $\text{FEV}_1/\text{FVC} < 70\%$ were included in the study. They were subjected to other additional investigations (complete blood counts, blood absolute eosinophil counts [AECs], two-dimensional (2D) echocardiogram, and chest X-ray posteroanterior view as considered appropriate) and all results were recorded on follow-up visits. Informed written consent was obtained from all patients.

**Spirometry**

For all patients, an FVC manoeuvre was performed in the pulmonary function testing laboratory of the department using a flow-based pneumotachometer spirometer (model KoKo Px, company NSpire). The following spirometric indices were recorded: $\text{FEV}_1$, FVC, $\text{FEV}_1/\text{FVC}$, and the absolute volume as well as the percentage reversibility in $\text{FEV}_1$ and FVC. Patients were encouraged to perform the test to ensure optimum results were achieved as per the American Thoracic Society-European Respiratory Society (ATS-ERS) guidelines in force since 2005.\cite{8} This included achieving a target expiratory time of six or more seconds, and repeating the test a minimum of three times, and up to a maximum of 8 times but no more, to achieve a minimum of at least 3 technically acceptable and reproducible results. The highest measurements from the best 3 results were taken. Predicted percentage values of $\text{FEV}_1$, FVC, and $\text{FEV}_1/\text{FVC}$ were calculated using the software in the spirometer. The spirometer was frequently calibrated to ensure performance as per the laboratory protocol. A value of $\text{FEV}_1/\text{FVC} < 70\%$ was diagnosed as obstructive pattern and the severity of obstruction as per the FEV$_1$% predicted was classified according to the ATS-ERS guidelines of 2005. Significant and high bronchodilator reversibility were defined as the increase in $\text{FEV}_1$ or FVC by 12% and 200ml, and 15% and 400 ml, respectively, after administration of 400 μg of salbutamol by pressurized metered dose inhaler along with spacer as 4 actuations of 100 micrograms each every 15 s.\cite{9}

Results of the spirometry, along with other patient details were recorded in patient-specific pro forms. Statistical analysis was performed using Stata statistical analysis software. A descriptive analysis was performed. Categorical variables were expressed as frequency (percentages), and quantitative variables were expressed as mean ± standard deviation or median interquartile range. Statistical significance was calculated using Pearson's Chi-square test, and results were deemed statistical significant if $P < 0.05$.

**RESULTS**

Of the 324 spirometry procedures performed over 3 months (January 2017 to March 2017), postbronchodilator $\text{FEV}_1/\text{FVC} < 70\%$ was identified in 100 patients. Forty-five of the 100 patients had significant bronchodilator reversibility and were diagnosed with ACOS. Except for the FVC absolute volume and FVC% predicted values ($P < 0.05$), there was no significant difference in the baseline characteristics of the 2 study groups [Table 1].

Using the data available from the individual patient pro forms, the clinical profile of the 2 study groups was compared [Table 2]. The ACOS group was more likely
to report wheeze ($P = 0.02$) and ankle edema ($P < 0.05$) when compared to the non-ACOS group. There was no significant difference in the duration of symptoms between the 2 groups and the 2 groups did not differ with respect to history of atopy, family history of wheeze, history of tuberculosis (defined as having consumed antituberculous therapy for either microbiological or radiological proven tuberculosis), and presence of comorbid illnesses such as diabetes mellitus and sleep apnea (based on a screening STOP BANG score ≥3). The significant difference noted between the 2 patient groups in the presence of systemic hypertension may be disregarded in view of the small number of patients with systemic hypertension in the study group.

Although smoking was significantly higher in the ACOS group ($P = 0.01$), they were more likely to be “light” smokers (smoking index [SI] <200, $P = 0.03$). Frequent (2 or more) ER visits were significantly higher in the ACOS group ($P = 0.04$), whereas, very frequent hospital admissions (3 or more) per year was significantly higher in the non-ACOS group ($P < 0.01$), and they were more likely to require IMV ($P = 0.02$). The 2 groups did not differ with respect to inhaler use or compliance to therapy. A review of investigations available showed pulmonary hypertension to be significantly more in the non-ACOS group ($P = 0.01$). There was no significant difference in the blood AEC levels between the 2 groups.

**DISCUSSION**

The prevalence of ACOS among patients with COPD at our center was high (45%). Whether this represents true prevalence in the community can be argued as there may be a referral bias with respect to our center. Variable prevalence rates (15% to 55%) have been reported from other centres, probably attributed to different prevalent rates of COPD in the community as well as different diagnostic criteria used to define ACOS. In this study, we defined ACOS in patients having significant bronchodilator reversibility in the background of persistent postbronchodilator airflow limitation (FEV/FVC <70%). Other studies have used exhaustive criteria (such as younger age, presence of asthma, atopy, significant smoking, high reversibility on spirometry, elevated serum immunoglobulin E [IgE] and blood AEC levels, sputum eosinophilia, and fractional exhaled nitric oxide [FeNO] levels) to identify this group of patients.

Baseline characteristics were very similar between the groups except for the postbronchodilator FVC absolute volume and FVC % predicted values, which were higher in the ACOS group. This may be attributed to the immediate effect of the bronchodilator in improving expiratory airflow and hence an increase in the FVC at the expense of reduction in air trapping in the group of patients who had a potential for “reversibility.” There was no difference between the 2 groups in other parameters in our study unlike in other studies, where ACOS patients were identified to be younger and were more likely to be obese.

Both groups had similar presenting complaints. However, the ACOS group reported to perceive wheeze as more troublesome when compared to the non-ACOS group. We believe that in the ACOS group, there is a consistent variability in the wheeze attributed to the “ reversible” element in airflow limitation. This probably makes the patient often recognize the wheeze as its intensity frequently changes with time. However, in the non-ACOS patient, there is persistent and slowly progressive airflow limitation with no sudden variability. As a result, the non-ACOS patient does not experience sudden episodes of worsening airflow limitation over and above the existing and persistent airflow limitation and hence, fails to report wheeze ‘troubling’ him or her. The ACOS group reported ankle edema more often than the non-ACOS group, the reason for which is not clear. History of atopy was not significantly different between the 2 groups unlike previously published literature.

History of smoking was significantly higher in the ACOS group. This may be a selection bias, as the ACOS group is a selective subset within the COPD cohort and hence, there will be a concentration of cases within this subset. The SI was significantly lower (SI <200) in the ACOS group, similar to previously published literature. No significant difference was identified in comorbid illnesses such as diabetes mellitus and sleep apnea, family history of wheeze, and history of tuberculosis between the two groups. Interestingly, an earlier study had shown an increased incidence of pulmonary tuberculosis in patients with ACOS.

Utilization of hospital services threw an interesting picture. Patients from both groups have had ER visits for exacerbations in the past one year. However, the ACOS group had more frequent (≥2) ER visits for exacerbations in the past year. This compares with data available from China and the American continents, but contrasts with data available from other studies where no association was found between ACOS and exacerbation rates.

### Table 2: Clinical profile of the study group (n=98)

| Clinical features                              | NonACOS group (n=53) | ACOS group (n=45) | Pearson χ² (asymptotic significant 2-sided) |
|------------------------------------------------|---------------------|------------------|-----------------------------------------|
| Duration of symptoms (years)                  | 12.6±11.5 (1-60)    | 15.5±10.3 (1-40) | 0.206                                   |
| History                                       |                     |                  |                                         |
| Atopy                                         | 36 (67.9)           | 29 (64.4)        | 0.72                                    |
| Dyspnea                                       | 53 (100)            | 45 (100)         | 0.02                                    |
| Wheeze                                        | 42 (79.2)           | 43 (95.6)        | 0.46                                    |
| Cough                                         | 52 (98.1)           | 43 (95.6)        | 0.76                                    |
| Ankle edema                                   | 17 (32.1)           | 17 (37.8)        | <0.05                                   |
| History of smoking                            |                     |                  |                                         |
| Number of smokers a                          | 34 (65.4)           | 31 (68.9)        | 0.01                                    |
| SI>200                                        | 6 (20.1)            | 11 (37.9)        | 0.03                                    |
| ≥200                                          | 23 (79.3)           | 18 (62.1)        |                                         |
| Comorbidities                                 |                     |                  |                                         |
| Sleep apnea                                   | 4 (7.5)             | 3 (6.7)          | 0.87                                    |
| Diabetes mellitus                             | 21 (39.6)           | 16 (35.6)        | 0.68                                    |
| Systemic hypertension                         | 4 (7.5)             | 0 (0)            | 0.04                                    |
| Other history                                 |                     |                  |                                         |
| Family history of wheeze                      | 20 (37.7)           | 24 (53.3)        | 0.12                                    |
| History of tuberculosis                       | 14 (26.4)           | 11 (24.4)        | 0.82                                    |
| Farming occupation                            | 17 (32.1)           | 20 (44.4)        | 0.21                                    |
| ER visits and hospitalization                 |                     |                  |                                         |
| Number of ER visits in last one year          |                     |                  |                                         |
| 1                                             | 31 (58.5)           | 24 (53.3)        | 0.04                                    |
| >2                                            | 22 (41.5)           | 21 (46.7)        |                                         |
| Number of hospitalizations in last one year   |                     |                  |                                         |
| 0                                             | 6 (11.3)            | 8 (17.8)         | <0.01                                   |
| 1                                             | 4 (7.5)             | 11 (24.4)        |                                         |
| 2                                             | 18 (33.9)           | 19 (42.2)        |                                         |
| ≥3                                            | 25 (47.2)           | 7 (15.6)         |                                         |
| NIV requirement during hospitalization in last year | 0 (0)               | 0 (0)            | -                                       |
| Requirement for invasive mechanical ventilation during hospitalization in last one year | 6 (11.3)            | 0 (0)            | 0.02                                    |
| Medication use and compliance                 |                     |                  |                                         |
| Inhaler use c                                 | 34 (64.2)           | 29 (64.4)        | 0.86                                    |
| On home nebulizers                            | 2 (3.8)             | 2 (4.4)          | 0.87                                    |
| On home oxygen                                | 0 (0)               | 1 (2)            | 0.28                                    |
| Results of investigations                    |                     |                  |                                         |
| Blood AEC d                                  | 192.0±295.5 (10-1411) | 330.2±665.4 (12.4-4022) | 0.17f                                   |
| Pulmonary hypertension on 2D echocardiogram e| 25 (58.1)           | 15 (71.4)        | <0.01                                   |

Values expressed as n (%), or mean±SD (range). *Smoking history was available in 97 patients, of which 65 were smokers. †SI is defined as the number of bidis or cigarettes smoked per day multiplied by the number of years smoked. SI data were available for 58 of 65 smokers. ‡Data on regular inhaler use were available in 97 patients. ‡Blood AEC values were available for 64 patients. *Pulmonary hypertension was diagnosed on 2D echocardiography based on tricuspid regurgitation flow. 2D echocardiogram results were available in 64 patients. Statistical significance calculated by independent sample t-test. ACOS: Asthma-COPD Overlap Syndrome, COPD: Chronic obstructive pulmonary disease, ER: Emergency room, SI: smoking index, NIV: Noninvasive ventilation, AEC: Absolute eosinophil counts, 2D: 2 dimensional, SD: Standard deviation.
physiologically behaving as acute asthma, and hence do not proceed to get hospitalized. Or are there other factors contributing to reduced admission rates in contrast to higher ER visits? More research is probably required in this regard. In addition, the requirement for IMV was significantly higher in the non-ACOS COPD group. In the absence of a “reversible” element to their bronchospasm, such patients may not have improved with continuous nebulized bronchodilators and hence may have required IMV. However, the significantly higher use of IMV in the non-ACOS COPD group may be multifactorial and might be determined by presenting arterial blood gases, unavailability of non-invasive ventilation and the presence or absence of contraindications to the latter (hemodynamic instability and loss of consciousness).

There was no significant difference between the 2 groups with respect to the use of medications and blood AEC levels, unlike in other studies where patients with ACOS use more medications and have higher blood AEC levels.\textsuperscript{11,13,14} The latter may be due to the ACOS phenotype itself consisting of other subphenotypes such as COPD with eosinophilic inflammation and COPD with a history of asthma. Our patients may be a mix of several subphenotypes and that may lead to an absence of statistical significance with respect to AEC.\textsuperscript{21,22} A subgroup analysis also failed to show any significance between ACOS patients with high reversibility and blood AEC levels, again contradicting with literature published elsewhere.\textsuperscript{23} We found pulmonary hypertension to be diagnosed significantly more in the non-ACOS COPD group. Perhaps, patients with persistent airflow limitation without a “reversibility” element probably experience greater periods of oxygen desaturation which may lead to pulmonary vascular remodeling and pulmonary hypertension. However, these patients did not undergo right heart catheterization to accurately measure pulmonary artery pressures since pulmonary artery pressure measurements on 2D echocardiography are subject to operator variation. Hence, further invasive hemodynamic studies are required in this regard.

This question probably begs attention: why differentiate ACOS from COPD? Treatment of ACOS patients differs from the initial treatment of patients with COPD. There is a role for considering inhaled corticosteroids upfront in addition to inhaled long-acting bronchodilator.\textsuperscript{23,24} This is important, especially at a time when research has shown that dual long-acting bronchodilators to be equally effective, if not better when compared to a combination of inhaled corticosteroid with long-acting bronchodilator in reducing exacerbations.\textsuperscript{25} This may however, not be applicable to the ACOS phenotype, which appears to be a “frequent exacerbator” phenotype to simply put it, one size does not fit all.\textsuperscript{26} It is understood that ACOS patients have lower quality of life, higher symptom burden (translate to frequent ER visits) and will probably consume higher health resources.\textsuperscript{24} Certain other studies have identified patients with ACOS to have increased comorbidities, such as pulmonary thromboembolism and tuberculosis.\textsuperscript{15,27} One study concluded that patients admitted for heart failure or pneumonia were more likely to get readmitted within 30 days of discharge if they also had underlying ACOS.\textsuperscript{28} Hence, it becomes imperative to identify this phenotype to ensure appropriate treatment of these patients.

This study is not without limitations; being a retrospective study, it comes with fallacies attributed to the study design, namely, selection, referral, and recall bias. Furthermore, our study group may not be representative of the population. We considered FEV1/FVC <70% as diagnostic of the obstructive pattern rather than comparing it with LLN levels. We did not perform a subgroup analysis by comparing the patients within the groups as per the Global Initiative for Chronic Obstructive Lung Disease severity classification. We did not have results of AEC and 2D echocardiography for all patients as some did not come for follow-up. Furthermore, we did not perform sputum examination for eosinophilia and exhaled breath FeNO levels in our study due to logistic and financial restraints of our study patients. One may argue, that with the absence of investigations such as blood AEC, sputum examination for eosinophilia and serum total IgE, applying only a spirometric criteria to diagnose ACOS may be overtly simplistic an approach, and may lead to many patients with “pure” COPD being wrongly labeled as having ACOS. This is however not true, as shown by our study. The two different groups differ significantly in several features, and features attributed to the ACOS group have been identified to be similar to those identified in patients diagnosed with ACOS as per stringent criteria in other studies.

**CONCLUSION**

Patients with ACOS have higher postbronchodilator FVC values, are more likely to complain of wheeze and ankle edema, tend to be smokers with lower cumulative smoking, and have frequent ER visits for exacerbations when compared to patients with non-ACOS COPD. When these clinical features are present in patients with COPD, they may be taken as predictors of possible ACOS, and one must review the history again and look for a pattern of variability in symptoms over a background of persistent airflow limitation in the natural course of illness in these patients. The results of our study show that the ACOS phenotype differs in clinical characteristics between regions and countries, and that data on ACOS from one region cannot be applied on ACOS patients from other regions.

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**Conflicts of interest**

There are no conflicts of interest.
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