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Original Research Article

Alpha-1-antitrypsin level as a predictor of acute exacerbations in chronic obstructive pulmonary disease: a prospective observational study

Ravindran Chetambath[1]*, Rayees A. Kathim[2], Ramseena Ibrahim[3]

[1]Department of Pulmonary Medicine, Baby Memorial Hospital, Calicut, Kerala, India
[2]Department of Critical Care Medicine, Baby Memorial Hospital, Kannur, Kerala, India
[3]Department of General Medicine, Baby Memorial Hospital, Kannur, Kerala, India

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***Correspondence:**
Dr. Ravindran Chetambath,
E-mail: crcalicut@gmail.com

ABSTRACT

Background: This prospective study investigated if alpha-1-antitrypsin (AAT) levels could predict chronic obstructive pulmonary disease (COPD) exacerbations needing hospitalization.
Methods: 106 COPD subjects hospitalized for acute exacerbations were enrolled. Past 2-years' records were evaluated for prior exacerbation hospitalizations. AAT levels and post-stabilization FEV1 were assessed during current hospitalization. Exacerbation frequency correlated to current AAT levels and lung function.
Results: Significant inverse association found between AAT levels and hospitalized exacerbations, indicating utility as a predictive biomarker for COPD patients prone to recurrent severe flares requiring admission. Patients with lower AAT levels also exhibited poorer lung function per lower FEV1 values.
Conclusions: Monitoring AAT levels may promote timely interventions in high risk individuals susceptible to relapsing catastrophic exacerbations needing inpatient care. Further research warranted to validate findings and explore if supplementing deficient AAT reduces exacerbation frequency, thereby improving prognosis in this debilitating disease.

Keywords: Alpha1 antitrypsin, Acute exacerbations, FEV1, COPD

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is one of the major causes of chronic morbidity and mortality throughout the world. This airflow limitation is caused by a mixture of airway disease and parenchymal destruction (emphysema). Globally, COPD has been expected to become the 3rd most leading cause of death and the 5th leading cause of loss of 'disability adjusted life years' (DALYs) as per projection of the Global Burden of Disease Study (GBDS).[1] Chronic obstructive pulmonary disease (COPD) exacerbations are episodes of symptom worsening that have major impacts on a variety of health outcomes, including quality of life, hospital admission, and death.[2] Exacerbation reduction is now a key outcome for pharmacological therapies in COPD.

It is well established that there is a correlation between FEV1 and exacerbation risk; an improved lung function is related to a lower risk of exacerbation.[3-7] London COPD cohort study reported that in patients with a history of more frequent exacerbations, there was an increased rate of decline of 8 ml per year compared with infrequent exacerbators.[8] The relationship between exacerbation frequency and FEV1 decline in COPD has also been seen in the UPLIFT study and another study from Greece.[9,10]

Alpha-1-antitrypsin is a serine protease inhibitor belonging to the SERPINA superfamily and has 394 amino

acids and 3 glycosylated side chains coupled to asparagines. The amino acid methionine is present at position 358 and it is susceptible to convert methionine sulfoxide by oxidants from cigarette smoke, rendering it a much less potent inhibitor of neutrophil elastase. Lowered α1-antitrypsin was associated with increased odds of exacerbations. Plasma α1-antitrypsin is a positive acute phase protein, and several previous studies have corroborated that elevation of positive acute phase proteins is associated with an increased risk of exacerbations in COPD. However, previous studies have also shown that plasma α1-antitrypsin lowered by the Z-allele is associated with an increased risk of emphysema and thus COPD.[11]

This prospective cohort study is undertaken to investigate whether AAT levels can serve as a predictive marker for acute exacerbations in patients with COPD. Estimation of AAT levels can be used by general practitioners and family physicians to predict exacerbation and take timely corrective measures.

Objectives

Objectives were to study whether AAT levels can serve as a predictive marker for acute exacerbations in patients with COPD, and to study the correlation between AAT levels and FEV1 in COPD patients during exacerbation.

METHODS

A prospective observational study was conducted at a tertiary care hospital in North Malabar, Kerala, India, from June 2016 to February 2018. A total of 106 COPD patients with acute exacerbation were enrolled in the study as per the calculated sample size. The study was undertaken after obtaining patients' informed consent and institutional ethics committee approval. The diagnosis of COPD was based on clinical history, physical examination, and pulmonary function tests as per GOLD criteria. Patients with known alpha-1-antitrypsin deficiency (AATD) were excluded from the study.

Inclusion criteria

All adult patients having a physician diagnosis of COPD and admitted with features of acute exacerbation, and COPD confirmed by demonstrating obstructive spirometry with poor reversibility were included.

Exclusion criteria

Patients with coexisting asthma, bronchiectasis, or any other chronic lung diseases, and patients with COPD who were already diagnosed to have AAT deficiency were excluded.

Diagnosis of COPD was confirmed by clinical evaluation, radiological examination, and spirometry. History of acute exacerbation and hospitalization during the past 2 years were recorded. AAT levels were measured using the immunoturbidimetry method with a fully automated COBAS-C system. All the patients underwent spirometry after the control of acute symptoms and FEV1 values were recorded. Based on FEV1 patients were categorized into the 4 severity groups as per GOLD-COPD guidelines. Statistical analysis was performed using an unpaired t-test to compare AAT levels in COPD patients and Pearson's correlation to investigate the relationship of AAT levels with FEV1.

RESULTS

A total of 106 COPD patients who met the eligibility criteria were evaluated in this study from June 2016-February 2018. On assessing the demography, 65.1% of the study population were males and the rest 34.9% were females (Figure 1). The mean age group of the study population is 63.68±9.41 with a male-female ratio of 1.86:1. When a graph was plotted correlating age with COPD, the prevalence of COPD was highest in the age group of 61-70 (Figure 2). Among the subjects 35.8% were current smokers, 10.4% were reformed smokers and 53.8% were nonsmokers (Figure 3).

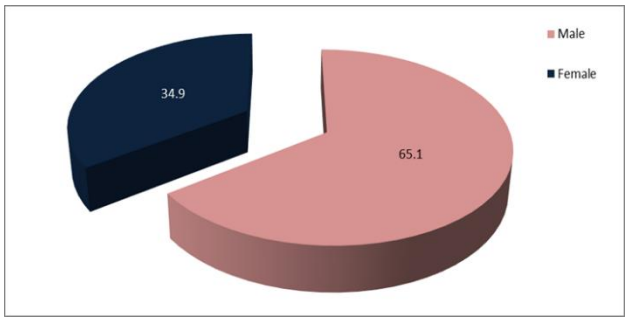

Figure 1: Gender distribution in the study population.

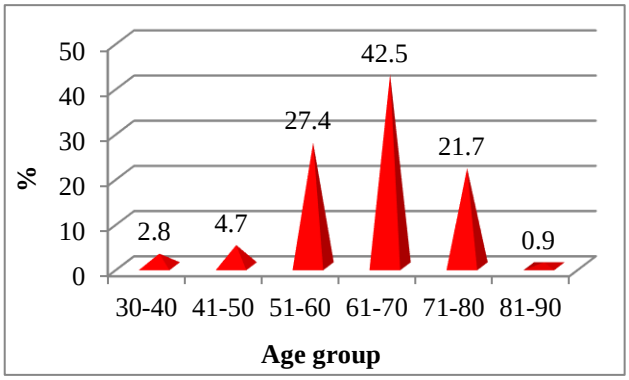

Figure 2: Age distribution of the study population.

In this study after taking the history of number of exacerbations in the last two years, we did a correlation analysis between AAT level and no of exacerbations and plotted in a graph. The graph showed a significant linear inverse relation. It is found that the number of exacerbations increases when the AAT level decreases (Figure 4). There were 1, 2, 3, 4, 5, and 6 exacerbations in the last 2 years in 6, 21, 25, 34, 17, and 3 patients

respectively (Table 1). The mean AAT value of the patient group who had 6 exacerbations was 1.28 and the group who had 1 exacerbation was found to be 1.50 (Figure 5).

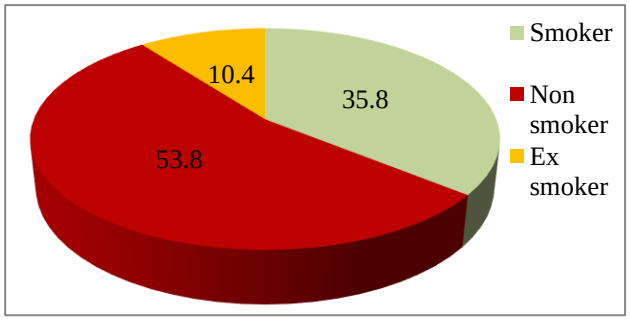

Figure 3: Smoking status of the study population.

Table 1: Showing no. of exacerbations in the last 2 years.

No. of exacerbations in the last 2 years	No. of subjects	Percentage (n=106)
1	6	5.66
2	21	19.81
3	25	23.58
4	34	32.07
5	17	16.03
6	3	2.83

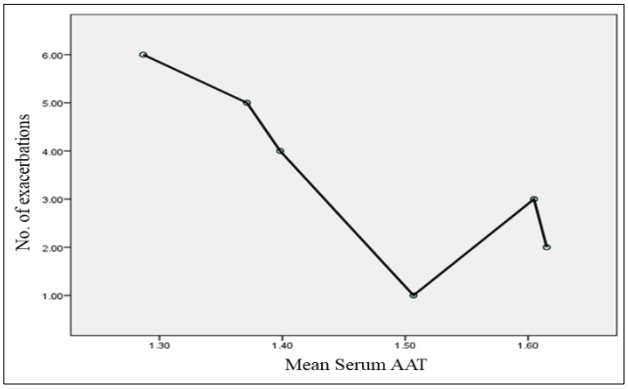

Figure 4: Showing the inverse relationship of mean AAT level with exacerbations.

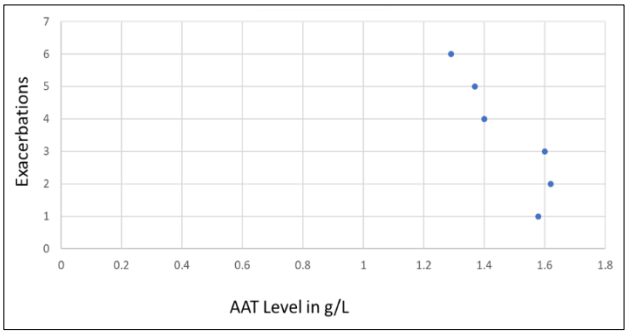

Figure 5: Scattered diagram showing the correlation of AAT level with exacerbations.

The spirometry data of all patients were collected, and different parameters of PFT were analyzed, the patients were then categorized according to GOLD criteria. EEV1 values were subjected to correlation analysis with AAT levels (Figures 6 and 7). The FEV1-AAT levels analysis showed a significant linear relation on the graph plotted with an R2 linear value of 0.240, the FEV1 was found to be low in patients with low AAT levels (Figure-8). When the analysis was done correlating the GOLD criteria of severity of disease and the AAT levels, it showed that patients who had low AAT levels had more severity of the disease as per GOLD criteria of severity staging.

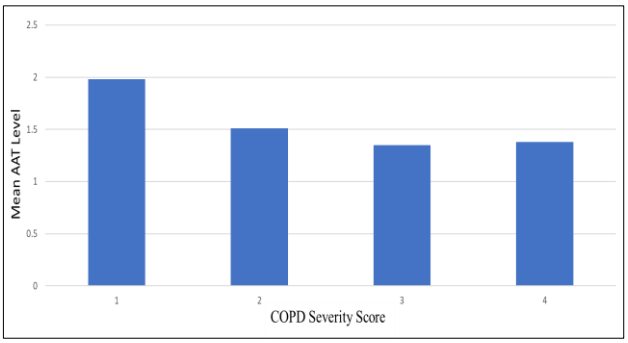

Figure 6: Relationship between mean AAT level and COPD severity.

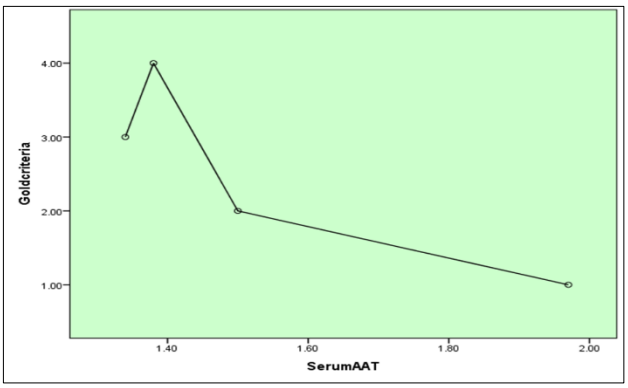

Figure 7: Graph showing the correlation of AAT level with COPD severity.

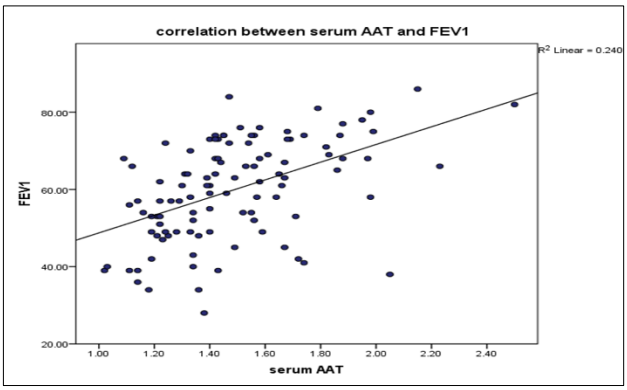

Figure 8: Graph showing a significant linear relationship between FEV1 and AAT levels.

DISCUSSION

Exacerbations of COPD are episodes of respiratory symptom worsening requiring additional therapy and/or hospitalization. Exacerbations are important events with a significant influence on prognosis, and prevention of exacerbations is a central element in the management of COPD.[12-15]

α1-antitrypsin is observationally associated with an increased risk of exacerbations. Lowered α1-antitrypsin was associated with increased odds of exacerbations.[16] Plasma α1-antitrypsin is a positive acute phase protein, and several previous studies have corroborated that elevation of positive acute phase proteins is associated with an increased risk of exacerbations in COPD.[11] However, previous studies have also shown that plasma α1-antitrypsin lowered by the Z-allele is associated with an increased risk of emphysema and thus COPD.[11]

Interestingly, we observed that lower levels of α1-antitrypsin were strongly associated with an increased risk of exacerbations in COPD. There is suggestive evidence that plasma α1-antitrypsin genetically lowered by the Z-allele is associated with an increased risk of exacerbations in individuals with COPD from the general population.

Among the 106 subjects studied, we could not detect an absolute deficiency of AAT in any one of them. But it is observed that most of the patients had value closer to the lower limit of normal and the number of exacerbations were inversely related to the AAT values. Lower levels of AAT also correspond to lower FEV1 among these subjects proving that lower AAT values are linked with severe COPD,

Subjects with severe AATD have decreased lung protection against the effects of neutrophil elastase and susceptible subjects are at risk for early-onset COPD, with most affected individuals being diagnosed around the age of 44–45 years.[17,18] During acute exacerbations, the excess neutrophil burden is significantly higher in AATD than in non-AATD COPD subjects.[19] Whether this translates into more frequent and/or more severe exacerbations is not known, as only a few studies have addressed exacerbations in this specific population. In a more recent study of 265 subjects with AATD, 54% of subjects recalled having at least one COPD exacerbation during the prior year.[11]

The issue of the importance of lung function decline in COPD first arose when Fletcher and Peto explored lung function in a cohort of 792 male British postal workers.[8] These subjects were studied over 8 years and it was found that exacerbations were associated with the ratio of forced expiratory volume in 1 s (FEV1) to the cube of the height, although the exacerbation definition was limited at that time. This work was followed in close succession by a study from Utah in which Kanner et al showed that exacerbation frequency was related to COPD severity, thus implicating exacerbation frequency as a factor in FEV1 decline.[20]

The following year, the London COPD cohort study reported that in patients with a history of more frequent exacerbations, there was an increased rate of decline of 8 mL per year compared with infrequent exacerbators.[8] The relationship between exacerbation frequency and FEV1 decline in COPD has also been seen in the UPLIFT study and another study from Greece.[9,10] Similarly, the R2 linear value on FEV1-AAT levels in the study by Mittal et al was 0.252 in nonsmokers and 0.113 in smokers.[21] Hence, this implies that there is a significant association between the airway pathology of the disease and AAT levels. When the analysis was done correlating the GOLD criteria of severity of disease and the AAT levels, it showed patients who had low AAT levels had more severity of the disease as per GOLD criteria of severity. And there is a positive correlation of pulmonary functions with serum AAT. Therefore, correction of AAT level may be beneficial in COPD patients for the prevention of frequent exacerbations.

Our findings are consistent with previous studies demonstrating the chances of frequent exacerbations in COPD subjects having lower levels of AAT. AAT level also correlates with FEV1 values and the severity of COPD.

Limitations

The limitations of this study include the small sample size from a single center. Multicentre studies on larger COPD populations are warranted to further validate the findings.

CONCLUSION

This prospective observational study establishes a link between low alpha-1-antitrypsin levels and an increased risk of acute exacerbations in COPD. Low levels of AAT also correlated with reduced FEV1. Monitoring AAT levels in patients with COPD may aid in identifying individuals at higher risk for exacerbations, allowing for timely interventions and improved management of this debilitating respiratory condition. Further research is warranted to validate these findings and explore the potential therapeutic implications of AAT supplementation in COPD patients with low AAT levels. Testing AAT levels in COPD patients may aid general practitioners and family physicians in predicting exacerbation risk more accurately and customizing treatment plans accordingly. Supplementing deficient levels could potentially help reduce episodes requiring hospitalization.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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