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ORIGINAL ARTICLE

Prevalence of Alpha-1 Antitrypsin Deficiency Among Patients with Early-Onset Chronic Obstructive Pulmonary Disease

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ABSTRACT

Background: *Chronic Obstructive Pulmonary Disease (COPD) is a heterogeneous respiratory disorder in which genetic factors contribute significantly to disease susceptibility, particularly in early-onset cases. Alpha-1 antitrypsin deficiency (AATD), caused by mutations in the SERPINA1 gene, is an important but underdiagnosed cause of COPD. Limited data exist regarding its prevalence and clinical association in South Asian populations, especially in Bangladesh.* ***Objective:*** *This study aimed to determine the prevalence of AATD among patients with early-onset COPD and evaluate its association with disease severity.* ***Methods & Materials:*** *A descriptive cross-sectional study was conducted at the Department of Respiratory Medicine, NIDCH, Dhaka, from July to December 2025. A total of 80 early-onset COPD patients were enrolled. Data were collected using structured questionnaires and spirometric records. Serum alpha-1 antitrypsin levels were measured quantitatively using nephelometry. Participants with low serum AAT levels underwent confirmatory targeted genotyping for the PiS and PiZ alleles via real-time PCR. COPD severity was classified using GOLD criteria. Statistical analysis was performed using SPSS version 25.0.*

Results: *AATD was identified in 12.5% of patients. PiMZ was the most common variant (6.25%), followed by PiSZ (3.75%) and PiZZ (2.5%). A significant association was observed between AATD status and COPD severity (p = 0.02), with 80% of AATD cases presenting in GOLD III and IV stages. Non-AATD cases were predominantly in milder stages.* ***Conclusion:*** *AATD is a notable contributor to early-onset COPD and is significantly associated with increased disease severity. Routine screening for SERPINA1 mutations may facilitate early diagnosis and improved clinical management in COPD patients.*

Keywords: *Alpha-1 antitrypsin deficiency, COPD, early-onset COPD, GOLD classification.*

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INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a progressive respiratory disorder characterized by persistent airflow limitation and chronic inflammatory response in the airways and lung parenchyma. Although smoking remains the primary risk factor, a subset of patients develops COPD at a younger age and without significant exposure history, suggesting an underlying genetic predisposition. Among these genetic determinants, alpha-1 antitrypsin deficiency (AATD) has been widely recognized as a significant but underdiagnosed cause of early-onset COPD. Alpha-1 antitrypsin (AAT) is a protease inhibitor primarily produced in the liver that protects lung tissue from neutrophil elastase-mediated damage. Deficiency or dysfunction of this protein leads to unchecked proteolytic activity and progressive emphysematous changes [1].

The genetic basis of AATD is primarily linked to mutations in the SERPINA1 gene, with PiZZ, PiSZ and PiMZ being the most clinically relevant phenotypes. Studies have shown that PiZZ homozygosity is associated with severe AAT deficiency and early development of emphysema, while heterozygous PiMZ and PiSZ states confer variable risk depending on environmental exposures and other modifying factors [2]. Current evidence suggests that AATD-related COPD exhibits distinct clinical and functional characteristics compared to non-genetic COPD, often presenting at a younger age with more rapid lung function decline [3].

Epidemiological studies indicate that AATD is significantly underdiagnosed worldwide, with delayed recognition contributing to disease progression and poor outcomes. Strnad et al. highlighted that diagnostic delays are common due to overlapping clinical features with smoking-related COPD [4]. Similarly, Blanco et al. reported substantial variability in PiZZ prevalence across different populations, emphasizing the need for targeted screening strategies [5]. Furthermore, Ghosh et al. demonstrated that PiMZ heterozygosity represents a distinct COPD endotype associated with measurable clinical risk [6].

The clinical burden of AATD extends beyond pulmonary manifestations, affecting quality of life and healthcare utilization. Miravitlles et al. reported that AATD-associated COPD is linked with increased exacerbation frequency and greater healthcare resource utilization [7]. Molloy et al. further emphasized that PiMZ individuals exhibit an intermediate risk

phenotype, particularly when exposed to environmental triggers such as smoking [8]. Environmental interactions, including biomass exposure and tobacco smoke, significantly modulate disease expression, contributing to variability in clinical outcomes [9].

Despite increasing awareness, screening for AATD remains inconsistent in clinical practice. Barnes et al. described COPD as a heterogeneous disease with multiple endotypes requiring individualized diagnostic approaches [10]. Greulich and Vogelmeier emphasized that under-recognition of AATD continues to limit early diagnosis and timely intervention [11]. Quinn et al. further identified barriers such as lack of routine testing and limited awareness among clinicians [12]. Population-based studies also indicate that PiMZ genotype prevalence is higher than previously estimated, reinforcing the importance of systematic evaluation in COPD patients [13].

In Bangladesh, data on AATD among early-onset COPD patients remain limited and local epidemiological evidence is scarce. Given the increasing burden of respiratory disease and limited genetic screening infrastructure, understanding the prevalence and genotype distribution of AATD is essential. Therefore, this study aims to determine the prevalence of alpha-1 antitrypsin deficiency among patients with early-onset COPD and to evaluate its association with disease severity in a tertiary care setting in Dhaka, Bangladesh.

OBJECTIVES

The objective of this study was to determine the prevalence of alpha-1 antitrypsin deficiency among patients with early-onset chronic obstructive pulmonary disease and to evaluate its association with disease severity based on the GOLD classification in a tertiary care hospital setting in Dhaka, Bangladesh.

METHODS & MATERIALS

This descriptive cross-sectional study was conducted at the Department of Respiratory Medicine, National Institute of Diseases of the Chest and Hospital (NIDCH), Dhaka. The study period extended from July to December 2025. The study population comprised patients diagnosed with early-onset Chronic Obstructive Pulmonary Disease (COPD). A total of 80 participants were enrolled consecutively based on eligibility criteria.

Selection Criteria

Inclusion Criteria:

- Patients diagnosed with early-onset COPD (onset before 55 years of age)
- Clinically stable patients attending outpatient or inpatient services
- Patients with available spirometric confirmation of COPD

Exclusion Criteria:

- Patients with known asthma or asthma-COPD overlap syndrome
- Individuals with active pulmonary tuberculosis or other chronic lung diseases
- Patients with significant comorbid conditions affecting lung function (e.g., congestive heart failure, malignancy)

Data Collection Procedure

Data were collected using a structured, pre-tested questionnaire and clinical evaluation form designed specifically for this study. Participants were recruited from both inpatient and outpatient departments of the Respiratory Medicine unit. After initial screening, eligible patients were interviewed to obtain detailed socio-demographic information, including age, sex, smoking history and exposure to biomass fuel. Clinical history was recorded with emphasis on respiratory symptoms, duration of disease and prior exacerbations.

Spirometric data confirming COPD diagnosis and severity classification according to GOLD criteria were collected from hospital records and verified by the attending respiratory physicians. Blood samples were obtained for serum alpha-1 antitrypsin (AAT) quantification using nephelometry as the primary screening test. Participants with low serum AAT levels (< 50 mg/dL) underwent confirmatory targeted genotyping for the PiS and PiZ alleles via real-time PCR to identify PiZZ, PiSZ, PiMZ and PiMM variants. Participants with normal serum AAT levels were classified as non-AATD without further genotyping.

All collected data were checked for completeness and consistency before entry into a secure computerized database. Unique identification codes were assigned to each participant to maintain confidentiality and anonymity throughout the study process. Access to identifiable patient information was strictly restricted to the principal investigator. Data quality was ensured through double-entry verification and periodic cross-checking of records. No personal identifiers were disclosed at any stage of analysis or reporting. The entire process was conducted in a standardized manner to ensure reliability and reproducibility of findings while maintaining strict confidentiality of patient information.

Statistical Analysis

Data were analyzed using SPSS version 25.0. Descriptive statistics such as frequency and percentage were used for categorical variables. Chi-square test was applied to assess the association between AATD status and COPD severity. A p-value <0.05 was considered statistically significant. Results were presented in tables and interpreted according to standard epidemiological conventions.

RESULTS

Table I shows the baseline socio-demographic and clinical characteristics of the study participants (N = 80). The age distribution indicates that 22.5% were below 40 years, 42.5% were between 40–49 years and 35.0% were between 50–55 years. Males constituted 68.8% of the sample, while females accounted for 31.2%. Smoking history was present in 65.0% of participants, whereas 35.0% were non-smokers. Exposure to biomass fuel was reported in 27.5% of cases, with 72.5% having no such exposure.

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Table I: Baseline Socio-demographic and Clinical Characteristics of Study Participants (N = 80).

Variables	Categories	Frequency (n)	Percentage (%)
Age (years)	<40	18	22.5
	40–49	34	42.5
	50–55	28	35.0
Sex	Male	55	68.8
	Female	25	31.2
Smoking status	Smoker	52	65.0
	Non-smoker	28	35.0
Biomass exposure	Yes	22	27.5
	No	58	72.5

Table II presents the prevalence of alpha-1 antitrypsin deficiency (AATD) among early-onset COPD patients. A total of 12.5% (n=10) were identified as AATD cases. Among these, PiZZ (severe deficiency) accounted for 2.5%, PiSZ (moderate deficiency) 3.75% and PiMZ (mild deficiency) 6.25%. The remaining 87.5% were classified as non-AATD (PiMM phenotype).

Table II: Prevalence of Alpha-1 Antitrypsin Deficiency Among Early-Onset COPD Patients (*n* = 80).

AATD Status	Subtype	Frequency (n)	Percentage (%)
AAT Deficient	PiZZ (severe deficiency)	2	2.5
	PiSZ (moderate deficiency)	3	3.75
	PiMZ (mild deficiency)	5	6.25
Total AATD cases	-	10	12.5
Non-AATD	PiMM (normal phenotype)	70	87.5

Table III shows the association between AATD status and COPD severity based on GOLD classification. Among AATD cases, 40.0% were in GOLD III and 40.0% in GOLD IV stages, while none were in GOLD I. A statistically significant association was observed (p = 0.02), indicating higher disease severity among AATD patients compared to non-AATD cases.

Table III: Association Between AATD Status and COPD Severity (GOLD Classification).

GOLD Stage	AATD Cases (n=10)	Non-AATD Cases (n=70)	Total	p-value
GOLD I	0 (0.0%)	15 (21.4%)	15	0.02
GOLD II	2 (20.0%)	28 (40.0%)	30	
GOLD III	4 (40.0%)	21 (30.0%)	25	
GOLD IV	4 (40.0%)	6 (8.6%)	10	
Total	10	70	80	

DISCUSSION

The present study demonstrated that alpha-1 antitrypsin deficiency (AATD) was present in 12.5% of patients with early-onset COPD, with PiMZ representing the most frequent genotype among affected individuals. This prevalence aligns with prior observational evidence indicating that AATD remains an under-recognized contributor to COPD, particularly in younger patients who may not have extensive cumulative smoking exposure. Rahaghi et al. reported that clinically relevant AATD is more frequently detected in COPD cohorts when systematic screening is performed, suggesting that routine testing significantly increases diagnostic yield [14]. Similarly, Menga et al. observed a comparable prevalence of AATD among COPD patients in a South American cohort, reinforcing that regional differences exist but overall burden remains clinically important [15].

In the present study, PiZZ genotype accounted for 2.5% of total cases, representing the most severe form of deficiency. This finding is consistent with Strnad et al., who described PiZZ as the classical severe phenotype associated with markedly reduced serum AAT levels and early-onset panacinar emphysema [4]. Blanco et al. also emphasized that PiZZ individuals often present at a younger age with more rapid functional decline compared to other genotypes [5]. The relatively lower proportion of PiZZ in this study may reflect population variability, underdiagnosis, or survival bias, as severe cases may present earlier or progress rapidly before formal COPD evaluation.

The predominance of PiMZ heterozygosity (6.25%) observed in this study is clinically relevant, as emerging literature increasingly recognizes PiMZ as a disease-modifying genotype rather than a benign carrier state. Ghosh et al. demonstrated that PiMZ heterozygosity represents a distinct COPD endotype associated with increased susceptibility to airflow limitation, particularly in the presence of environmental risk factors such as smoking [6]. Molloy et al. similarly reported that PiMZ individuals exhibit intermediate reductions in lung function and an elevated risk of COPD compared to PiMM individuals, especially when exposed to tobacco smoke [8]. These findings support the clinical significance of heterozygous SERPINA1 mutations in early-onset COPD populations.

A statistically significant association was found between AATD status and COPD severity (p = 0.02), with most AATD-positive patients classified as GOLD stage III and IV. This suggests a strong relationship between genetic deficiency and advanced disease progression. Miravitlles et al. reported that AATD-related COPD is frequently associated with more severe airflow obstruction and accelerated decline in lung function compared to non-AATD COPD [7]. Stockley et al. further demonstrated that individuals with AATD experience a more rapid decline in FEV1, contributing to earlier development of severe COPD phenotypes [16]. These findings are consistent

with the current study, which indicates that genetic susceptibility may significantly influence disease severity.

Environmental factors likely play a synergistic role in disease expression. In this study, 65% of participants were smokers, highlighting the strong interaction between genetic and environmental risk factors. Alam et al. showed that cigarette smoke amplifies neutrophilic inflammation and protease-antiprotease imbalance in AATD patients, accelerating lung tissue destruction [17]. Rangaraju et al. further emphasized that environmental exposures, including smoking and biomass fuel, are key determinants of phenotypic variability in AATD-related COPD [9]. This interaction may explain why some heterozygous individuals in the present cohort developed moderate to severe disease.

Biomass exposure was also present in a subset of participants, which may contribute to airway inflammation and small airway dysfunction. Toumpanakis and Usmani described small airways disease as a central pathological feature in COPD progression, particularly in genetically predisposed individuals [18]. Lazarinis et al. further highlighted that small airways impairment is an early driver of airflow limitation in COPD and may precede overt emphysema [19]. These mechanisms may contribute to the severity observed among AATD-positive individuals in this study.

The predominance of PiMM genotype among non-AATD patients (87.5%) reflects expected population distribution and supports the notion that environmental factors alone can drive COPD development in genetically normal individuals. Piras et al. reported that a substantial proportion of COPD patients without AATD still exhibit severe disease due to cumulative environmental exposures and aging-related lung changes [20]. Barnes et al. further emphasized that COPD is a heterogeneous disease with multiple biological endotypes and not all cases are driven by single genetic mutations [10].

From a clinical perspective, the findings underscore the importance of early detection of AATD in COPD patients. Evidence from augmentation therapy trials demonstrates that early identification can alter disease trajectory. Chapman et al. showed that augmentation therapy helps preserve lung density in severe AATD cases [21], while Fraughen et al. reported improved survival outcomes among treated individuals in large registry analyses [22]. These findings highlight the potential benefits of incorporating routine AATD screening into COPD evaluation, particularly in early-onset cases.

Overall, this study reinforces the global evidence that AATD contributes significantly to early-onset COPD and is associated with more severe disease phenotypes. The observed genotype distribution and severity association are consistent with international literature, supporting the biological plausibility of these findings. These results further emphasize the need for increased clinical awareness, early diagnostic testing and integration of genetic evaluation into COPD management pathways, particularly in resource-limited settings where underdiagnosis remains a major challenge.

CONCLUSION

This study demonstrates that alpha-1 antitrypsin deficiency is present in a significant proportion of patients with early-onset COPD, with PiMZ being the most frequent genotype among affected individuals. A strong association was observed between AATD status and increased COPD severity, particularly in advanced GOLD stages. A two-step screening approach—serum AAT quantification followed by targeted genotyping for PiS and PiZ alleles in those with low levels—offers a practical and cost-effective strategy for identifying AATD in resource-limited settings. The findings highlight the contributory role of genetic factors in early-onset COPD and emphasize the importance of targeted screening. Early identification of AATD may facilitate risk stratification and timely clinical intervention. Incorporating routine genetic evaluation into COPD assessment could improve disease management and patient outcomes in similar clinical settings.

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CONFLICTS OF INTEREST

There are no conflicts of interest.

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