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Characterization of Copd in Alpha-1 Antitrypsin Deficiency: Insights from Patient Cohort Retrospective Study

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KEYWORDS

Alpha-1 antitrypsin deficiency (AATD), Chronic obstructive pulmonary disease (COPD), Diagnostic delay, Genotype (PiZZ, PiSZ), Age at diagnosis, Emphysema, Underdiagnosis

ABSTRACT:

Background:

Alpha-1 Antitrypsin Deficiency (AATD) is a genetic condition that predisposes individuals to early-onset chronic obstructive pulmonary disease (COPD). This study aimed to assess the clinical, functional, and demographic characteristics of AATD-COPD patients.

Methods:

A cross-sectional analysis was conducted on 100 patients with confirmed AATD-COPD in our tertiary care hospital. Data on demographics, smoking history, genotype, comorbidities, pulmonary function, exacerbation frequency, clinical indices, and treatment modalities were collected and analysed.

Results:

The mean age of patients was 60.1 years, with a male predominance (59%). The average age at COPD diagnosis was 52 years, and the mean diagnostic delay was 4.84 years. Most patients (88%) were index cases. Smoking history was significant in 75% of patients, with a mean exposure of 24.7 pack-years. The predominant genotype was Pi*ZZ (66%). GOLD category B was most common (54%), and 15% had ≥2 ambulatory exacerbations per year. Comorbidities included bronchiectasis (19%) and liver disease (15%). The mean FEV_1 was 56.5% predicted, and DLCO was 55.6%, indicating moderate airflow obstruction and gas exchange impairment. Augmentation therapy was received by 37% of patients, and emphysema was present in 87%. The mean serum AAT level was 37.5 mg/dL.

Conclusion:

AATD-COPD presents with significant clinical heterogeneity, but is commonly associated with early-onset COPD, high prevalence of emphysema, and moderate impairment in lung function. Early diagnosis and targeted therapies such as augmentation can benefit this population, emphasizing the need for routine screening in appropriate clinical settings.

Introduction:

Alpha-1 antitrypsin deficiency (AATD) is most commonly identified in younger individuals, particularly those with minimal smoking history or a family background of chronic obstructive pulmonary disease (COPD) and emphysema. As a result, cases presenting at an older age are frequently missed. The overall awareness of AATD remains low, contributing to its underdiagnosis. Although some countries have experimented with newborn screening programs for AATD, targeted screening appears to be more practical due to the condition's low prevalence and the fact that many carriers do not develop clinical symptoms. Nevertheless, even targeted screening strategies face

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considerable limitations, including missed or underestimated diagnoses. [1-6]

Despite recommendations advocating AATD testing for all COPD patients, younger individuals continue to be prioritized, while older patients are often overlooked. Research has shown that being under the age of 55 significantly increases the likelihood of undergoing AATD testing (OR 2.4, $p < 0.001$). A study by Soriano et al. analysing UK data further confirmed this, showing that testing rates peaked among patients aged 45–65 and were lowest among those over 65 [7,8]

AATD commonly causes early-onset emphysema, often developing one to two decades earlier than in smokers with normal AAT levels, even with relatively low tobacco exposure. The condition is associated with reduced life expectancy, with cumulative survival rates dropping to 52% by age 50 and 16% by age 60【7,8】. However, more recent longitudinal studies tracking PiZZ and PiSZ individuals up to ages 43–45 revealed no significant difference in survival compared to the general Swedish population【9】.

Interestingly, symptomatic AATD patients over 60 often report milder symptoms, fewer exacerbations, and better health-related quality of life (HRQoL) than their younger counterparts. These factors may contribute to the longer diagnostic delays observed in this age group. Delayed diagnosis is linked to the progression of COPD symptoms, worsening airflow limitation, and decreased functional capacity. Notably, the first study to explore the prognostic impact of diagnostic delay found that prolonged delays were independently associated with poorer overall and transplant-free survival—even after adjusting for age, BMI, lung function, smoking, and oxygen dependence. [10,11]

Therefore, enhancing early detection strategies—especially in high-risk groups such as COPD patients—is crucial for timely intervention and improved outcomes. Given the limited research on how age at diagnosis influences clinical outcomes in AATD-COPD patients, our study aimed to explore the clinical characteristics associated with age at diagnosis in this specific population.

Materials and Methods

This retrospective study was conducted in department of pulmonology in our tertiary care hospital from May 2022- May 2025. Individuals diagnosed with severe alpha-1 antitrypsin deficiency (AATD), regardless of their clinical presentation or disease severity, were included in our study. The criteria for participation included: a confirmed diagnosis of AATD; serum AAT levels below 11 μM (50 mg/dL); and/or genetic deficiency characterized by heterozygous or homozygous forms of proteinase inhibitor genotypes such as PIZZ, PISZ, or other rare functionally deficient variants. Data on demographics, smoking history, genotype, comorbidities, pulmonary function, exacerbation frequency, clinical indices, and treatment modalities were collected and analysed.

Smoking status was divided into 3 categories: never smokers, former smokers, and current smokers. Participants were asked about pulmonary symptoms, which included shortness of breath, chronic cough, tightness in the chest, and wheezing. Comorbidities were noted down. Participants were asked about a variety of factors that they believed may have contributed to their lung disease; of those, smoking and genetic factors were considered in this study. Participants were asked about the number of times they felt they were short of breath in the previous 2 weeks and how many times they had been admitted to a hospital with lung-related health issues. They were also asked how many days of work or school they had been absent in the past year due to their condition.

Data analysis was performed using SPSS software (IBM Corp. Released 2023. IBM SPSS Statistics for Windows, Version 29.0.2.0, Armonk, NY: IBM Corp). Baseline characteristics were summarized as means with standard deviations for continuous variables, and as frequencies with percentages for categorical variables. The Shapiro-Wilk test was used to assess the normality of continuous variables; since none followed a normal distribution, the Kruskal-Wallis test was applied to compare age at diagnosis across three groups. For comparisons between age groups and categorical variables, the Chi-square test was utilized.

RESULTS

PATIENTS DEMOGRAPHICS

The mean current age of AATD-COPD patients in the study cohort was 60.1 years (±11.1), with 62.3% of patients being under the age of 65 and 37.7% aged 65 or

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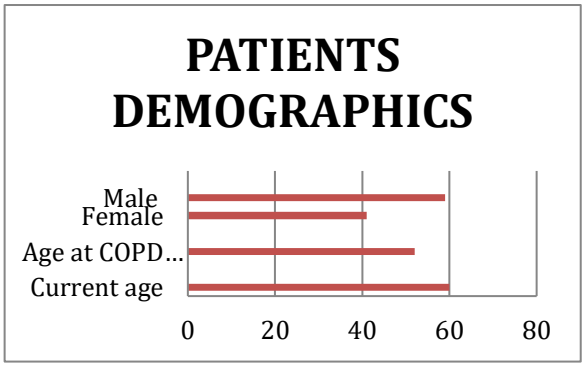
older. The average age at COPD diagnosis was 52.0 years (±12.4), suggesting a considerable delay between symptom onset and formal diagnosis. In terms of sex distribution, 59% of patients were male and 41% were female, indicating a slight male predominance. The average body mass index (BMI) was 25.9 (±5.01), placing the cohort, on average, in the normal to overweight category

TABLE 1: PATIENTS DEMOGRAPHICS

Parameter	Total Patients with AATD-COPD (n = 100)	p-value
Current age (mean ± SD)	60.1 ± 11.1	< 0.001
Current age group	< 65: 62 (62.3%) ≥ 65: 38 (37.7%)	< 0.001
Age at COPD diagnosis (mean ± SD)	52.0 ± 12.4	< 0.001
Sex	Female: 41 Male: 59	0.694
BMI (mean ± SD)	25.9 ± 5.01	0.023

FIGURE 1: PATIENTS DEMOGRAPHICS



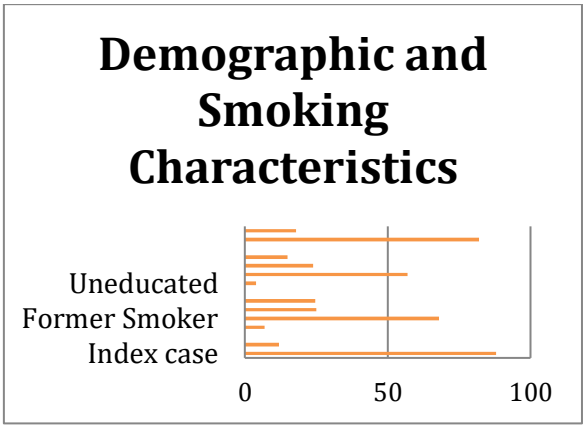
DEMOGRAPHIC AND SMOKING CHARACTERISTICS

The average diagnostic delay was 4.84 years, with symptoms beginning around a mean age of 47.5 years. Most patients (88%) were tested as index cases, while 12% were identified via family screening. Smoking history revealed 68% former smokers, 7% current smokers, and 25% never smokers, with a mean exposure of 24.7 pack-years. Educationally, 57% had less than university-level education, 24% were graduates or higher, and 19% were unspecified. A majority (82%) were actively employed.

TABLE 2: Demographic and Smoking Characteristics

Diagnostic delay (mean ± SD)	4.84 ± 6.61	< 0.001
Symptom onset age (mean ± SD)	47.5 ± 13.9	< 0.001
AATD testing reason	Index case: 88 Family screening: 12	0.001
Smoking status	Current: 7 Former: 68 Never: 25	< 0.001
Smoking pack-years (mean ± SD)	24.7 ± 20.6	< 0.001
Education level	Below university: 57 University+: 24 Unknown: 19	0.001
Occupation	Working: 82 Others: 18	< 0.001

FIGURE 2: Demographic and Smoking Characteristics



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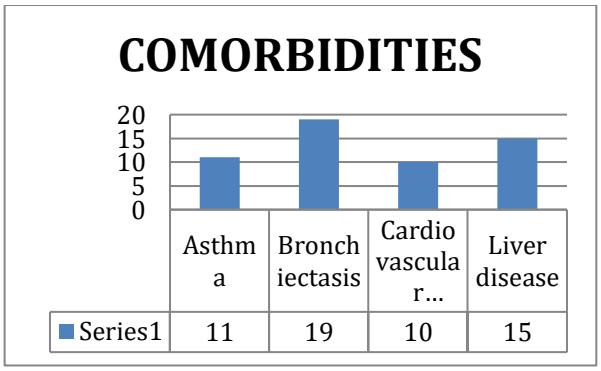
COMORBIDITIES

Among the AATD-COPD patients, 11% had coexisting asthma, 19% had bronchiectasis, and 10% had cardiovascular diseases. Liver disease was present in 15% of the cohort, indicating a notable burden of extrapulmonary comorbidities in this population.

TABLE 3: COMORBIDITIES

Any comorbidity present	Number of patients
Asthma	11
Bronchiectasis	19
Cardiovascular diseases	10
Liver disease	15

FIGURE 3: COMORBIDITIES



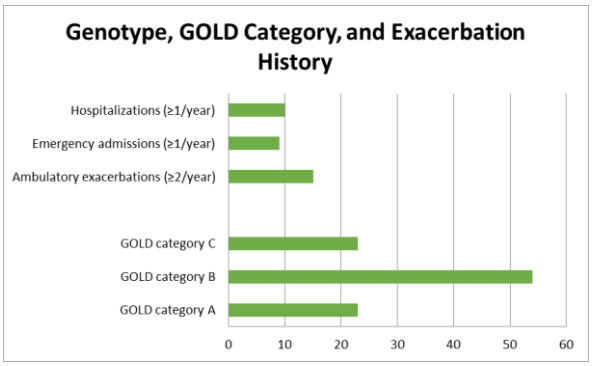
GENOTYPE, GOLD CATEGORY, AND EXACERBATION HISTORY

The most common genotype among patients was Pi*ZZ (66%), followed by Pi*SZ (16%), Pi*SS (5%), and other rare variants (13%). Based on GOLD classification, category B was most prevalent (54%), while categories A and E each accounted for 23% of patients. Regarding disease activity, 15% experienced two or more ambulatory exacerbations per year, 9% had at least one emergency admission, and 10% required hospitalization.

TABLE 4: Genotype, GOLD Category, and Exacerbation History

Genotype	Pi*ZZ: 66 Pi*SZ: 16 Pi*SS: 5 Others: 13	< 0.001
GOLD category	A: 23 B: 54 E: 23	0.808
Ambulatory exacerbations (≥2/year)	15	0.136
Emergency admissions (≥1/year)	9	0.827
Hospitalizations (≥1/year)	10	0.152

FIGURE 4: Genotype, GOLD Category, and Exacerbation History



CLINICAL INDICES AND SYMPTOM SCORES

The mean BODE index was 2.53, indicating mild to moderate disease severity. The Charlson comorbidity index averaged 3.98, reflecting a notable burden of associated illnesses. Health-related quality of life was moderately impacted, with an EQ-5D index of 0.79. Symptom burden was evident, with a mean CAT score of 14.7, and 54% of patients reported significant breathlessness with an mMRC score ≥2.

TABLE 5: Clinical Indices and Symptom Scores

BODE index (mean ± SD)	2.53 ± 2.08	0.003
Charlson index (mean ± SD)	3.98 ± 1.80	< 0.001
EQ-5D index	0.79 ± 0.23	0.021

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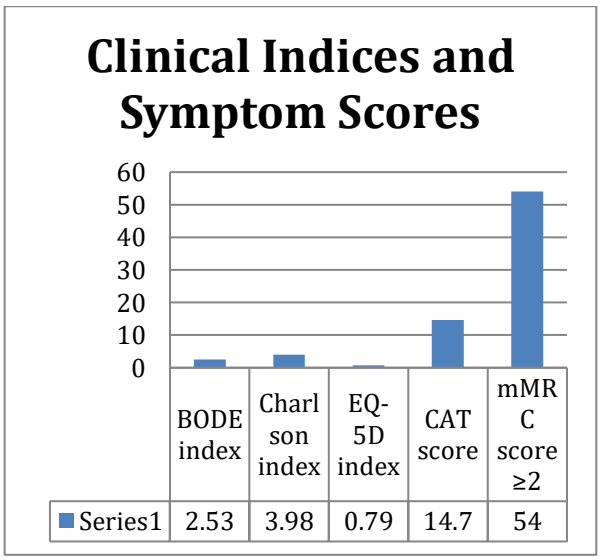
(mean ± SD)		
CAT score (mean ± SD)	14.7 ± 8.86	0.007
mMRC score ≥2	54	0.631

FIGURE 5: Clinical Indices and Symptom Scores



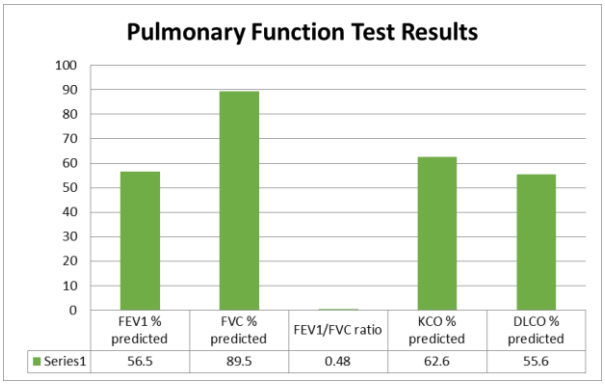
PULMONARY FUNCTION TEST RESULTS

Pulmonary function testing revealed a mean FEV_1 of 56.5% predicted, indicating moderate airflow limitation. The mean FVC was relatively preserved at 89.5% predicted, while the FEV_1/FVC ratio was reduced to 0.48, consistent with obstructive lung disease. Gas transfer capacity was also impaired, with KCO and DLCO values averaging 62.6% and 55.6% predicted, respectively, reflecting underlying emphysematous changes.

TABLE 6: Pulmonary Function Test Results

FEV1 % predicted (mean ± SD)	56.5 ± 24.3	< 0.001
FVC % predicted (mean ± SD)	89.5 ± 24.7	0.003
FEV1/FVC ratio (mean ± SD)	0.48 ± 0.14	0.002
KCO % predicted (mean ± SD)	62.6 ± 25.8	0.001
DLCO % predicted (mean ± SD)	55.6 ± 22.7	0.040

FIGURE 6: Pulmonary Function Test Results



TREATMENT HISTORY AND DISEASE CHARACTERISTICS

Long-term oxygen therapy was used by 17% of patients, while 37% received augmentation therapy. Lung volume reduction was performed in 2%, and emphysema was present in 87%. The mean serum AAT level was 37.5 mg/dL, and 59% of patients were on inhaled corticosteroids.

TABLE 7: Treatment History and Disease Characteristics

LTOT usage (yes)	17	0.730
Augmentation therapy (yes)	37	< 0.001
Lung volume reduction (yes)	2	0.049
Emphysema (yes)	87	0.047
Serum AAT level (mean ± SD, mg/dL)	37.5 ± 25.1	< 0.001
Inhaled corticosteroid use (yes)	59	0.002

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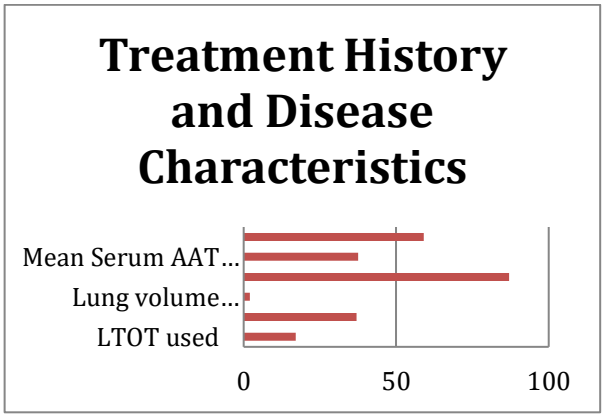
FIGURE 7: Treatment History and Disease Characteristics



Discussion

Our study offers a contemporary, real-world snapshot of Alpha-1 Antitrypsin Deficiency-associated COPD (AATD-COPD), demonstrating persistent diagnostic delays, phenotypic variability, and ongoing treatment gaps—despite decades of recommendations and awareness campaigns. Our findings, integrated with seminal registry data (EARCO), diagnostic review, and longitudinal analyses, highlight where progress has occurred and where urgent gaps remain.

Our cohort's mean diagnostic delay of 4.84 years remains concerning. In comparison, Campos et al. (2005) documented an average delay of 8.3 years, even after the 1996 WHO call for universal AATD screening in all COPD patients. Despite the increasing availability of simplified testing techniques (e.g., dried blood spot), diagnostic age has increased over time, and fewer diagnoses are made by the first or second physician. Similar to our study, Campos' cohort reported that over 20% of patients saw ≥4 physicians before diagnosis. [12-15]

This stagnation suggests that awareness and implementation of guidelines have not translated effectively into routine practice. The ATS/ERS's 2003 statement—calling for AATD testing in all symptomatic COPD and asthma patients—appears to have limited impact on early detection in real-world settings. [12-15]

Campos et al. also noted that diagnosis occurred later in women and was associated with longer symptom intervals compared to men—paralleling our findings of a mild male predominance (59%). While our diagnostic delay is shorter on average, we echo Campos' finding that older patients (≥55 years) face the longest delays, often exceeding 9 years, further emphasizing the need for lifespan-inclusive screening, especially in those with atypical or milder presentations. [12-15]

Our cohort reflected that AATD suspicion frequently arose in the context of COPD or asthma. Campos' study reinforces this, showing an increasing number of AATD diagnoses made in patients with prior asthma or COPD diagnoses, yet a substantial proportion of these patients were still diagnosed late. This suggests a missed opportunity—when AATD is not considered in obstructive lung disease, particularly when symptoms are non-responsive to conventional therapies. [12-15]

Consistent with Campos and Gene Reviews®, our patients also showed substantial extrapulmonary manifestations—particularly liver disease (15%) and bronchiectasis (19%)—underlining the systemic impact of AATD. However, awareness of these features remains low among non-pulmonologists, contributing further to delays in appropriate referrals and diagnosis. Despite documented efficacy in delaying FEV_1 decline and possibly enhancing survival, only 37% of our patients received augmentation therapy. In Campos' Alpha Net cohort, all participants were augmentation-eligible, yet the systemic lack of early diagnosis likely deprived many others of this intervention. As observed in multiple studies, therapy is most effective when started early—typically between FEV_1 35%–60% predicted, matching our cohort's average FEV_1 of 56.5% [12-15]

CONCLUSION

Overall, our findings mirror global patterns observed in the EARCO registry, reinforcing the heterogeneity in clinical presentation and disease progression among AATD-COPD patients. Diagnostic delays, especially in patients with milder genotypes and lower smoking exposure, highlight the need for increased awareness and universal screening protocols across all COPD age groups. Early identification and personalized management strategies remain critical in optimizing outcomes for this genetically predisposed population.

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