

Distribution of SERPINA1 variants in chronic obstructive pulmonary disease, bronchiectasis, and the combined phenotype: a single-center cross-sectional study

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Abstract

Background

This single-center cross-sectional study aimed to determine the frequency and genotypic distribution of alpha-1 antitrypsin deficiency (AATD)-associated SERPINA1 variants in patients with chronic obstructive pulmonary disease (COPD), bronchiectasis, and the combined COPD-bronchiectasis phenotype, and to describe the clinical, functional, and radiological features of variant-positive patients.

Methods

Between December 2022 and May 2026, 500 adults evaluated at the Department of Pulmonary Diseases, Balıkesir Atatürk City Hospital, were assigned to three mutually exclusive groups: COPD only (n = 382), bronchiectasis only (n = 51), and combined COPD-bronchiectasis (n = 67). Dried blood spot samples were analyzed using an allele-specific genotyping assay covering 14 common SERPINA1 alleles.

Results

AATD-associated SERPINA1 variants were detected in 13 of 500 patients (2.6%): 2.1% (8/382) in the COPD-only group, 0% (0/51) in the bronchiectasis-only group, and 7.5% (5/67) in the combined COPD-bronchiectasis group. The most frequent genotypes were PI*M/Z (n = 5, 38.5%), PI*M/I (n = 3, 23.1%), and PI*M Procida (n = 2, 15.4%). All variant-positive patients had emphysema on high-resolution computed tomography, panacinar in 76.9% and centriacinar in 23.1%.

Conclusions

The markedly higher frequency of AATD-associated SERPINA1 variants in the combined COPD-bronchiectasis group suggests that this phenotype may represent a clinically relevant group for AATD evaluation, and the genotypic heterogeneity observed indicates that approaches focusing only on classical variants may be insufficient, supporting broader genotypic evaluation.

Background

Alpha-1 antitrypsin deficiency (AATD) is a genetic disorder caused by pathogenic variants in the SERPINA1 gene and characterized by reduced serum alpha-1 antitrypsin (AAT) levels, with codominant inheritance. AAT deficiency predisposes individuals to early-onset emphysema, chronic obstructive pulmonary disease (COPD), bronchiectasis, and liver disease [1, 2]. It is estimated that fewer than 10% of individuals with AATD are diagnosed, and the disease remains substantially underdiagnosed [3]. Accordingly, international guidelines recommend evaluation for AATD in at-risk groups, particularly patients with COPD, as well as those with unexplained bronchiectasis or early-onset emphysema [4, 5].

The association between AATD and COPD is well established, and AATD is an important genetic cause of emphysema, particularly when it presents at an early age and with a panacinar pattern. In Türkiye, the frequency of AATD-associated SERPINA1 variants among patients with COPD has been reported to range from 2.8% to 7.1%. In these studies, in addition to the classical PI*Z and PI*S alleles, rare variants such as PI*M Malton, PI*M Procida, PI*I, and PI*P Lowell have also been identified, indicating substantial heterogeneity in the distribution of AATD genotypes in Türkiye; a novel SERPINA1 variant has also been described [6–12]. Similarly, genotypic distributions including rare SERPINA1 variants have been reported from Kazakhstan and Italy [13, 14].

The association between AATD and bronchiectasis has also become increasingly well recognized. When bronchiectasis occurs in conjunction with COPD, it constitutes a clinically important combined phenotype associated with more frequent exacerbations, accelerated decline in pulmonary function, and increased mortality [15]. Data from the European Alpha-1 Research Collaboration (EARCO) indicate that bronchiectasis frequently accompanies emphysema in individuals with severe AATD, particularly those with the PI*ZZ genotype [16, 17]. However, bronchiectasis has also been reported to be associated with AATD independently of COPD and emphysema [18].

Nevertheless, data on the frequency of AATD among patients with coexisting COPD and bronchiectasis are limited, and studies directly comparing this combined phenotype with COPD-only and bronchiectasis-only groups remain scarce. This study therefore aimed to compare the distribution of SERPINA1 genotypes and the frequency of AATD-associated variants across three diagnostic groups—COPD only, bronchiectasis only, and combined COPD-bronchiectasis—and to characterize the clinical, functional, and radiological features of patients in whom variants were detected.

Methods

Study design and population

This single-center cross-sectional study was conducted at the outpatient Department of Pulmonary Diseases, Balıkesir Atatürk City Hospital, between December 2022 and May 2026, and is reported in accordance with the STROBE statement for observational studies. Patients aged 18 years or older

who were evaluated for COPD, bronchiectasis, or both diseases were consecutively enrolled. Patients who had previously been tested for AATD, refused fingertip blood sampling, or had missing demographic or genotyping data were excluded.

The study protocol was approved by the Balıkesir Atatürk City Hospital Non-Interventional Clinical Research Ethics Committee (Date: August 21, 2025; Decision No.: 2025/08/97). The study was conducted in accordance with the principles of the Declaration of Helsinki, and written informed consent was obtained from all participants.

Patient grouping

Patients were divided into three mutually exclusive groups according to the presence of COPD and bronchiectasis. The COPD group comprised patients with a post-bronchodilator FEV1/FVC ratio < 0.70 in the presence of appropriate clinical features and no evidence of bronchiectasis on high-resolution computed tomography (HRCT). The bronchiectasis group comprised patients with bronchiectasis confirmed by HRCT in accordance with the clinical findings who did not meet the diagnostic criteria for COPD. The COPD-bronchiectasis group comprised patients who met the diagnostic criteria for both COPD, confirmed by a post-bronchodilator FEV1/FVC ratio < 0.70, and bronchiectasis confirmed by HRCT.

AATD genotyping

Dried blood spot samples were prepared from fingertip capillary blood obtained from all patients. Allele-specific AATD genotyping was performed using AlphaKits (GE Healthcare Ltd., Cardiff, United Kingdom) at the Progenika Clinical Diagnostics Laboratory (Grifols, Derio, Spain). This polymerase chain reaction- and hybridization-based in vitro diagnostic assay simultaneously screened for 14 variants in the SERPINA1 gene: PI*I, PI*M Procida, PI*M Malton, PI*S Iiyama, PI*Q0 Granite Falls, PI*Q0 West, PI*Q0 Bellingham, PI*F, PI*P Lowell, PI*S, PI*Z, PI*Q0 Mattawa, PI*Q0 Clayton, and PI*M Heerlen. Samples in which none of the variants included in the panel were detected were considered PI*M/M. Samples that could not be characterized by the panel and required further evaluation were analyzed by DNA sequencing at the Progenika reference laboratory.

Clinical and functional assessments

Demographic and clinical characteristics of all patients, including age, sex, smoking history, and comorbidities, were recorded. Pulmonary function tests were performed during a clinically stable period in accordance with European Respiratory Society standards; forced vital capacity (FVC), forced expiratory volume in one second (FEV1), and the FEV1/FVC ratio were assessed.

Patients with AATD-associated SERPINA1 variants underwent additional clinical, functional, and radiological assessments. Body mass index (BMI) was calculated, the Modified Medical Research Council (mMRC) dyspnea score was recorded, and a six-minute walk test was performed. Pulmonary artery systolic pressure was assessed by echocardiography. Serum AAT levels were measured by nephelometry in a single accredited laboratory during a clinically stable period and while C-reactive protein levels were within the normal range. HRCT images were evaluated for emphysema pattern (centriacinar, panacinar, or paraseptal) and bronchiectasis morphology (tubular, varicose, or cystic, according to the Reid classification). Whole-abdominal ultrasonography was performed to assess hepatic findings.

Statistical analysis

Statistical analyses were performed using SPSS for Windows, version 22.0 (SPSS Inc., Chicago, IL, USA). Categorical variables were expressed as numbers and percentages. Continuous variables were summarized as mean ± standard deviation or as median, according to their distribution.

Results

A total of 500 patients were included in the study between December 2022 and May 2026. The mean age of the study population was 63.0 ± 10.2 years; 83 patients (16.6%) were female and 417 (83.4%) were male. According to diagnostic group, 382 patients (76.4%) had COPD, 67 (13.4%) had combined COPD-bronchiectasis, and 51 (10.2%) had bronchiectasis. Of the patients, 185 (37.0%) were current smokers, 250 (50.0%) were former smokers, and 65 (13.0%) had never smoked. Mean smoking exposure was 46.5 ± 34.2 pack-years. Mean FVC was 2.22 ± 0.91 L (61.6 ± 20.5% predicted), FEV1 was 1.38 ± 0.68 L (47.9 ± 20.0% predicted), and the mean FEV1/FVC ratio was 60.9 ± 13.2% (Table 1).

Table 1
Baseline demographic and pulmonary function characteristics of the study population

Characteristics	COPD (n = 382)	COPD-bronchiectasis (n = 67)	Bronchiectasis (n = 51)	Total (n = 500)
Female, n (%)	26 (6.8)	18 (26.9)	39 (76.5)	83 (16.6)
Male, n (%)	356 (93.2)	49 (73.1)	12 (23.5)	417 (83.4)
Age (years)	64.5 ± 8.1	61.6 ± 11.3	52.7 ± 15.3	63.0 ± 10.2
Smoking status, n (%)				
Non-smoker	2 (0.5)	25 (37.3)	38 (74.5)	65 (13.0)
Ex-smoker	212 (55.5)	29 (43.3)	9 (17.6)	250 (50.0)
Current smoker	168 (44.0)	13 (19.4)	4 (7.8)	185 (37.0)
Pack-years	54.8 ± 31.6	28.8 ± 32.5	5.5 ± 12.4	46.5 ± 34.2
FVC (L)	2.28 ± 0.91	1.82 ± 0.83	2.27 ± 0.97	2.22 ± 0.91
FVC (% predicted)	62.2 ± 20.2	52.7 ± 21.0	68.4 ± 18.8	61.6 ± 20.5
FEV1 (L)	1.32 ± 0.62	1.24 ± 0.60	1.86 ± 0.82	1.38 ± 0.68
FEV1 (% predicted)	45.6 ± 18.3	45.4 ± 20.3	68.2 ± 20.3	47.9 ± 20.0
FEV1/FVC (%)	56.6 ± 8.7	70.0 ± 16.3	81.4 ± 12.1	60.9 ± 13.2
COPD: chronic obstructive pulmonary disease; FVC: forced vital capacity; FEV1: forced expiratory volume in one second. Data are presented as mean ± standard deviation unless otherwise indicated.				

SERPINA1 genotyping identified the PI*M/M genotype in 487 patients (97.4%), while AATD-associated SERPINA1 variants were detected in 13 patients (2.6%). The most frequently detected genotype was PI*M/Z (n = 5, 1.0%), followed by PI*M/I (n = 3, 0.6%), PI*M Procida (n = 2, 0.4%), PI*M Malton (n = 1, 0.2%), PI*P Lowell (n = 1, 0.2%), and PI*M/S (n = 1, 0.2%) (Table 2). The frequency of AATD-associated SERPINA1 variants was 2.1% (8/382) in the COPD group and 7.5% (5/67) in the combined COPD-bronchiectasis group; no variants were detected in the bronchiectasis group (0/51).

Table 2
Distribution of SERPINA1 genotypes in the study population

Genotype	n	%
PI*M/M	487	97.4
PI*M/Z	5	1.0
PI*M/I	3	0.6
PI*M Procida	2	0.4
PI*M Malton	1	0.2
PI*P Lowell	1	0.2
PI*S	1	0.2
Total	500	100

The clinical, functional, and radiological characteristics of patients with AATD-associated SERPINA1 variants are presented in Table 3. Their mean age was 61.5 years; 12 were male and one was female. Seven patients (53.8%) were current smokers, four (30.8%) were former smokers, and two (15.4%) had never smoked. Mean BMI was 24.3 ± 3.6 kg/m². HRCT revealed a panacinar emphysema pattern in 10 patients (76.9%) and a centriacinar pattern in three (23.1%); no paraseptal emphysema was observed. Among the five patients with bronchiectasis, three had tubular and two had cystic bronchiectasis. Mean serum AAT level was 1.24 ± 0.32 g/L, FVC was 2.48 ± 0.75 L, FEV1 was 1.56 ± 0.53 L, and the FEV1/FVC ratio was 59.5 ± 16.5%. The mean six-minute walk distance was 356 ± 63 m. Abdominal ultrasonography showed normal findings in six patients, whereas varying degrees of hepatic steatosis and/or hepatomegaly were detected in the remaining patients. Estimated pulmonary artery pressure on echocardiography ranged from 19 to 49 mmHg.

Table 3
Characteristics of patients with alpha-1 antitrypsin deficiency

Case (genotype)	Age/Sex	BMI	Smoking status	COPD-BE	HRCT pattern	AAT level (N: 0.9-2 g/L)	FVC L (%)	FEV1 L (%)	FEV1/FVC %	6MWD m	mMRC	USG	PAP mmHg
Case 1 (PI*M/Z)	63/M	22.1	Smoker	COPD-BE	Panacinar-TBE	1.2	1.69 (47)	0.82 (29)	48	270	1	N	30
Case 2 (PI*M/Z)	68/M	23.4	Ex-smoker	COPD-BE	Panacinar-TBE	1.0	2.72 (81)	1.73 (66)	63	340	1	N	35
Case 3 (PI*M/Z)	67/F	29.3	Ex-smoker	COPD	Panacinar	0.9	1.68 (67)	0.70 (35)	41	340	2	H	49
Case 4 (PI*M/Z)	44/M	27.1	Smoker	COPD	Centriacinar	0.8	3.61 (97)	2.36 (78)	65	330	1	N	36
Case 5 (PI*M/Z)	65/M	17.3	Smoker	COPD	Panacinar	1.52	2.97 (53)	1.35 (32)	45	410	1	N	30
Case 6 (PI*I)	64/M	30.9	Smoker	COPD-BE	Panacinar-TBE	1.4	3.06 (111)	1.58 (68)	52	420	1	G1S	19
Case 7 (PI*I)	60/M	20.6	Smoker	COPD	Centriacinar	1.41	3.43 (75)	1.87 (53)	54	470	1	N	30
Case 8 (PI*I)	73/M	22.5	Smoker	COPD	Centriacinar	1.88	2.46 (66)	1.53 (54)	62	280	3	N	45
Case 9 (PI*M Procida)	58/M	24.2	Non-smoker	COPD-BE	Panacinar-CBE	1.75	1.04 (33)	0.89 (34)	86	330	2	G2S	20
Case 10 (PI*M Procida)	60/M	29.3	Smoker	COPD	Panacinar	0.9	2.25 (50)	0.95 (27)	43	396	1	G2S + H	24
Case 11 (PI*M Malton)	58/M	22.1	Smoker	COPD	Panacinar	1.0	3.04 (77)	2.17 (69)	72	372	1	G1S + H	36
Case 12 (PI*P Lowell)	63/M	22.1	Ex-smoker	COPD	Panacinar	1.2	2.97 (78)	1.87 (63)	63	308	2	N	48
Case 13 (PI*S)	63/M	25.4	Ex-smoker	COPD-BE	Panacinar-CBE	1.07	1.73 (49)	1.17 (43)	67	300	3	G1S + H	28
COPD: chronic obstructive pulmonary disease; COPD-BE: chronic obstructive pulmonary disease with bronchiectasis; HRCT: high-resolution computed tomography; TBE: tubular bronchiectasis; CBE: cystic bronchiectasis; AAT: serum alpha-1 antitrypsin level; FVC: forced vital capacity; FEV1: forced expiratory volume in one second; 6MWD: six-minute walk distance; mMRC: Modified Medical Research Council dyspnea scale; USG: abdominal ultrasonography; N: normal; G1S: grade 1 hepatic steatosis; G2S: grade 2 hepatic steatosis; H: hepatomegaly; PAP: pulmonary artery pressure.													

Discussion

In this study of 500 patients with COPD, bronchiectasis, and combined COPD-bronchiectasis phenotypes, the overall frequency of AATD-associated SERPINA1 variants was 2.6%. Variant frequency was 7.5% in the combined COPD-bronchiectasis group and 2.1% in the COPD group, whereas no variants were detected in the bronchiectasis group. These findings suggest that AATD-associated SERPINA1 variants may be more frequent in the phenotype characterized by coexisting COPD and bronchiectasis.

Our study contributes to the existing literature in two respects. First, previous studies from Türkiye [6–10] have not reported the frequency of AATD-associated SERPINA1 variants specifically in patients with coexisting COPD and bronchiectasis as a distinct phenotype. Although a multicenter Turkish study included patients with both COPD and bronchiectasis, the variant frequency in this subgroup was not reported separately [7]. In the present study, COPD, bronchiectasis, and combined COPD-bronchiectasis groups were evaluated at the same center using the same genotyping method, allowing direct comparison of variant frequencies across the three clinical phenotypes. Second, unlike previous studies, patients with detected AATD-associated SERPINA1 variants were evaluated not only for genotypic and radiological characteristics but also for exercise capacity, degree of dyspnea, echocardiographic findings, and abdominal ultrasonography findings. Although hepatic steatosis and/or hepatomegaly and elevated pulmonary artery pressure values were observed in some variant carriers, these findings were assessed only in variant-positive patients; therefore, a direct association between these findings and SERPINA1 variants cannot be established.

The 2.6% frequency of AATD-associated SERPINA1 variants observed in our study was relatively low compared with the 2.8%-7.1% rates reported from Türkiye, although it remained within a similar range [6–10]. Variable variant frequencies have also been reported in studies from Kazakhstan, Italy, and Spain [13, 14, 19]. Differences between studies may be related to the clinical characteristics of the study populations, patient selection criteria, genotyping methods used, and genetic heterogeneity between populations. Larger multicenter studies are needed to confirm these differences and, particularly, the high variant frequency observed in the combined COPD-bronchiectasis phenotype.

PI*M/Z was the most frequently detected genotype in our study, followed by PI*M/I, PI*M Procida, PI*M Malton, PI*P Lowell, and PI*M/S; no patient had a homozygous PI*Z/Z genotype. The detection of multiple rare SERPINA1 variants in addition to the classical S and Z alleles is consistent with the genotypic heterogeneity reported from Türkiye [6–10], Kazakhstan [13], and Italy [14]. The importance of rare SERPINA1 variants within the genetic spectrum of AATD has also been highlighted in previous studies and recent systematic assessments [20, 21]. In a study by Veith et al. including 18,736 patients, PI*M/Z (22.0%) and PI*Z/Z (9.1%) genotypes were prominent, demonstrating that genotype distributions may vary across different clinical populations [22]. This heterogeneity supports the possibility that limited screening approaches targeting only the PI*S and PI*Z alleles may fail to identify some rare SERPINA1 variants and underscores the importance of broader genotyping panels [23].

In a previous bronchiectasis study from Türkiye [10], concomitant emphysema was not reported among patients with AATD-associated SERPINA1 variants. However, the exclusion of patients with emphysema in that study suggests that this finding may have been related to the patient selection criteria. In our study, the presence of emphysema was not an exclusion criterion, and all 13 patients with AATD-associated SERPINA1 variants had emphysema; 76.9% had a panacinar pattern, and 38.5% had coexisting COPD and bronchiectasis. This difference demonstrates the importance of study population selection criteria when evaluating the relationship between AATD and bronchiectasis and supports existing evidence that bronchiectasis may occur in AATD either with or independently of emphysema [16, 17].

The mean serum AAT level in patients with AATD-associated SERPINA1 variants was 1.24 ± 0.32 g/L, which was close to the lower limit of the normal range. The predominance of heterozygous genotypes and the absence of homozygous PI*Z/Z genotypes may explain why severe AAT deficiency was not observed. Nevertheless, normal or near-normal serum AAT levels do not exclude the presence of heterozygous or rare SERPINA1 variants. Serum AAT levels should therefore be interpreted together with genotypic findings when evaluating AATD.

The principal clinical implication of our study is the importance of recommended AATD screening approaches, particularly in patients with coexisting COPD and bronchiectasis. International recommendations advise evaluation for AATD in risk groups such as patients with COPD and unexplained bronchiectasis [4, 5]. The high frequency of SERPINA1 variants observed in the combined COPD-bronchiectasis group supports the view that this phenotype may represent a patient group that should not be overlooked when evaluating for AATD.

Our study has several limitations. First, detailed clinical, functional, and imaging assessments were performed only in patients with detected AATD-associated SERPINA1 variants, precluding comparison of these characteristics between variant-positive and variant-negative patients. Consequently, it cannot be determined whether the clinical and imaging findings observed in variant carriers are related to SERPINA1 variants or to the characteristics and severity of the underlying respiratory disease. Second, the imbalance in the number of patients among the diagnostic groups, particularly the limited sample size of the bronchiectasis group, may have reduced the likelihood of detecting low-frequency variants in this group. In addition, the single-center design and the limited number of patients with AATD-associated SERPINA1 variants restrict the generalizability of the findings and the ability to perform detailed subgroup analyses. Because the genotyping panel was limited to 14 SERPINA1 variants and comprehensive DNA sequencing was not performed, rare or novel variants outside the panel may have been missed. Finally, because of the cross-sectional design, the relationship between SERPINA1 variants and disease progression or long-term clinical outcomes could not be assessed.

Conclusions

Our findings suggest that the combined COPD-bronchiectasis phenotype may represent a particularly relevant clinical group for AATD evaluation. The observed genotypic heterogeneity supports the possibility that approaches focusing only on classical variants may be insufficient for AATD assessment and highlights the importance of broader genotypic evaluation. Confirmation of these findings in larger, multicenter cohorts will contribute to better defining the role of the COPD-bronchiectasis phenotype in AATD screening.

Declarations

Ethical approval and consent to participate

The study protocol was approved by the Balıkesir Atatürk City Hospital Non-Interventional Clinical Research Ethics Committee (Date: August 21, 2025; Decision No.: 2025/08/97). The study was conducted in accordance with the principles of the Declaration of Helsinki, and written informed consent was obtained from all participants.

Clinical trial number

Not applicable.

Consent for publication

Not applicable. This manuscript does not contain any individual person's identifiable data, images, or other personal or clinical details that would require separate consent for publication.

Availability of data and materials

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare no conflicts of interest.

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Authors' contributions

D.A. contributed to study conception and design, data acquisition, analysis and interpretation of data, and drafting of the manuscript. G.A. contributed to data interpretation and critical revision of the manuscript for important intellectual content. Both authors approved the final version for submission and agree to be accountable for all aspects of the work.

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Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this manuscript, the author(s) used Claude (Anthropic, Claude Sonnet 5) to assist with language editing and with formatting the manuscript in accordance with the journal's author guidelines. All AI-assisted content was reviewed, verified, and revised by the author(s), who take full responsibility for the accuracy, integrity, and originality of the manuscript.

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