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Alpha-1 Antitrypsin Deficiency: the Challenge of Reducing the Underdiagnosis

Déficit de alfa-1 antitripsina: El desafío de reducir el subdiagnóstico

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ABSTRACT

Introduction: Alpha-1 antitrypsin deficiency (AATD) is a hereditary genetic disorder characterized by a reduction in serum concentrations of this protein, predisposing affected individuals to a significantly increased risk of pulmonary and hepatic diseases. Despite being a well-recognized condition, AATD remains substantially underdiagnosed globally and regionally, largely because of low clinical suspicion.

Objective: This cross-sectional, retrospective study aimed to determine the prevalence and clinical characteristics of AATD in patients evaluated at a university hospital in Córdoba, Argentina, between June 2023 and June 2025.

Materials and methods: The study included 339 patients, of whom 18 had serum alpha-1 antitrypsin levels < 120 mg/dL.

Results: A 0.88% prevalence of severe AATD was confirmed. Low alpha-1 antitrypsin levels were significantly associated with pulmonary emphysema, independent of smoking history, age, and sex. In addition, serum alpha-1 antitrypsin levels were positively correlated with forced expiratory volume in 1 second (FEV_1). Among patients with concentrations in the lower reference range, liver disease and eosinophilia were the most frequent associated findings.

Conclusions: Systematic screening for AATD in patients with chronic obstructive pulmonary disease (COPD) or liver disease is crucial for ensuring timely diagnosis.

Key words: alpha-1 antitrypsin deficiency | pulmonary Emphysema | chronic obstructive pulmonary disease | phenotype | Argentina

RESUMEN

Introducción: El déficit de alfa-1 antitripsina es un trastorno genético hereditario caracterizado por una reducción en las concentraciones séricas de esta proteína, lo que genera una predisposición significativa a enfermedades pulmonares y hepáticas. A pesar de ser una condición reconocida, el subdiagnóstico persiste a nivel global y regional debido a la falta de sospecha clínica.

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Objetivo: Este estudio transversal y retrospectivo se realizó con el objetivo de describir la prevalencia y las características clínicas de esta deficiencia en pacientes de un hospital universitario de Córdoba, Argentina, entre junio de dos mil veintitrés y junio de dos mil veinticinco.
Materiales y métodos: Se analizaron los registros de 339 pacientes, de los cuales dieciocho presentaron niveles de alfa-1 antitripsina inferiores a 120 mg/dL.
Resultados: Se confirmó una prevalencia de deficiencia grave del 0,88 %. Se identificó una asociación estadísticamente significativa entre los niveles bajos de la proteína y la presencia de enfisema pulmonar, independientemente del historial de tabaquismo, la edad o el sexo. Asimismo, se observó una correlación positiva entre los niveles de alfa-1 antitripsina y el volumen espiratorio forzado en el primer segundo. En los casos con valores en el límite inferior, predominó la asociación con enfermedades hepáticas y eosinofilia.
Conclusiones: El estudio concluye que es fundamental implementar un cribado sistemático en pacientes con enfermedad pulmonar obstructiva crónica y hepatopatías para mejorar la detección temprana de esta patología.

Palabras clave: Déficit de alfa 1-antitripsina | enfisema pulmonar | enfermedad pulmonar obstructiva crónica | fenotipo | Argentina

INTRODUCTION

Alpha-1 antitrypsin deficiency is a complex hereditary genetic disorder and a potentially life-threatening congenital condition that typically manifests during adulthood.[1,2] It is characterized by reduced serum concentrations of alpha-1 antitrypsin, a glycoprotein synthesized primarily by hepatocytes.[1,3] The main biologic function of this glycoprotein is to protect the pulmonary extracellular matrix from proteolytic degradation by neutrophil elastase.[1,2] AATD is caused by mutations in the SERPINA1 gene, located on chromosome 14, and is transmitted via an autosomal codominant inheritance pattern.[1,3,4]

From a genetic perspective, approximately 125 SERPINA1 variants have been identified.[4] The normal allele, PiM, is present in 80% to 95% of the population.[4] The most common deficient variants are PiS and PiZ. Most cases of severe clinical disease are associated with the homozygous PiZZ genotype, which results in plasma AAT levels of approximately 10% to 15% of normal values.[1] The pathophysiology involves a dual mechanism: a "loss of function" in the lungs that predisposes to premature panacinar emphysema, and a "toxic gain of function" in the liver, where the polymerization of the abnormal protein within the endoplasmic reticulum of hepatocytes can lead to cirrhosis and hepatocellular carcinoma.[1,4,5]

The epidemiology of AATD is characterized by marked geographic and ethnic variation. Recent estimates indicate that approximately 235,000 individuals worldwide have the Pi*ZZ genotype, with 50% residing in Europe and 37% in the Americas.[6] Within Europe, the highest prevalence of the PiZZ genotype is reported in Northern and Western European countries, including Italy, Spain, France, and the United Kingdom.[7,8] In these countries, there is a strong association between the PiZZ genotype and chronic obstructive pulmonary disease, with a mean prevalence of one Pi*ZZ patient for every 850 individuals with COPD.[9]

In Latin America, the prevalence of AATD is estimated to be up to fivefold lower than that reported in Europe.[4] However, the DAAT.AR study conducted in Argentina reported an adjusted prevalence of severe AATD (SZ and ZZ genotypes) of 0.83% among patients with COPD aged ≥ 40 years.[7] This represents around 17,000 to 18,000 affected individuals in Argentina, the vast majority of whom remain undiagnosed.[7] In Brazil, approximately 6,000 individuals are estimated to have the Pi*ZZ genotype, highlighting that AATD is not confined to white populations in the Northern Hemisphere but affects diverse racial and ethnic groups worldwide.[1,3,4]

Despite its clinical relevance, AATD remains markedly underdiagnosed, with more than 85% of affected individuals estimated to remain un-

detected.[4,6] Diagnostic delays of 5 to 8 years from the onset of respiratory symptoms have been consistently reported.[6,9,10] Patients often consult multiple physicians before receiving a precise diagnosis, frequently after unsuccessful treatment for asthma or COPD.[6,10]

Accordingly, the World Health Organization (WHO) and the American Thoracic Society/European Respiratory Society (ATS/ERS) and Spanish Society of Pulmonology and Thoracic Surgery (SEPAR) guidelines recommend measuring serum AAT levels at least once in a lifetime in all patients with COPD, regardless of age or smoking history.[1,2] Early screening is essential to facilitate the integration of preventive measures, enable family screening, and identify candidates for purified AAT augmentation therapy, the only disease-specific treatment shown to slow the decline in lung density in appropriately selected patients.[1,2,4]

Hypothesis

We hypothesized that AATD is underdiagnosed at our institution because of the lack of systematic screening among patients with emphysema, uncontrolled asthma, persistent eosinophilia, or liver disease, resulting in reduced detection of clinically relevant cases.

OBJECTIVES

Overall objective

To determine the prevalence and describe clinical characteristics of alpha-1 antitrypsin deficiency among patients evaluated at Hospital Privado Universitario de Córdoba, Argentina, during the study period.

To characterize the epidemiologic and clinical profile of patients with low or borderline serum A1AT levels and evaluate their association with respiratory manifestations and ancillary clinical findings.

Secondary objectives

To evaluate the demographic distribution and clinical association of alpha-1 antitrypsin deficiency in patients from a private healthcare facility in Córdoba, with particular emphasis on its relationship with pulmonary imaging and lung function findings.

To evaluate the prevalence of the association between peripheral eosinophilia and low A1AT levels.

To investigate the coexistence of a history of liver disease and its association with alpha-1 antitrypsin deficiency.

MATERIALS AND METHODS

We conducted a retrospective, observational, analytical, cross-sectional study.

Study design and setting

This retrospective and descriptive study was conducted by the Department of Pulmonology at Hospital Privado Universitario de Córdoba.

Study population

Consecutive adults (aged ≥ 18 years) who received care at this institution between June 2023 and June 2025 were included.

Data collection

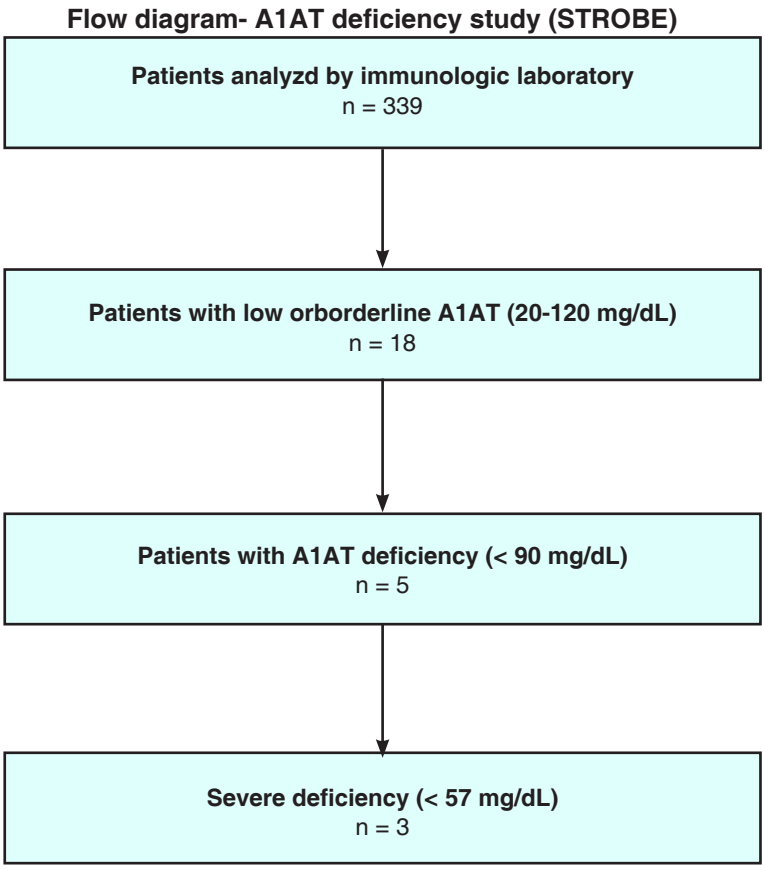
Data were obtained from the hospital's electronic health record system. Medical records were extracted. Then, medical records were reviewed, and eligible patients were identified after application of the predefined inclusion and exclusion criteria. The following variables were collected: epidemiologic data, smoking history, clinical symptoms, spirometry results, immunologic test results, and high-resolution CT (HRCT) findings.

Statistical analysis

Data from the electronic medical records were entered into an Excel-like database, which was later used for statistical analysis. Absolute and percentage distributions were calculated for categorical variables. To evaluate the association between clinical symptoms and immunological, spirometric, and tomographic findings, the chi-square test was applied. The same approach was applied to all other analyses involving categorical variables of interest. A significance level of 0.05 was used in all cases. Statistical analyses were performed using InfoStat software (version 2020). Results are presented as tables or figures, as appropriate.

RESULTS

A total of 339 laboratory results from the Immunology Department were analyzed to evaluate



serum alpha-1 antitrypsin levels (measured in mg/dL).

Serum levels greater than 120 mg/dL were considered normal, borderline values were defined as 91 to 119 mg/dL, decreased values as less than 90 mg/dL, and severely decreased values as less than 57 mg/dL.

From the initial cohort (n = 339), 18 patients (5.3%) exhibited values less than 120 mg/dL and were classified as suspected cases.

Within this group, 5 patients (1.47% of the total cohort) had levels less than 90 mg/dL, and 3 patients (0.88% of the total cohort) had levels less than 57 mg/dL. At the time of data collection, only the latter three patients had undergone genetic testing.

The genomic variants identified were: homozygous Z, homozygous S, and heterozygous ZS.

Consequently, the confirmed true prevalence was 0.88% based on immunological A1AT serum testing. The prevalence of suspected cases based on borderline values was 5.3%; however, neither genetic testing, buccal swab, nor dried blood spot testing was performed in these remaining patients.

Regarding age distribution, 14 men and 4 women were identified, with a mean age of 53 +/- 1 years.

To facilitate the analysis of associations, patients were divided into two groups based on a cutoff value of ≥ 90 mg/dL.

A male predominance was observed in the overall cohort (77.8%).

In the subgroup with A1AT levels < 90 mg/dL, 3 patients were men and 2 were women, whereas the subgroup with levels ≥ 90 mg/dL was also predominantly male (11 men vs. 2 women).

Proportionally, 50.0% of the women had A1AT levels < 90 mg/dL compared with 21.4% of the men. However, due to the small sample size –particularly within the female subgroup– it was not possible to demonstrate a statistically significant association between sex and serum A1AT levels.

Regarding smoking history, 8 patients were smokers with a smoking load of more than 15 pack-years.

In terms of underlying conditions, 9 patients had liver disease (autoimmune hepatitis, n = 3; HCV-related cirrhosis, n = 2; NASH cirrhosis, n = 2; alcoholic cirrhosis, n = 1; and hemochromatosis, n = 1).

To simplify the statistical analysis, the 18 patients were stratified into 2 groups according to their serum A1AT concentration: > 90 mg/dL and < 90 mg/dL.

Only 1 of the 5 patients (20.0%) with A1AT less than 90 mg/dL had an underlying liver disease. This difference in liver disease distribution between the two A1AT cohorts did not reach statistical significance (p = .35, Fisher exact test).

4 of these 5 patients (80.0%) with A1AT < 90 mg/dL did not show liver disease.

The remaining 8 patients showed values > 90 mg/dL.

Regarding the analysis of patient phenotypes, a total of 17 patients had peripheral blood eosinophil counts available for evaluation.

A trend toward higher eosinophil counts (> 300 cells/µL) was observed in patients with A1AT levels ≥ 90 mg/dL (7 cases) compared with those with levels < 90 mg/dL (0/4 cases). However, no statistically significant association was identified. The proportions of eosinophilia were comparable between both A1AT groups (p > 0.05).

Patients with < 90 mg/dL had eosinophilia (> 150); nonetheless, this did not reach statistical significance due to the high prevalence of

Table 1. Association between A1AT levels and sex

Sexo	G1 (<90 mg/dL)	G2 (≥90 mg/dL)	% of deficiency
Male (14)	3	11	21.40%
Female(4)	2	2	50%

Table 2. Association between A1AT levels and sex

		A1AT category	
Patient	SEX	G2 (≥90 mg/dL)	G1 (<90 mg/dL)
1	female	1	0
2	male	1	0
3	male	1	0
4	female	0	1
5	male	1	0
6	male	1	0
7	female	1	0
8	female	0	1
9	male	1	0
10	male	1	0
11	male	1	0
12	male	1	0
13	male	1	0
14	male	1	0
15	male	1	0
16	male	0	1
17	male	0	1
18	male	0	1

Figure 1. Association between A1AT levels and sex

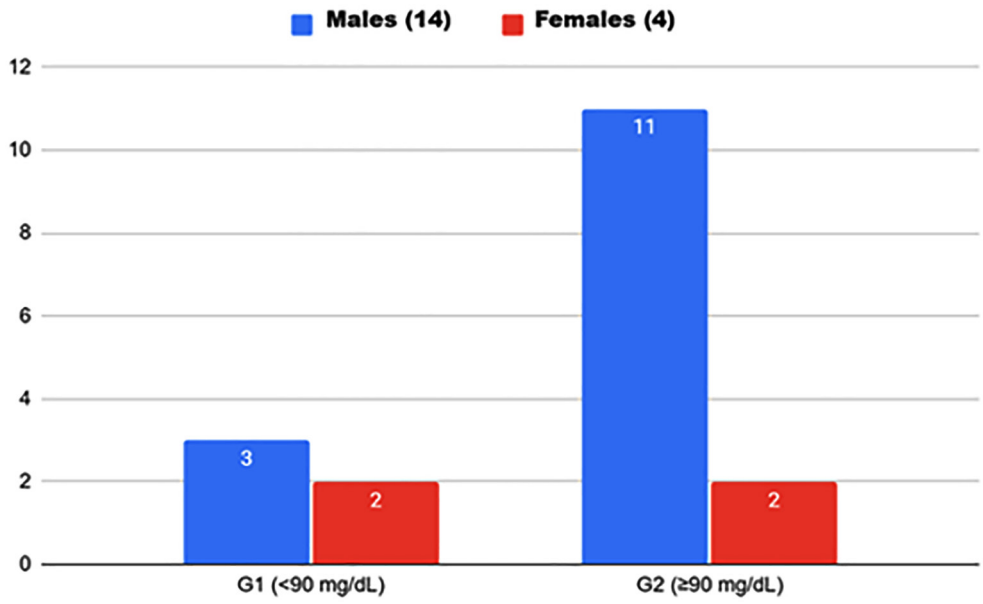


Table 3. Distribution of liver disease by A1AT level

A1AT category	Wit hliver disease	Without liver disease	Total
< 90 mg/dL	1	4	5
≥ 90 mg/dL	8	5	13
Total	9	9	18

Table 4. Distribution of eosinophilia by A1AT levels

Distribution of eosinophilia by A1AT levels			
A1AT category	≤150 cells/µL	>150 cells/µL	>300 cells/µL
<90 mg/dL	0	4	0
≥90 mg/dL	3	3	7
Total	3	7	7

eosinophilia within the cohort with values ≥ 90 mg/dL.

Regarding chest imaging patterns, high-resolution chest CT scans were available for all patients (n = 18).

Emphysema was identified in 6 patients, of whom 3 had A1AT levels < 90 mg/dL.

Only 2 of the 12 patients without emphysema had A1AT levels < 90 mg/dL.

A statistically significant association was identified between low A1AT levels (< 90 mg/dL) and the presence of emphysema (p = .049, Fisher exact test), demonstrating a significantly higher prevalence of emphysema among patients with A1AT deficiency.

Emphysema was present in 3/5 of patients with A1AT levels < 90 mg/dL compared with 3/13 of patients in the cohort with A1AT levels ≥ 90 mg/dL.

Figure 2. Association between A1AT levels and eosinophil counts.

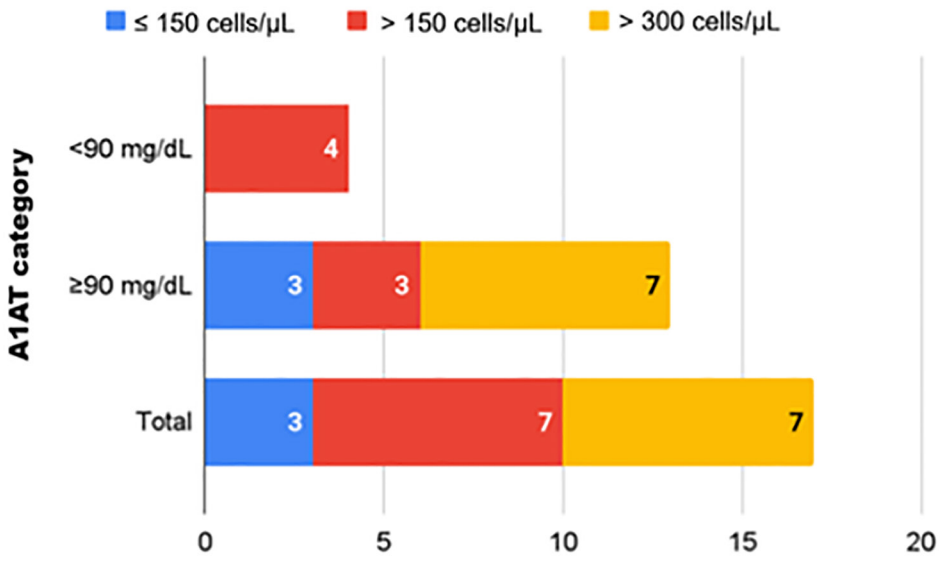
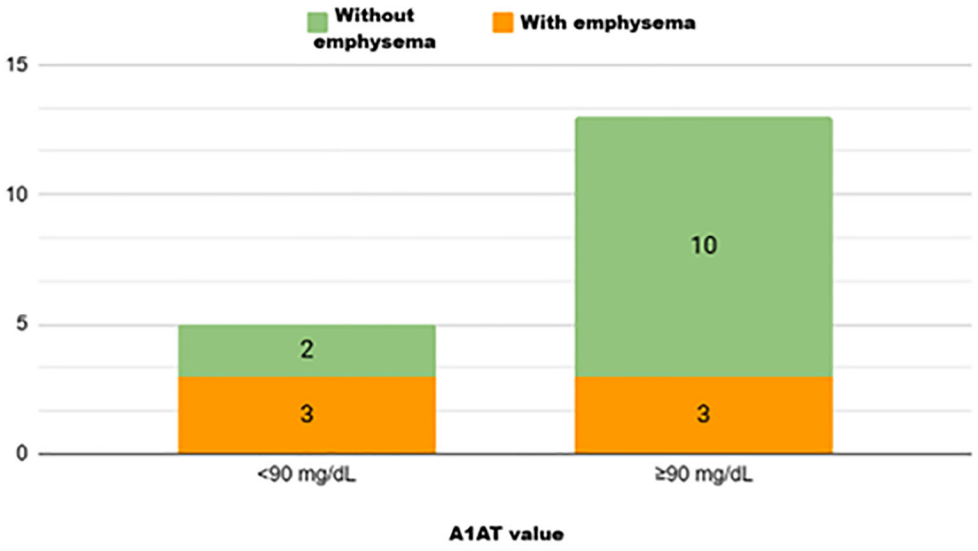


Figure 3. Distribution of emphysema by A1AT level



The three patients with emphysema exhibited individual serum values of 90 mg/dL, 114 mg/dL, and 120 mg/dL, respectively.

Regarding functional assessment, spirometry data were available for 15 patients. The distribution of spirometric patterns was as follows: 8 normal, 3 obstructive, and 4 restrictive.

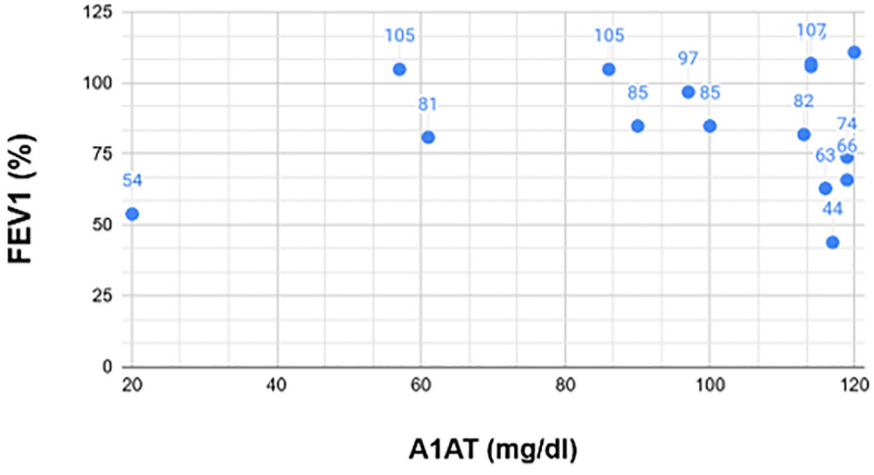
A moderate positive correlation was identified between serum A1AT levels and FEV1% ($p = .42$; $p = .061$).

Notably, after excluding a single case with severe A1AT deficiency (20 mg/dL), this correlation reached statistical significance ($p = .48$; $p = .037$).

Table 5. Association between A1AT levels and the presence of emphysema

A1AT (mg/dL)	A1AT (mg/dL)
100	0
114	1
120	0
61	0
119	0
119	0
117	0
20	1
97	0
116	0
113	0
93	0
114	0
20	1
90	1
86	1
20	1
57	0

Figure 4. Correlation between FEV1 (%) and A1AT (mg/dL)



The distribution of FEV1 percentages plotted against A1AT levels demonstrates a reciprocal relationship between normal values, respectively.

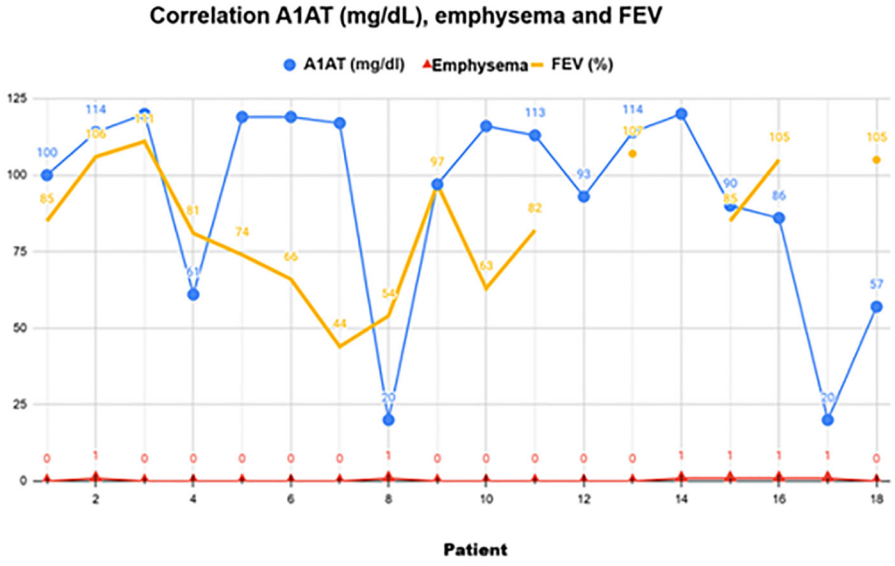
The exploratory analysis demonstrated a trend toward greater respiratory functional impairment in patients with reduced serum alpha-1 antitrypsin levels, particularly in those with concomitant emphysema.

Cases with severe deficiency consistently exhibited coexistence of emphysema and functional decline. However, notable clinical heterogeneity was observed across the cohort, which was likely

Table 6. Correlation among spirometric findings, chest CT patterns, and serum A1AT levels

Patient	A1AT (mg/dL)	Emphysema	FEV
1	100	0	85
2	114	1	106
3	120	0	111
4	61	0	81
5	119	0	74
6	119	0	66
7	117	0	44
8	20	1	54
9	97	0	97
10	116	0	63
11	113	0	82
12	93	0	NR
13	114	0	107
14	120	1	NR
15	90	1	85
16	86	1	105
17	20	1	NR
18	57	0	105

Figure 5. Correlation among spirometric findings, chest CT patterns, and serum A1AT levels



influenced by concomitant factors such as smoking history and phenotypic variability.

Among all of the patients who were analyzed (n = 18), 8 were smokers and 6 had emphysema.

Smokers with emphysema: 3/8

Smokers without emphysema: 5/8

Non-smokers (n= 10) with emphysema: 3. (These 3 patients had A1AT levels < 90)

1 every 5 patients with A1AT levels < 90 was a smoker without emphysema

1 every 5 patients with A1AT levels < 90 was non- smoker without emphysema

These findings suggest an association between low A1AT levels and emphysema that may be stronger than the association observed with smoking history.

Smoking was associated with emphysema in only 37.5% of cases.

No statistical significance can be established with this small sample size (n = 18), but there is a clinically relevant trend.

DISCUSSION

The findings of this study support that alpha-1 antitrypsin deficiency (AATD) remains underdiagnosed in our setting. The prevalence of severe deficiency observed in our cohort (0.88% for serum A1AT concentrations < 57 mg/dL) is highly consistent with the findings of the DAAT.AR study, which reported an adjusted prevalence of 0.83% among Argentine patients with COPD aged ≥ 40 years. In contrast, higher prevalences have been reported in European populations, where the PI*ZZ genotype is more common because of ethnic and geographic factors.(2,3)

Our findings may underestimate the local epidemiologic reality because systematic genotyping was not routinely available. Only 3 patients from the sample underwent confirmatory genetic testing.(2,4) The statistically significant association between low serum A1AT concentrations and the presence of emphysema (p = .049) is consistent with the established pathophysiology of AATD, in which an imbalance between proteases and antiproteases promotes neutrophil elastase-mediated degradation of the pulmonary extracellular matrix. Consistent with previous studies, higher serum A1AT concentrations were associated with higher FEV1%, suggesting that more severe obstruction is associated with greater degrees of AAT deficiency. Furthermore, the data suggest that the relationship between AATD and emphysema may be more determinant than smoking history, as non-smoking patients with emphysema were found to have deficient serum AAT levels.

A point of particular interest in this discussion is the behavior of patients with "borderline" serum levels (90-120 mg/dL). Within this subgroup, a predominant association with hepatic diseases and peripheral blood eosinophilia was observed, raising critical questions regarding the role of heterozygous variants (such as PiMZ or PiSZ) in extrapulmonary manifestations and systemic inflammatory processes. It is well established that hepatic pathology in AATD does not stem from a loss of protein function; rather, it is driven by a toxic gain of function resulting from polymer accumulation within hepatocytes –a mechanism that can be active even in individuals with moderately reduced serum levels.

Despite the relevance of these findings, this study has several limitations, including a small sample size (n = 18) and potential selection bias inherent to data from a single private center, which limits the generalizability of the results to the broader population. Nevertheless, the diagnostic delay and lack of clinical suspicion identified herein remain persistent global challenges. International studies document diagnostic delays ranging from 5 to 8 years –and up to 10 years in certain regions– demonstrating that early detection rates have not significantly improved over recent decades.[8,9]

Finally, these results underscore the imperative need to implement systematic screening protocols. In alignment with guidelines from the WHO and international scientific societies, serum AAT quantification should be performed at least once in a lifetime in all patients with COPD or difficult-to-control asthma, regardless of their smoking history.

Early identification not only optimizes clinical management and allows for the timely consideration of augmentation therapy, but it also facilitates the screening of consanguineous relatives to detect other individuals at risk before irreversible organic damage develops.

CONCLUSIONS

This study suggests that AATD remains an underdiagnosed condition within our population. Low A1AT levels were significantly associated with pulmonary emphysema, independent of smoking history, age, and sex. In patients with "borderline" serum values, liver disease predominated over pulmonary involvement, and peripheral blood eosinophilia was detected within this subgroup.

These findings reinforce the need to use systematic screening protocols in patients with diagnosed COPD, early-onset emphysema (with and

without significant tobacco exposure), and chronic liver disease, in strict alignment with international guidelines.

Future recommendations

Universal screening in COPD/severe asthma patients, even in the absence of emphysema.

Multicenter studies to estimate the true prevalence of AATD in Argentina, incorporating systematic genotypic analysis.

Finally, it is crucial to underscore that within this Argentine cohort, a negative correlation was observed between AAT levels and age, tobacco consumption (pack-years), and FEV1%. This evidence strongly reinforces the importance of maintaining a high index of suspicion for AATD in patients with early-onset COPD, non-smokers or individuals with minimal tobacco exposure, and those exhibiting more severe functional impairment and lower FEV1 values.

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