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Clinical letter

Routine blood biomarkers in patients with the PI*SZ genotype of alpha-1 antitrypsin deficiency: Data from the EARCO Registry

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To the Director,

Alpha-1 antitrypsin deficiency (AATD) is a rare genetic disorder of codominant inheritance, caused by a mutation in the SERPINA1 gene (1). It leads to low levels of alpha-1 antitrypsin (AAT), resulting in low anti-elastase activity (2). More than 1000 variants of this gene have been identified, being the proteinase inhibitor (PI)*S and Z the most common of all (3). PI*S is highly prevalent in the northwest of the Iberian Peninsula and PI*Z has its origins in Northern Europe (4). The highest risk for the development of emphysema corresponds to the PI*ZZ genotype, with AAT levels of approximately 15% in blood (5), and the PI*SZ genotype, with around 40% protein serum levels, is the next most frequent severe deficient genotype. Some studies suggest an increased susceptibility to developing COPD in smokers with PI*SZ genotype, and an elevated risk of liver disease (6,7); however, information about this genotype is scarce.

There is great variability in the clinical presentation and severity of lung and liver disease in patients with AATD (8). Therefore, it is important to identify markers and biomarkers that can predict respiratory involvement, both in terms of clinical phenotypes and severity. Recently, biomarkers such as proinflammatory interleukins, desmosine and isodesmosine, and circulating AAT polymers have been found to be associated with prognosis of lung disease (9-11). Nevertheless, the use of these biomarkers remains largely confined to research settings and they are rarely incorporated into routine clinical practice. In this context, a recent study reported that certain serum biomarkers—including higher hematocrit levels, gamma-glutamyl transferase (GGT), and the platelet-to-lymphocyte ratio (PLR)—were associated with more severe forms of emphysema in patients with the PI*ZZ genotype, although the prognostic accuracy of these markers was low.

This study aimed to compare routine serum biomarkers between PI*SZ individuals with and without emphysema, and assess their correlations with lung disease severity across the entire PI*SZ population.

This multicentre cross-sectional study included patients from the European Alpha-1 Antitrypsin Deficiency Research Collaboration (EARCO) international registry database who had confirmed AATD and PI*SZ genotype (13). Patients on augmentation therapy were excluded. Demographic data, smoking history, comorbidities, respiratory symptoms, presence of lung and/or liver disease, past medical history of respiratory exacerbations within the past 12 months and lung function tests (forced expiratory volume in the first second [FEV_1] and the carbon monoxide transfer coefficient [KCO]) were collected. Routine serum biomarkers were obtained and the neutrophil-to-lymphocyte ratio (NLR), eosinophil-to-lymphocyte ratio (ELR) and PLR were calculated. Normally distributed variables were compared using the Student *t* test, whereas non‑normally distributed variables were analyzed with the Mann‑Whitney *U* test. Categorical variables were analyzed using the chi-square or Fisher exact test, as appropriate, and correlations were assessed using Pearson or Spearman correlation coefficients according to data distribution.

The EARCO registry (ID: NCT04180319) was approved by *Hospital Universitario Vall d'Hebron* Ethics Committee and written informed consent was obtained from all participants prior to their inclusion in the study.

Of the 2,419 patients included in the EARCO Registry as of October 2024, 571 (23.6%) had the Pi*SZ genotype and were not receiving augmentation therapy. Among them, 51% were men, with a mean age of 51.8 years (SD, 16.3) and 46.7% had never been smokers. Mean FEV1 (%) was 92.3% (SD, 25.9%), mean KCO (%) was 89% (SD, 22.2%), and emphysema was reported in 118 (20.7%). Overall, 12.3% of patients were current smokers, 41.0% were former smokers, and 46.7% had never smoked. Emphysema was present in 22 patients (31.4%): 85 (36.5%) were current smokers, 11 (4.2%) were never smokers, and the remainder were former smokers.

Individuals with emphysema were older, with a higher proportion of men, greater smoking history, and worse lung function vs individuals without emphysema. Biomarker analysis in emphysema patients showed significantly elevated levels of AAT, aspartate aminotransferase (AST), GGT, fibrosis-4 index (FIB-4), hemoglobin, leukocytes, neutrophils, and the NLR (Table 1). In addition, among all PI*SZ patients, weak but significant negative correlations were observed between FEV1(%) and serum levels of AAT, GGT, FIB-4 index, hemoglobin, leukocytes, lymphocytes, neutrophils, and the NLR. Similarly, for KCO(%), weak but significant negative correlations were found with AAT, FIB-4 index, leukocytes, neutrophils, platelets, and the NLR, while a positive correlation was observed with ALT (Figure 1).

Only a limited number of studies have investigated the role of blood biomarkers in AATD, and almost all have focused on patients with the PI*ZZ genotype (9-12). Therefore, our study addresses an important gap in the literature by evaluating routine blood biomarkers in a large, well-characterised PI*SZ population. In addition to contributing novel genotype-specific data, these findings complement and extend previous work from the same EARCO registry in PI*ZZ individuals, allowing for comparisons across genotypes and providing a valuable resource for future research in AATD (14).

Clinical trials have suggested that individuals with the PISZ genotype exhibit respiratory features more similar to those observed in PIMZ than in PI*ZZ, and that the emphysema pattern may resemble smoking-related COPD. (15). Consequently, and as expected, our patients with PI*SZ genotype and emphysema were older, with a higher smoking exposure and worse lung function vs those without emphysema. Data on the comparison of biomarkers in Pi*SZ individuals with or without lung disease are scarce. We found that PI*SZ patients with emphysema displayed a distinct biomarker profile vs those without the disease, indicating increased systemic inflammation, liver changes, and potential metabolic changes. These findings are mostly aligned with previous observations in PI*ZZ individuals from the EARCO registry, where patients with established lung disease also showed higher levels of hemoglobin, GGT, NLR, PLR, and ELR, with weak but significant negative correlations with spirometric parameters (12). Of note, the distinction is limited by differences in disease definition (emphysema vs COPD), yet the overlap in biomarker patterns suggests possible genotype-specific differences in systemic inflammatory responses, thus reinforcing that routine blood biomarkers alone have limited ability to predict the severity of lung disease in PI*SZ individuals.

Regarding the associations between biomarkers and lung disease severity, former studies have suggested that markers, such as GGT or fibrinogen cleavage product Aα-Val360 may be associated with lung function in AATD (16,17). In our cohort, although some correlations reached statistical significance, they were consistently weak, reflecting the marked heterogeneity of pulmonary involvement in this population. Factors such as the distribution and extent of emphysema, presence of comorbidities, and smoking exposure may contribute to this variability. These findings underscore that, while serum biomarkers can offer valuable insights into systemic inflammation or metabolic alterations, they should be interpreted with caution when assessing pulmonary disease severity in any given individual.

Limitations of our study include its cross-sectional design, which excludes any possibility of deducing causality between biomarker levels and the presence or severity of lung disease. Additionally, neither can determine the value of these biomarkers in predicting disease and clinical progression. Therefore, prospective follow up studies in PI*SZ individuals are needed to validate the prognostic value of blood biomarkers. Furthermore, lung phenotypes were based on physician-reported diagnoses without standardized imaging or centralized validation, which may be a source of misclassification or diagnostic variability. In addition, the study was limited to routine blood biomarkers and did not include disease-specific markers, such as circulating AAT polymers, desmosine or pro-inflammatory cytokines, which may be source of pathophysiological insight. Furthermore, the number of C-reactive protein (CRP) measurements in our cohort were too low to be included in the analysis.

In conclusion, AAT PI*SZ deficiency with emphysema was associated with a distinct biomarker profile, reflecting systemic inflammation, liver changes, and potential metabolic changes. Moreover, although some correlations between serum biomarkers and lung disease severity reached statistical significance, they were consistently weak, illustrating the heterogeneity of pulmonary involvement and suggesting caution when using serum biomarkers to assess disease severity in this population.

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Conflicts of interest

Ane Lopez-Gonzalez declared to have received speaker fees from AstraZeneca, Chiesi, GlaxoSmithKline and CSL Behring. **Cristina Esquinas** declared to have received honoraria within the past 3 years for scientific advice and scientific activities from Chiesi and CSL Behring. **Hanan Tanash** declared to have received speaker fees from AstraZeneca, GlaxoSmithKline, Boehringer Ingelheim, Chiesi and Grifols.

María Torres-Durán declared to have received either speaker and consulting fees from CSL Behring and Grifols, and support for attending meetings from CSL Behring, Grifols, Chiesi and FAES Farma. **Alice M Turner** declared to have received grants or speaker fees from AstraZeneca, GlaxoSmithKline, Boehringer Ingelheim, Chiesi, CSL Behring, Takeda, Vertex and Grifols Biotherapeutics. **Carlota Rodríguez-García** declared to have received speaker fees from AstraZeneca, GlaxoSmithKline, Grifols, Chiesi, and CSL Behring, expert testimony for Chiesi, support for attending meetings from Chiesi and Grifols. **Angelo Corsico** declared to have received speaker fees and honoraria for his participation on advisory board from CSL Behring, and honoraria for manuscript writing from Grifols. **Catarina Guimarães** declared to have received speaker fees from CSL Behring. **José Luis López-Campos** declared to have received honoraria within the past 3 years for lecturing, scientific advice, participation in clinical trials or drafting for publications for (alphabetical order): AstraZeneca, Bial, Boehringer, Chiesi, CSL Behring, Faes, Gebro, Grifols, GSK, Menarini, Sanofi, Zambon. **José María Hernández-Pérez** declared to have received consulting fees from Grifols and CSL Behring, speaker fees from AstraZeneca, Bial, CSL Behring, FAES laboratory, GlaxoSmithKline, and Grifols, support for attending meetings from Grifols and CSL Behring, and honoraria for participation on advisory board from Grifols. **Christian F. Clarenbach** has received advisory fees from Roche, Novartis, Boehringer, GSK, AstraZeneca, Sanofi, Vifor, OM Pharma, CSL Behring, Grifols and MSD. **Juan Luis Rodriguez-Hermosa** declared to have received speaker or consulting fees from AstraZeneca, Bial, CSL Behring, GlaxoSmithKline, Grifols, Menarini and Zambon. **Maria Sucena** declared to have received consulting fees from Bial, CSL Behring, GSK, Grifols and Sanofi, and speaker fees from AstraZeneca, CSL Behring, GSK and Grifols. **Cristina Aljama** declared to have received speaker fees from FAES farma, Chiesi, AstraZeneca, Zambon, GSK and CSL Behring. **Marc Miravitlles** declared to have received speaker fees from AstraZeneca, Boehringer Ingelheim, Kamada, Chiesi, Cipla, Menarini, Rovi, Bial, Sandoz, Takeda, Zambon, CSL Behring, Specialty Therapeutics, Grifols, Sanofi-Regeneron and Novartis, consulting fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Bial, Gebro Pharma, Kamada, CSL Behring, Laboratorios Esteve, Ferrer, Mereo Biopharma, Verona Pharma, TEVA, Spin Therapeutics, pH

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Artificial intelligence involvement

The authors declare that this manuscript was not produced, in whole or in part, with the assistance of any artificial intelligence software or tool.

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Sí

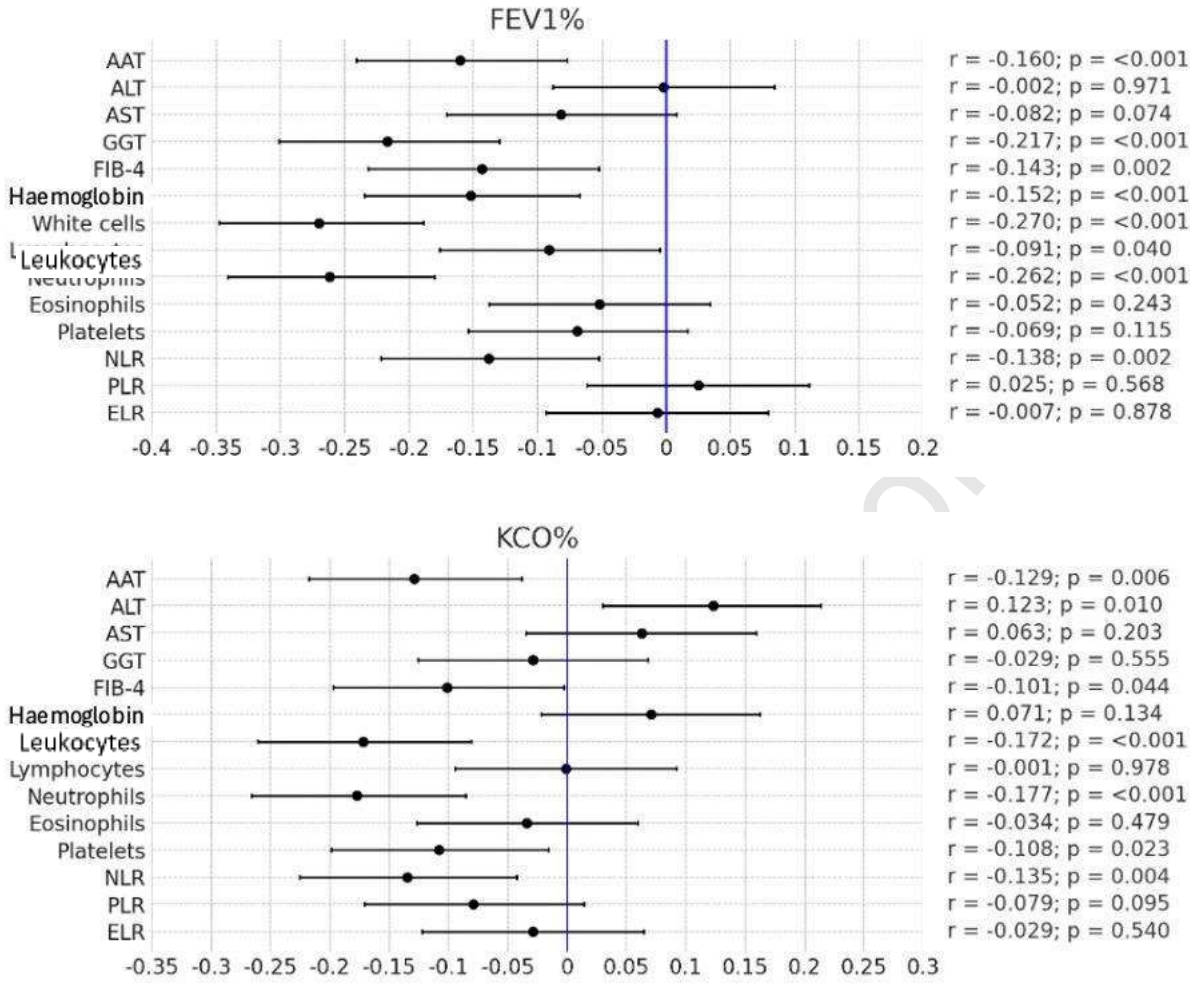
TABLE 1. Comparison of blood biomarker levels in subjects with and without emphysema

Variables	PI*SZ	Emphysema		p value
		No (N = 451)	Yes (N = 118)	
Age, years	51.9 (16.3)	48.9 (16.2)	63.0 (10.8)	< 0.001
Male sex	291 (51.1)	207 (45.9)	84 (71.2)	< 0.001
Smoking status				
Current smoker	70 (12.3)	48 (10.7)	22 (18.7)	< 0.001
Former smoker	233 (41)	148 (33)	85 (72)	
Never smoker	266 (46.7)	253 (56.3)	11 (9.3)	
Pack-years	27.6 (24.1)	19.4 (20.3)	41.0 (23.8)	< 0.001
BMI, kg/m^2	26.8 (5.3)	26.8 (5.3)	26.8 (5.1)	0.811
FEV1, %	92.2 (25.9)	98.4 (20.6)	68.3 (30.2)	< 0.001
KCO, %	88.9 (22.2)	94.0 (18.2)	69.5 (25.3)	< 0.001
AAT, mg/dL	57.8 (13.1)	57.5 (12.4)	59.2 (15.4)	0.013
ALT, IU/L	30.9 (21.0)	30.4 (20.1)	32.6 (24.4)	0.211
AST, IU/L	27.9 (21.7)	26.9 (19.5)	31.6 (28.7)	0.021
GGT, IU/L	35.4 (39.0)	34.1 (40.2)	40.5 (33.3)	< 0.001
FIB-4, score	1.2 (1.5)	1.1 (1.3)	1.6 (2.0)	< 0.001
Hemoglobin, g/dL	14.4 (1.7)	14.2 (1.7)	14.9 (1.3)	< 0.001
Leukocytes, $10^9/L$	7.1 (2.3)	6.8 (2.1)	8.0 (2.5)	< 0.001
Lymphocytes, $10^9/L$	2.5 (1.4)	2.4 (1.4)	2.7 (1.5)	0.065
Neutrophils, $10^9/L$	4.0 (1.8)	3.8 (1.6)	4.8 (2.1)	< 0.001
Eosinophils, $10^9/L$	0.2 (0.2)	0.2 (0.2)	0.1 (0.1)	0.845

Platelets, 10^9/L	253.9 (71.9)	252.9 (70.2)	257.8 (78.3)	0.790
Neutrophil-to-lymphocyte ratio	1.8 (1.1)	1.8 (1.0)	2.1 (1.3)	0.009
Eosinophil-to-lymphocyte ratio	0.1 (0.1)	0.1 (0.1)	0.0 (0.0)	0.265
Platelet-to-lymphocyte ratio	116.9 (48.2)	118.0 (48.6)	112.3 (46.6)	0.452

Continuous variables express mean (SD), and the categorical ones, number (percentage).
AAT: alpha-1 antitrypsin; ALT: alanine aminotransferase; AST: aspartate aminotransferase; FEV1: forced expiratory volume in one second; FIB-4: fibrosis-4 score; GGT: gamma-glutamyl transferase; KCO: carbon monoxide transfer coefficient.

Figure 1. Correlations between routine serum biomarkers and FEV1% and KCO%



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