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# Characterization of the Mmalton carrier's cohort within the EARCO (European Alpha- 1 Antitrypsin Research Collaboration) registry

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## Abstract

**Introduction** The PI*Mmalton variant is a rare form of alpha-1-antitrypsin (AAT) deficiency, caused by a mutation in the SERPINA1 gene and associated with reduced AAT levels. Its clinical significance remains uncertain due to the limited number of reported cases.

**Methods** This study characterizes PI*Mmalton carriers within the EARCO (European Alpha-1 Antitrypsin Research Collaboration) registry and compares them with PI*ZZ individuals. Patients were categorized into moderate PI*Mmalton (combined with PI*S or PI*I) and severe PI*Mmalton (combined with PI*Z, PI*Mmalton, PI*MProcida, or PI*MHerleen). Demographic data, lung function, respiratory symptoms, disease prevalence, and augmentation therapy use were analyzed.

**Results** Among 2074 individuals, 59 (2.8%) carried a PI*Mmalton allele. Severe PI*Mmalton patients exhibited lung function impairment comparable to PI*ZZ individuals, with a significantly lower $FEV_1$/FVC ratio (55.9% vs. 57.6%) and similar AAT levels (~ 25 mg/dL). Moderate PI*Mmalton patients had better lung function and higher AAT levels (median 54 mg/dL). Emphysema was more prevalent in severe PI*Mmalton (54.5%) and PI*ZZ (61.2%) than in moderate PI*Mmalton (34.6%). Augmentation therapy use was highest in severe PI*Mmalton (45.2%). Liver disease prevalence was comparable across groups.

**Conclusion** Severe PI*Mmalton patients exhibit clinical and functional similarities to PI*ZZ individuals, suggesting a comparable disease burden. Moderate PI*Mmalton patients, however, show milder impairment. These findings reinforce the need for genotype-specific management strategies and suggest that PI*Mmalton carriers, particularly those with severe variants, should be considered in future clinical trials.

**Keywords** Alpha-1 antitrypsin, PI*Mmalton, Lung disease, Registries

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## Background

Alpha- 1 antitrypsin protein (AAT) is the main elastase inhibitor in human plasma. It is a very polymorphic protein, with multiple pathogenic and non-pathogenic variants [1]. Its deficiency is a predisposing factor for the development of emphysema and liver disease [2]. However, the risk depends not only on the variant of protein present, but in environmental factors, mainly exposure to smoke [3].

AAT genetic variants are inherited following an autosomal co-dominant pattern. This pattern of inheritance implies multiple possibilities of composite homozygous or heterozygous genotypes, which increase the heterogeneity of clinical presentation, and makes the understanding of this condition more complex. Within the catalogue of AAT variants already described, PI*Z allele is by far the most common deficient variant, followed by PI*S allele [4, 5], while PI*Mmalton ranks as the fourth most common rare variant in Europe [6].

A geographical distribution has been previously described, for these mutations: PI*Z has a decreasing gradient of incidence from Northern Europe to South and it is more prevalent in North America, while PI*S gradient is the opposite [7, 8]. Prevalence in other continents is less known. The PI*Mmalton variant has been reported as the most common deficient mutation in some parts of the Mediterranean area, such as Sardinia and Tunisia [9, 10].

Alpha- 1 antitrypsin deficiency (AATD) is considered a rare condition. In the specific case of PI*Mmalton mutation, its frequency has been estimated as low as $10^{-4}$ in European descendent [11], counting for < 5% of the cases identified in Europe [12]. This mutation [deletion of the phenylalanine residue at position 52 (c.227 229 delTCT; p.Phe52 del)] results in abnormal AAT protein that readily aggregates in vitro and forms stable inclusion bodies in the liver [13]. The effect of the PI*Mmalton mutation on plasma concentration is due to a decrease in glycoprotein secretion due to the self-aggregation phenomenon [14, 15].

PI*Mmalton protein behaviour on agarose gel isoelectric focusing is very similar to the normal variant PI*M which may led to misdiagnosis, despite the less intense glycoform bands produced. By examining DNA polymorphisms, PI*Mmalton haplotype is identical to the most common M2 haplotype, from which it must be derived [11]. However, this mutation and its tendency to aggregate, forming polymers, make its biological dysfunction more like PI*Z mutation. The PI*Mmalton protein deficiency is associated with low (< 15% of normal) plasma concentrations and liver inclusions [16]. Its decreased anti-elastase effect may trigger emphysema development, especially in the presence of harmful environmental exposures of risk and increase the risk of liver disease due to the accumulation of polymers.

Moreover, understanding the clinical implications of this rare variant is difficult due to the small number of cases reported and the paucity of large enough cohorts with longitudinal follow-up. This issue is common in rare diseases and to address this, international collaboration is essential and has been identified as a successful strategy in rare diseases [17]. In this regard, European Respiratory Society has encouraged the creation of Research Collaborations in the form of registries, such as the European Alpha- 1 antitrypsin Research Collaboration: EARCO [18, 19]. The EARCO Registry is a non-interventional, multicentre, international, prospective, observational cohort study that includes patients with AATD, confirmed by biochemical and genetic data. EARCO has a global vision to increase the early diagnosis of AATD, understand better the natural history of the disease and ensure optimal access to effective care, emphasizing ambitions that serve collective needs of the AATD research community and bringing people with AATD to the centre of the research environment in a real-world context [20].

The main objective of this study is the characterization of the cohort of patients included in EARCO who are carriers of a PI*Mmalton allele and the comparison with the cohort of individuals homozygous (PI*ZZ). The PI*ZZ patients were chosen as a comparison cohort since it is the best-characterized genotype [4].

## Methods

### Study design

The EARCO protocol has been already described [16]. Data are entered into a secure database through an electronic case report form hosted by the EARCO website (www.earco.org), registered in clinicaltrials.gov (ID: NCT04180319). The research ethics committee of the Vall d'Hebron University Hospital in Barcelona, Spain granted central ethical approval for the study protocol (PR(AG)480/2018), which was then accepted by all participating centers. The Declaration of Helsinki was followed in the conduct of the study, and all subjects gave written informed permission. Recently, the EARCO study's baseline data results were released [21, 22].

The study's inclusion criteria mirrored those of the EARCO protocol: individuals diagnosed with severe AATD, characterized by an AAT serum level < 11 μM (50 $mg \cdot dL^{-1}$) and/or a proteinase inhibitor genotype of PI*ZZ, PI*SZ, or compound heterozygotes or homozygotes of additional uncommon deficient variations [20]. Consequently, patients with the PI*M/Mmalton genotype are excluded from the present investigation [20]. The sample analysed included carriers of at least one

PI*Mmalton allele enrolled in EARCO from 5 February 2020 to 21 September 2023, and individuals homozygous ZZ (PI*ZZ).

The patients with a PI*Mmalton variant were subdivided according to the allele they were combined: those with PI*Mmalton combined with allele PI*S or allele PI*I formed the PI*Mmalton moderate cohort, while the remaining patients, combined with another PI*Mmalton allele, allele PI*Z, allele PI*MProcida, or allele PI*MHerleen, formed the PI*Mmalton severe cohort. Both of PI*Mmalton allele groups were compared between each other and with PI*ZZ cohort.

We evaluated the demographic data, proteinase inhibitor genotype, comorbidities, pulmonary function, respiratory symptoms, occurrence of respiratory diseases, including emphysema, COPD, chronic bronchitis, asthma, and/or bronchiectasis and pulmonary exacerbations. These conditions were diagnosed through a comprehensive evaluation of the patients by the center that is responsible for their inclusion in the database, including clinical criteria, spirometry, and CT scans. Respiratory symptom burden and functional status were assessed using the modified Medical Research Council (mMRC) scale, the Chronic Obstructive Pulmonary Disease (COPD) Assessment Test (CAT) questionnaire [23], alongside documentation of the treatment administered. The severity of COPD was assessed using the body mass index, obstruction, dyspnoea, and exacerbations (BODEx) index [24].

### Statistical analysis

Qualitative variables were described with absolute frequencies and percentages. Quantitative variables were described as mean (± standard Deviation) or median and interquartile range (IQR). The Kolmogorov–Smirnov test and graphical criteria were used to assess the normality of the distributions. The sociodemographic and clinical characteristics were compared between cohorts (moderate PI*Mmalton, severe PI*Mmalton and PI*ZZ). In the case of quantitative variables, one-way ANOVA (analysis

**Table 1** Socio-demographic, anthropometric characteristics and inhaled and occupational exposures of PI*Mmalton (moderate and severe) and PI*ZZ patients

| | **Moderate PI*Mmalton *N* = 26** | | **Severe PI*Mmalton *N* = 33** | | **PI*ZZ *N* = 827** | | ***P*-value[1]** |
|---|---|---|---|---|---|---|---|
| Sex | | | | | | | |
| Male, n (%) | 14 | (53.8%) | 24 | (72.7%) | 432 | (52.3%) | 0.070 |
| Female, n (%) | 12 | (46.2%) | 9 | (27.3%) | 394 | (47.7%) | |
| Age, Mean ± SD | 50.8 | ± 19.1 | 53.0 | ± 15.5 | 55.2 | ± 14.2 | 0.221 |
| BMI, Mean ± SD | 24.7 | ± 4.5 | 25.5 | ± 4.4 | 26.0 | ± 5.1 | 0.379 |
| Smoking history | | | | | | | 0.128[2] |
| Smokers, n (%) | 2 | (7.7%) | 2 | (6.3%) | 23 | (2.8%) | |
| Former smokers, n(%) | 14 | (53.8%) | 23 | (71.9%) | 468 | (57.5%) | |
| Never smokers, n (%) | 10 | (38.5%) | 7 | (21.9%) | 323 | (39.7%) | |
| Pack-year, Median (IQR) | 21[a] | (18–41) | 16[ab] | (14–30) | 15[b] | (8–25) | **0.020**[3] |
| Inhaled exposure | | | | | | | |
| Biomass | 0 | (0.0%) | 2 | (6.1%) | 19 | (2.3%) | n.a |
| Cocaine | 0 | (0.0%) | 1 | (3.0%) | 8 | (1.0%) | n.a |
| E-cigarette | 0 | (0.0%) | 0 | (0.0%) | 5 | (0.6%) | n.a |
| Marijuana | 0 | (0.0%) | 0 | (0.0%) | 19 | (2.3%) | n.a |
| Others | 1 | (3.8%) | 2 | (6.1%) | 19 | (2.3%) | n.a |
| Occupational exposures | | | | | | | |
| Gases | 1 | (3.8%) | 1 | (3.0%) | 25 | (3.0%) | n.a |
| Fumes | 1 | (3.8%) | 1 | (3.0%) | 50 | (6.0%) | n.a |
| Dust | 4 | (15.4%) | 6 | (18.2%) | 64 | (7.7%) | n.a |
| Asbestos | 0 | (0.0%) | 1 | (3.0%) | 11 | (1.3%) | n.a |
| Other | 6 | (23.1%) | 1 | (3.0%) | 37 | (4.5%) | n.a |

*Abbreviations*: *n.a* not applicable, *SD* standard deviation, *IQR* interquartile range, *BMI* body mass index

[1] *P*-value for the global comparison between moderate PI*Mmalton, severe PI*Mmalton and PI*ZZ patients

[2] To meet the test's assumptions, smoking history was dichotomized as Smokers versus Former or Never smokers

[3] Different lowercase letters are used to indicate significant differences ($P < 0.05$) between two groups of patients; if two groups have the same lowercase letter, the differences are not significant

of variance) or Kruskal–Wallis test was performed as appropriate. Proportions were compared using the Pearson Chi-squared test. Pairwise comparisons were used when significant differences were found. All statistical tests, were two-sided and a *p*-value lower than 0.05 was considered statistically significant. All data analysis was conducted using SPSS (Version 28).

## Results

The EARCO registry included until September 2023 a total of 2074 cases. From them 59 (2.8%) had at least one PI*Mmalton allele and 827 (39.8%) have a PI*ZZ genotype (ZZ cohort).

The genotype distribution was as follows: PI*Mmalton/Z in 24 patients (41%), PI*Mmalton/Mmalton in 6 patients (10%), PI*Mmalton/MHerleen in 2 patients (3%), and PI*Mmalton/MProcida in 1 patient (2%)—these formed the PI*Mmalton severe cohort (n = 33).

The PI*Mmalton moderate cohort (n = 26) included PI*Mmalton/S in 25 patients (42%) and PI*Mmalton/I in 1 patient (2%).

### Socio-demographic, anthropometric characteristics, and exposures

There is a higher proportion of males in the severe PI*Mmalton group (72.7%) compared to moderate PI*Mmalton (53.8%) and PI*ZZ (52.3%). The mean age of participants was similar across groups, with PI*Mmalton patients averaging 52 years and PI*ZZ patients 55.2 years. Body mass index (BMI) values were also comparable, with no significant differences among groups.

Regarding smoking history, severe PI*Mmalton patients had the highest percentage of former smokers (71.9%), while PI*ZZ patients had a higher proportion of never smokers (39.7%). Median pack-years of smoking were significantly different, with moderate PI*Mmalton showing the highest values (21 pack-years), followed by severe PI*Mmalton (16 pack-years) and PI*ZZ (15 pack-years). Occupational exposures, particularly dust and fumes, were more frequently reported among PI*Mmalton patients than PI*ZZ. Other inhaled exposures, such as biomass, marijuana, and cocaine, were uncommon across all groups (Table 1).

**Table 2** Distribution of Pi*Mmalton (moderate and severe) and Pi*ZZ patients included in EARCO by Country

| | **Patients in EARCO *N* = 2073** | **Moderate PI*Mmalton *N* = 26** | | | **Severe PI*Mmalton *N* = 33** | | | **PI*ZZ *N* = 827** | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n | n | (% by Total) | (% by Country) | n | (% by Total) | (% by Country) | n | (% by Total) | (% by Country) |
| Argentina | 31 | - | - | - | - | - | - | 22 | (2.7%) | (71.0%) |
| Austria | 8 | - | - | - | - | - | - | 7 | (0.8%) | (87.5%) |
| Belgium | 54 | - | - | - | - | - | - | 14 | (1.7%) | (25.9%) |
| Canada | 65 | - | - | - | - | - | - | 45 | (5.4%) | (69.2%) |
| Colombia | 3 | - | - | - | - | - | - | 1 | (0.1%) | (33.3%) |
| Croatia | 23 | - | - | - | - | - | - | 3 | (0.4%) | (13.0%) |
| Czech republic | 58 | - | - | - | - | - | - | 54 | (6.5%) | (93.1%) |
| Denmark | 48 | - | - | - | - | - | - | 48 | (5.8%) | (100.0%) |
| Estonia | 8 | - | - | - | - | - | - | 8 | (1.0%) | (100.0%) |
| France | 23 | - | - | - | - | - | - | 7 | (0.8%) | (30.4%) |
| Germany | 68 | - | - | - | - | - | - | 42 | (5.1%) | (61.8%) |
| Ireland | 9 | - | - | - | - | - | - | 2 | (0.2%) | (22.2%) |
| Italy | 90 | 2 | (7.7%) | (2.2%) | 6 | (18.2%) | (6.6%) | 36 | (4.4%) | (40.0%) |
| Netherlands | 37 | - | - | - | 1 | (3.0%) | (2.7%) | 22 | (2.7%) | (59.5%) |
| Poland | 5 | - | - | - | - | - | - | 4 | (0.5%) | (80.0%) |
| Portugal | 191 | 5 | (19.2%) | (2.6%) | 6 | (18.2%) | (3.1%) | 55 | (6.7%) | (28.8%) |
| Romania | 3 | - | - | - | - | - | - | 3 | (0.4%) | (100.0%) |
| Serbia and Montenegro | 2 | - | - | - | - | - | - | 1 | (0.1%) | (50.0%) |
| Spain | 803 | 16 | (61.5%) | (2.0%) | 14 | (42.4%) | (1.7%) | 216 | (26.1%) | (26.9%) |
| Sweden | 177 | - | - | - | - | - | - | 2 | (0.2%) | (1.1%) |
| Switzerland | 68 | 3 | (11.5%) | (4.4%) | 1 | (3.0%) | (1.5%) | 24 | (2.9%) | (35.3%) |
| Turkey | 5 | - | - | - | 1 | (3.0%) | (20.0%) | 4 | (0.5%) | (80.0%) |
| United Kingdom | 294 | - | - | - | 3 | (9.1%) | (1.0%) | 207 | (25.0%) | (70.4%) |

**Table 3** Lung disease characteristics of PI*Mmalton (moderate and severe) and PI*ZZ patients

| | **Moderate PI*Mmalton *N* = 26** | | **Severe PI*Mmalton *N* = 33** | | **PI*ZZ *N* = 827** | | ***P*-value**[1] |
|---|---|---|---|---|---|---|---|
| Reasons that led to the diagnosis | | | | | | | |
| Respiratory symptoms | 16 | (61.5%) | 24 | (72.7%) | 540 | (65.3%) | 0.620 |
| Liver symptoms | 3 | (11.5%) | 1 | (3.0%) | 68 | (8.2%) | n.a |
| Family screening | 4 | (15.4%) | 5 | (15.2%) | 138 | (16.7%) | 0.960 |
| Other | 3 | (11.5%) | 4 | (12.1%) | 54 | (6.5%) | n.a |
| Symptoms at presentation | | | | | | | |
| Dyspnea, n (%) | 14 | (53.8%) | 21 | (63.6%) | 527 | (63.7%) | 0.588 |
| Cough, n (%) | 9 | (34.6%) | 8 | (24.2%) | 269 | (32.5%) | 0.588 |
| Sputum, n (%) | 3 | (11.5%) | 5 | (15.2%) | 184 | (22.2%) | 0.278 |
| Jaundice, n (%) | 1 | (3.8%) | 0 | (0.0%) | 15 | (1.8%) | n.a |
| Abnormal liver function test, n(%) | 3 | (11.5%) | 1 | (3.0%) | 35 | (4.2%) | n.a |
| Other, n (%) | 1 | (3.8%) | 2 | (6.1%) | 55 | (6.7%) | n.a |
| Asymptomatic, n (%) | 7 | (26.9%) | 8 | (24.2%) | 122 | (14.8%) | 0.087 |
| Lung disease, n (%) | 13 | (50.0%) [a] | 27 | (81.8%)[b] | 646 | (83.6%) [b] | **< 0.001**[2] |
| COPD[3], n (%) | 8 | (30.8%) | 20 | (60.6)% | 429 | (51.9%) | 0.060 |
| Emphysema[3], n (%) | 9 | (34.6%) [a] | 18 | (54.5%)[a,b] | 506 | (61.2%) [b] | **0.019**[2] |
| Chronic Bronchitis[3], n (%) | 2 | (7.7%) | 1 | (3.0%) | 50 | (6.0%) | n.a |
| Bronchiectasis[3], n (%) | 2 | (7.7%) | 6 | (18.2%) | 183 | (22.1%) | 0.188 |
| Asthma[3], n (%) | 2 | (7.7%) | 2 | (6.1%) | 120 | (14.5%) | n.a |
| Lung cancer[3], n(%) | 0 | (0.0%) | 0 | (0.0%) | 1 | (0.1%) | n.a |
| Lung disease type (Other)[3], n(%) | 1 | (3.8%) | 0 | (0.0%) | 22 | (2.7%) | n.a |
| Exacerbations/Respiratory Infections | | | | | | | |
| Ambulatory exacerbations (Last 12 months) ≥ 2, n(%) | 3 | (11.5%) | 1 | (3.1%) | 95 | (11.6%) | n.a |
| Admissions in hospital related to COPD (Last 12 months) ≥ 1, n(%) | 0 | (0.0%) | 2 | (6.5%) | 66 | (8.1%) | n.a |
| Had pneumonia, n(%) | 6 | (24.0%) | 11 | (34.4%) | 226 | (31.6%) | 0.679 |
| No. episodes, Median (IQR) | 1 | (1–3) | 1 | (1–1) | 1 | (1–2) | 0.628 |
| Functional Respiratory Tests | | | | | | | |
| FEV1 (%) (Prebronchodilator) Mean ± SD | 85.3 | ± 28.5 | 62.2 | ± 24.6 | 71.5 | ± 30.5 | 0.058 |
| FVC (%) (Prebronchodilator), Mean ± SD | 100.5 | ± 21.6 | 83.1 | ± 23.5 | 94.5 | ± 23.3 | 0.051 |
| FEV1/FVC (%) (Prebronchodilator), Mean ± SD | 69.0[a] | ± 18.0 | 55.9[b] | ± 17.8 | 57.6[b] | ± 19.4 | **0.018**[2] |
| DLCO (%), Mean ± SD | 77.0[a] | ± 30.9 | 67.2[a,b] | ± 20.9 | 63.3[b] | ± 24.9 | **0.031**[2] |
| KCO (%), Mean ± SD | 77.9 | ± 34.4 | 68.9 | ± 26.2 | 67.7 | ± 22.9 | 0.140 |
| Comorbidities | | | | | | | |
| Charlson Comorbidity Index, Mean ± SD | 3.4 | ± 2.7 | 3.0 | ± 1.8 | 3.2 | ± 2.0 | 0.792 |
| Symptom Scores | | | | | | | |
| BODEX, Mean ± SD | 1.0 | ± 1.3 | 2.0 | ± 1.6 | 2.0 | ± 2.0 | 0.054 |
| CAT, Mean ± SD | 7.2[a] | ± 6.8 | 9.4[a,b] | ± 8.1 | 13.5[b] | ± 9.6 | **< 0.001**[2] |
| If dyspnea(current symptoms): mMRC, Median (IQR) | 2 | 1–2 | 2 | 1–2 | 2 | 1–2 | 0.355 |

*Abbreviations*: *n.a* not applicable, *BODEX* Body mass index, airflow obstruction, dyspnea, exacerbations index, *CAT* COPD Assessment Test, *COPD* Chronic obstructive pulmonary disease, *DLCO* Diffusing capacity of the lungs for carbon monoxide, *FEV1* Forced expiratory volume in 1 s, *FVC* Forced vital capacity, *IQR* Interquartile range, *KCO* Carbon monoxide transfer coefficient, *mMRC* Modified Medical Research Council dyspnea scale, *SD* Standard deviation

[1] *P*-value for the global comparison between moderate PI*Mmalton, severe PI*Mmalton and PI*ZZ patients

[2] Different lowercase letters are used to indicate significant differences ($P < 0.05$) between two groups of patients; if two groups have the same lowercase letter, the differences are not significant

[3] marked yes in the total sample

### Geographic distribution of patients

The geographic distribution of patients revealed a predominance of PI*Mmalton cases in Spain, Portugal, and Switzerland, whereas PI*ZZ patients were more evenly distributed across European countries. The highest frequency of PI*ZZ patients was found in Spain (26.1%), the United Kingdom (25.0%), and Germany (5.1%), with smaller populations in countries such as Denmark, Estonia, and Romania, where PI*ZZ patients accounted for nearly all registered cases (Table 2).

### Lung disease characteristics

Most patients in all groups were diagnosed due to respiratory symptoms rather than through family screening or liver abnormalities. The presence of dyspnea was reported in 53.8% of moderate PI*Mmalton, 63.6% of severe PI*Mmalton, and 63.7% of PI*ZZ patients, while chronic cough and sputum production were observed less frequently in PI*Mmalton patients than in PI*ZZ. The prevalence of lung disease was significantly higher in severe PI*Mmalton (81.8%) and PI*ZZ (83.6%) compared to moderate PI*Mmalton (50.0%). COPD was more frequent in severe PI*Mmalton (60.6%) and PI*ZZ (51.9%), while emphysema prevalence was highest in PI*ZZ (61.2%), followed by severe PI*Mmalton (54.5%) and moderate PI*Mmalton (34.6%). Other lung conditions, including bronchiectasis and chronic bronchitis, were observed at lower frequencies in all groups (Table 3).

### Functional respiratory tests

Lung function tests showed a progressive decline in $FEV_1$, FVC, and DLCO from moderate to severe PI*Mmalton and PI*ZZ patients. Mean Prebronchodilator $FEV_1$(%) was lowest in severe PI*Mmalton (62.2%), followed by PI*ZZ (71.5%) and moderate PI*Mmalton (85.3%). $FEV_1$/FVC ratio (%) was significantly reduced in severe PI*Mmalton (55.9%) and PI*ZZ (57.6%) compared to moderate PI*Mmalton (69.0%). Similarly, DLCO values were lower in severe PI*Mmalton (67.2%) and PI*ZZ (63.3%) compared to moderate PI*Mmalton (77.0%). These findings show a lung function impairment in severe PI*Mmalton comparable with PI*ZZ; however moderate PI*Mmalton cohort exhibited a milder impact (Table 3).

### Alpha- 1 antitrypsin (AAT) characteristics

AAT levels were relatively low across all groups, with median values of 54 mg/dL in moderate PI*Mmalton, 25 mg/dL in severe PI*Mmalton, and 24 mg/dL in PI*ZZ. The use of augmentation therapy (AT) was significantly higher in severe PI*Mmalton (45.2%) and PI*ZZ (35.2%) compared to moderate PI*Mmalton (15.4%)—Table 4.

Among those receiving AT, severe PI*Mmalton patients and PI*ZZ patients started therapy at a younger age (53.7 and 55.3 years-old, respectively) than moderate PI*Mmalton (65.3 years-old).

### Liver disease characteristics

Liver disease was generally uncommon in all groups. Transient elastography was performed in 34.6% of moderate PI*Mmalton, 41.9% of severe PI*Mmalton, and 45.1% of PI*ZZ patients, with comparable liver stiffness measurements across groups. Liver enzyme levels (AST, ALT, GGT, ALP) did not show significant differences (Table 1 of Appendix).

## Discussion

The EARCO registry enables standardised data collection of individuals with alpha- 1 antitrypsin deficiency. This approach facilitates accumulating information about rare variants, which constitute between 5–9% according to reports from national registries [6, 17], in a way that make comparison among patients from different countries feasible and accurate.

**Table 4** AAT characteristics of PI*Mmalton (moderate and severe) and PI*ZZ patients

| | **Moderate PI*Mmalton *N* = 26** | | **Severe PI*Mmalton *N* = 33** | | **PI*ZZ *N* = 827** | | ***P*-value[1]** |
|---|---|---|---|---|---|---|---|
| Age of onset of symptoms, mean ± SD | 43.9 | ± 19.7 | 47.6 | ± 14.8 | 43.3 | ± 15.6 | 0.406 |
| Age of diagnosis (AATD), mean ± SD | 46.3 | ± 18.7 | 48.6 | ± 15.7 | 45.9 | ± 16.9 | 0.662 |
| Alpha- 1 antitrypsin levels (mg/dl), Median (IQR) | 54 | (48–2277) | 25 | (20–29) | 24 | (18–97) | 0.191 |
| Patients under Augmentation Therapy, n (%) | 4* | (15.4%) | 14[β] | (45.2%) | 288 | (35.2%) | 0.054 |
| Age at the beginning of Augmentation Therapy, mean ± SD | 65.3 | ± 11.5 | 53.7 | ± 13.8 | 55.3 | ± 11.1 | 0.185 |
| Number of years after diagnosis, median (IQR) | 3 | (1–8) | 1 | (0–2) | 2 | (1–8) | 0.152 |

*Abbreviations*: *AATD* Alpha- 1 antitrypsin deficiency, *IQR* Interquartile range, *SD* Standard deviation

[*] 4 Pi*Mmalton/S patients

[β] 10 Pi*Mmalton/Z patients; 3 Pi*Mmalton/Mmalton patients and 1 Pi*Mmalton/MHerleen patient

[1] *P*-value for the global comparison between moderate PI*Mmalton, severe PI*Mmalton and PI*ZZ patients

**Table 5** Previous findings in case reports in alpha 1 anti trypsin deficiency associated with Mmalton

| Number of patients (n) | Gender (n) | Age (min–max) | AAT levels (mg/dl) | Genotypes | n | Lung disease | n | Liver disease | n | Paper |
|---|---|---|---|---|---|---|---|---|---|---|
| 16 | Male (7) Female (9) | 5–86 | 16–19 | PI*Mmalton/Mmalton | 2 | Severe Obstruction | .1 | Cirrhosis | *2* | *Pulmonology* 2018; 24: 48–49 [28] |
| | | | 19 | PI*Z/Mmalton | 1 | | | | | |
| | | | 25.9 | PI*S/Mmalton | 1 | Moderate obstruction | 2 | | | |
| | | | 66—94 | PI*M/Mmalton | 12 | Mild obstruction | 2 | | | |
| 7 | Male (5) Female (2) 2 | 17–73 | 30 | PI*Z/Mmalton | 1 | Severe Obstruction | 1 | NA | | Thorax 41(7):568–570 [29] |
| | | | 80–130 | PI*M/Mmalton | 6 | | | | | |
| 13 | Male (8) Female (5) | NA | NA | PI*Mmalton/Mmalton | 3 | Emphysema | 2 | Cirrhosis/HCC | 1 | Gastroenterology 93(1):181–187 [30] |
| | | | | PI*M/Mmalton | 10 | Emphysema | 3 | | | |
| 4 | Male (1) Female (3) | 37–80 | 34 | PI*Mmalton/Mmalton | 1 | | | Cirrhosis | 1 | Orphanet J. Rare Dis. 10:130 [31] |
| | | | 22–33 | PI*Z/Mmalton | 2 | Emphysema/COPD | 1/1 | | | |
| | | | 69 | PI*M/Mmalton | 1 | | | | | |
| 3 | Male (3) | 43–87 | 64–69 | PI*M/Mmalton | 3 | Asthma | 1 | NA | | Respirology Case Reports, 8(3), e00528 [12] |
| | | | | | | Emphysema/Pneumothorax | 1 | | | |

*Abbreviations*: *COPD* Chronic Obstructive Pulmonary Disease, *HCC* Hepatocellular Carcinoma, *NA* Non Applicable

We described here the biggest cohort of carriers of PI*Mmalton mutation so far. In EARCO, PI*Mmalton allele was present in 2.8% of subjects. As previously described, most of these patients live in Mediterranean countries [9, 10], or in island populated by individuals from Mediterranean background (Canary Islands) [25]. Our study corroborates that geographical distribution of this variant, with most of the individuals identified from Spain, Portugal and Italy, where the prevalence of PI*Mmalton allele ranges between 5–10% of total cases included in EARCO from these countries. This represents the highest prevalence reported, likely influenced by EARCO being the first international AAT registry. Information regarding background of those PI*Mmalton carriers diagnosed in other countries was not available.

Our clinical findings are like previously reported in terms of lung and liver disease (Table 5). Despite both cohorts of PI*Mmalton and PI*ZZ are comparable in some variables, the other combining allele of the PI*Mmalton cohort imply different grade of disease severity, as previously observed with the Z and S alleles [26, 27]. To overcome this problem the PI*Mmalton patients were divided in two subgroups: those who carried the PI*Mmalton allele in combination with another allele associated with severe deficiency (PI*Mmalton severe), and those who carried the PI*Mmalton allele in combination with an allele not associated with such a severe alpha- 1 antitrypsin deficiency (PI*Mmalton moderate).

We found that patients with severe PI*Mmalton are clinically and functionally closer to PI*ZZ patients than moderate PI*Mmalton patients. This similarity is evident in both pulmonary function and AAT levels. Severe PI*Mmalton patients had a significantly lower FEV1/FVC ratio compared to moderate PI*Mmalton patients, with values similar to those of the PI*ZZ group, indicating greater functional impairment in severe cases (Table 3). Additionally, AAT levels in severe PI*Mmalton patients were comparable to those found in PI*ZZ individuals, reinforcing the pathogenic similarity between these groups. These findings highlight the importance of distinguishing between subgroups within the PI*Mmalton mutation, as the severity of respiratory disease may vary depending on the conjugated allele.

Regarding liver disease, no statistically significant differences were found in liver function tests or liver elastography between PI*Mmalton and PI* ZZ patients, suggesting a similar risk of hepatic involvement [13]. This finding highlights the need for continuous clinical monitoring of these patients and suggests that liver screening strategies applied to PI*ZZ individuals may also be relevant for PI*Mmalton patients.

This study focused on the characterization of individuals carrying the Pi*Mmalton allele, classified into moderate and severe cases, and their comparison with Pi*ZZ patients. Severe Pi*Mmalton patients were compared with Pi*ZZ individuals, as the latter is the most well-characterized genotype. However, future studies could also explore comparisons between moderate Pi*Mmalton cases and genotypes carrying only one Z allele (Pi*SZ or Pi*IZ).

Lung disease features were thoroughly described, but only baseline data were analyzed. Longitudinal data from annual follow-ups, as established in the EARCO protocol, will be essential to address the remaining questions and represent the next step toward a better understanding of the implications and prognosis of this rare variant. Additionally, future research should investigate potential associations with sociodemographic and anthropometric characteristics, as well as inhaled and occupational exposures—including smoking history—which were not explored in the present study.

PI*Mmalton mutation produces similar conformational changes in the tri-dimensional structure to that of PI*Z mutation, which impact on its antielastase inhibiting capacity and cause it to polymerize. Therefore, similar clinical consequences can be expected. This conclusion may provide a rationale for opening clinical trials to patients with PI*Mmalton mutations, that in the past were restricted to PI*Z carriers.

This study is an example of how international collaboration in rare respiratory diseases can bring light to research and expedite our learning about the natural history of infrequent mutations and sub-cohorts of patients carrying them.

**Abbreviations**

| | |
|---|---|
| AAT | Alpha-1 Antitrypsin |
| AATD | Alpha-1 Antitrypsin Deficiency |
| ALP | Alkaline Phosphatase |
| ALT | Alanine Aminotransferase |
| AST | Aspartate Aminotransferase |
| AT | Augmentation Therapy |
| BMI | Body Mass Index |
| BODEX | Body mass index, airflow obstruction, dyspnea, exacerbations index |
| CAP | Controlled Attenuation Parameter |
| CAT | COPD Assessment Test |
| COPD | Chronic Obstructive Pulmonary Disease |
| DLCO | Diffusing Capacity of the Lungs for Carbon Monoxide |
| EARCO | European Alpha-1 Antitrypsin Research Collaboration |
| ERS | European Respiratory Society |
| $FEV_1$ | Forced Expiratory Volume in 1 Second |
| FVC | Forced Vital Capacity |
| GGT | Gamma-Glutamyl Transferase |
| HCC | Hepatocellular Carcinoma |
| IQR | Interquartile Range |
| KCO | Carbon Monoxide Transfer Coefficient |
| mMRC | Modified Medical Research Council Dyspnea Scale |
| NCT | National Clinical Trial |
| PI | Proteinase Inhibitor |
| SD | Standard Deviation |
| SPSS | Statistical Package for the Social Sciences |

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12890-025-03651-8.

Supplementary Material 1.

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**Authors' contributions**
BDF, BL, MS, MFC and MM conceptualization, methodology and investigation; BDF and BL writing of the manuscript; BL, MS and MM review and editing. MFC performed the statistical analysis. All authors participated in the design and acquisition of data. BDF, BL, MS, MFC, MM, AMT, JMHP, MTD, HT, CRG, JUJ, AC, JLLC, KC, CFC and JGread, performed a critical revision and approved the final manuscript and agree to be accountable for all aspects of the work, they also have read and agreed to the published version of the manuscript.

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**Data availability**
The data that support the findings of this study are available from EARCO Registry but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of EARCO Registry.

## Declarations

**Ethics approval and consent to participate**
The study protocol received central ethics approval by the research ethics committee of the Vall d'Hebron University Hospital of Barcelona, Spain (PR(AG)480/2018) and was subsequently approved by all participating centres. All participants provided written informed consent.

**Consent for publication**
Not applicable.

**Competing interests**
Beatriz D Ferraz has received speaker fees and support for attending meetings from CSL Behring. Maria Sucena has received consulting fees from Bial, GlaxoSmithKline, CSL Behring and Grifols, speaker fees from AstraZeneca, Bial, CSL Behring, Grifols, GlaxoSmithKline and Novartis, support for attending meetings from Bial, CSL Behring, Grifols and Medinfar, honoraria for participation on advisory board from Bial and CSL Behring.Alice M Turner has received either grants or speaker fees from AstraZeneca, GlaxoSmithKline, Boehringer Ingelheim, CSL Behring, Takeda, Vertex, Alpha 1 Foundation and Grifols. José María Hernández- Pérez has received speaker fees from Bial, CSL Behring and GlaxoSmithKline, and support for attending meetings from Grifols and CSL Behring. María Torres-Durán has received either grants or speaker fees from Grifols, IISCIII (Instituto de Investigación Sanitaria Carlos III), IISGS (Instituo de Investigación Sanitaria Galicia Sur), CSL Behring and GlaxoSmithKline, and support for attending meeting from FAES, Bial and Chiesi. Hanan Tanash has received speaker fees from AstraZeneca, GlaxoSmithKline, Boehringer Ingelheim, Chiesi and Grifols. Carlota Rodríguez-García has received speaker fees from GlaxoSmithKline, Bial, AstraZeneca and CSL Behring, and support for attending meetings from Chiesi and Grifols.Angelo Corsico has received consulting fees from GlaxoSmithKline, Grifols, CSL Behring, Zambon and Bruschettini and support for attending meetings from AstraZeneca and Chiesi. José Luis López-Campos has received honoraria during the last 3 years for lecturing, scientific advice, participation in clinical studies or writing for publications for (alphabetical order): AstraZeneca, Bial, Boehringer Ingelheim, Chiesi, CSL Behring, Faes, Gebro Pharma, GlaxoSmithKline, Grifols, Menarini and Zambon.Kenneth Chapman has received grant or contracts from BMS, Bellus, AstraZeneca, GlaxoSmithKline, Sanofi, Regeneron, Takeda and Novartis, consulting fees from AstraZeneca, GSK, Inhibrix, Mereo, Regeneron, Sanofi and Takeda; speaking fees from Valeo, Sanofi, Novartis, GSK and Takeda. Christian F Clarenbach has received consulting fees from AstraZeneca, Boehringer Ingelheim, CSL Behring, Daiichi Synkyo, GlaxoSmithKline, Novartis, Sanofi, OM Pharma, MSD, Grifols and Vifor and speaking fees from AstraZeneca, Boehringer Ingelheim, CSL Behring, Daiichi Synkyo, GlaxoSmithKline, Novartis, Sanofi, OM Pharma, MSD and Grifols, Vifor.Joana Gomes has received speaker fees from AstraZeneca, GlaxoSmithKline, CSL Behring and Tecnimede and support for attending meetings from Tecnimede. Marc Miravitlles has received grants or contracts from Grifols speaker fees from AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, Bial, GlaxoSmithKline, Menarini, Kamada, Takeda, Zambon, CSL Behring, Specialty Therapeutics, Janssen, Grifols, Zambon, Tabuk Pharmaceuticals, Glenmark Pharmaceuticals, Sanofi/Regeneron and Novartis, support for attending meetings from Boehringer Ingelheim, Menarini, Chiesi, Bial, CSL Behring and Grifols and consulting fees AstraZeneca, Atriva Therapeutics, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, CSL Behring, Inhibrx, Ferrer, Menarini, Mereo Biopharma, Spin Therapeutics, Specialty Therapeutics, BridgeBio, AstraZeneca, Atriva Therapeutics, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, CSL Behring, Inhibrx, Ferrer, Menarini, Mereo Biopharma, Spin Therapeutics, Specialty Therapeutics, BridgeBio, Palobiofarma SL, Takeda, Novartis, Beam therapeutics, Novo Nordisk, Sanofi/Regeneron, Zambon, Zentiva and Grifols. The remaining authors report no competing interests.

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