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Clinical and functional characteristics of individuals with alpha-1 antitrypsin deficiency: EARCO international registry

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Abstract

Background: Alpha-1 antitrypsin deficiency (AATD) is a rare disease that is associated with an increased risk of pulmonary emphysema. The European AATD Research Collaboration (EARCO) international registry was founded with the objective of characterising the individuals with AATD and investigating their natural history.

Methods: The EARCO registry is an international, observational and prospective study of individuals with AATD, defined as AAT serum levels < 11 µM and/or proteinase inhibitor genotypes PI*ZZ, PI*SZ and compound heterozygotes or homozygotes of other rare deficient variants. We describe the characteristics of the individuals included from February 2020 to May 2022.

Results: A total of 1044 individuals from 15 countries were analysed. The most frequent genotype was PI*ZZ (60.2%), followed by PI*SZ (29.2%). Among PI*ZZ patients, emphysema was the most frequent lung disease (57.2%) followed by COPD (57.2%) and bronchiectasis (22%). Up to 76.4% had concordant values of FEV1(%) and KCO(%). Those with impairment in FEV1(%) alone had more frequently bronchiectasis and asthma and those with impairment in KCO(%) alone had more frequent emphysema and liver disease. Multivariate analysis showed that advanced age, male sex, exacerbations, increased blood platelets and neutrophils, augmentation and lower AAT serum levels were associated with worse FEV1(%)

Conclusions: EARCO has recruited > 1000 individuals with AATD from 15 countries in its first 2 years. Baseline cross sectional data provide relevant information about the clinical phenotypes of the disease, the patterns of functional impairment and factors associated with poor lung function.

Trial registration www.clinicaltrials.gov (ID: NCT04180319)

Keywords: Registry, Alpha-1 antitrypsin, Phenotypes

Introduction

Alpha-1 antitrypsin deficiency (AATD) is a rare disease that is associated with an increased risk of pulmonary emphysema in adults, and liver disease and panniculitis in adults and children [1]. It has been estimated that approximately 1/3500 and 1/6000 individuals of

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European descent may be affected by severe AATD in its homozygous PI*ZZ form [2] and that around 1/800 patients with chronic obstructive pulmonary disease (COPD) in Europe have severe AATD [3].

Understanding the clinical characteristics and the natural history of a rare disease can be challenging due to the lack of large cohorts. This is even more challenging in the case of AATD because of the important influence of external factors, such as smoking, alcohol consumption or other toxic exposures, on the clinical manifestations in patients with the disease [1, 4]. Traditionally, some European countries have organised national registries that have had different success in collecting prospective follow-up data of patients with AATD [5–7]. Some 20 years ago, the Alpha-1 International Registry (AIR) tried to harmonise the collection of prospective data from different European and non-European countries and included more than 4000 patients with severe AATD [8], but less than 400 had long-term follow-up [9]. The standardised collection of follow-up data of patients with AATD from different countries and under different regimens of treatment in a large international registry was an unmet need identified by patients and researchers [10]. Similarly, the European Commission [11] and the European Respiratory Society (ERS) [12] recommended the setup of large international registries to collect structured, prospective data to better understand the natural history of AATD.

The European Alpha-1 antitrypsin Deficiency Research Collaboration (EARCO) international registry is an initiative of the EARCO Clinical Research Collaboration (CRC) of the ERS, with the objective of characterising AATD of different genotypes and investigating their natural history and the impact of different treatments, including augmentation therapy [13, 14]. Although the EARCO registry was created as a European initiative, it has extended beyond European boundaries to become a global registry. In this article we describe the characteristics of individuals with AATD included in the registry during the first 2 years, compare the characteristics of augmented versus non augmented patients and the factors associated with impaired lung function in individuals with the PI*ZZ genotype.

Method

Structure of EARCO

The EARCO international registry is an observational, multicenter, international study to describe the natural history of subjects with AATD [14]. Participation in the registry is open to every clinician who manages patients with AATD. The observational design implies that patients are treated and followed according to the attending physicians' criteria. The EARCO steering committee

comprises pulmonologists, researchers and patients' representatives, headed by two co-chairs.

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. The EARCO registry protocol has been registered in www.clinicaltrials.gov (ID: NCT04180319), published [14] and is hosted in www.earco.org. The personal data of the patients are kept under strict confidentiality in compliance with the provisions of the General Data Protection Regulation (GDPR) 2016/679 of the European Parliament and of the European Council of April 27th, 2016.

In countries with more than one recruiting center, there is a national coordinator that has access to fully anonymized data of the patients from their country for analysis and evaluation. Despite being an international registry, there is the possibility to build national registries in EARCO with an independent management [15–17].

Objectives of the EARCO registry

The main objectives of the EARCO registry are: (1) to generate longitudinal long-term, high-quality clinical data of individuals with AATD; (2) to understand the natural history and prognosis of AATD; (3) to investigate the effect of AAT augmentation and other therapies on the progression of lung disease, and (4) to learn more about the course of the disease in patients with severe AATD with genotypes other than PI*ZZ.

In the current publication, we describe the characteristics of the individuals included in the EARCO registry from its launch in February 2020 to May 2022.

Population and measurements

The inclusion criteria are: (1) individuals with diagnosed AATD; (2) deficiency is defined as AAT serum levels < 11 μ M (50 mg/dL) and/or proteinase inhibitor genotypes PI*ZZ, PI*SZ and compound heterozygotes or homozygotes of other rare deficient variants. The only exclusion criteria are having at least one normal M allele or lack of patient consent.

The data collected include: demographics, proteinase inhibitor genotype, comorbidities, lung function, respiratory symptoms, ultrasound-based elastography of the liver, exacerbations of respiratory disease, quality of life measured by the COPD Assessment Test (CAT) specific questionnaire [18] and the EuroQoL (EQ) 5D-3L generic questionnaire [19], physical activity measured by the Physical Activity Vital Sign (PAVS) [20] and the mean time walked per day [21], chest computed tomography (as applicable) and treatment.

Data are entered into a secure database through an electronic case report form (eCRF) hosted in the EARCO website (www.earco.org). Data are centrally monitored, and queries are sent for missing or invalid data.

Statistical analysis

Comparison of characteristics between augmented and non-augmented PI*ZZ subjects were conducted by the Student’s t-test or Mann–Whitney U-test (if normality was not assumed) in case of quantitative variables. The Chi-squared test (Fisher test for frequencies < 5) was used for the comparison of categorical variables.

The Fibrosis-4 (FIB-4) score was calculated as age (years) × AST [IU/L]/(platelet count [10⁹/L] × √ALT [IU/L]). A FIB-4 value < 1.45 has a high negative predictive value for ruling out advanced fibrosis and > 3.25 a high specificity and a 65% positive predictive value for ruling in advanced fibrosis.

Impairment in FEV1(%), KCO(%) or both was considered when values were < 80% of reference; the Kappa index was carried out to analyse the concordance between them. Comparison of characteristics of PI*ZZ patients according to their type of impairment in lung function was performed by the Anova test with Bonferroni correction for multiple comparisons. Linear relationships were analysed using Pearson’s correlation coefficient.

Linear regression models for all PI*ZZ, augmented and non-augmented PI*ZZ subjects were performed to identify variables related with FEV1(%). Clinical variables of interest were included as independent factors. The results were described with beta coefficients (B), 95% confidence interval (CI) and p-values. For all the tests, p-values < 0.05 were considered statistically significant. The statistical package R Studio (V2.5.1) was used for the analyses.

Results

Participating centers and characteristics of the population

The EARCO international registry was launched in February 2020 and by May 2022 there were 47 recruiting centers in 15 countries. The database included 1079 individuals, of which 35 (3.2%) were excluded, 20 because there was no information about AAT genotype and 15 had a normal M allele, leaving 1044 subjects for analysis.

The most frequent genotype was PI*ZZ (629, 60.2%), followed by PI*SZ (305, 29.2%), PI*SS (41, 3.9%) and rare variants (69, 6.6%) (Additional file 1: Table S1). Regarding the PI*ZZ participants, their mean age was 55.6 years (standard deviation (SD): 13.2), the age at diagnosis was 44.7 years (SD: 16.7), and 51.5% were male. Only 1.8% were active workers and 72.8% were index cases (i.e. diagnosed due to their presentation with symptoms

consistent with AATD), with lung disease reported by 81.4%. Emphysema was the most frequent lung disease (57.2%) followed by COPD (55.9%) and bronchiectasis (22%), only 5 patients had panniculitis. The majority of PI*ZZ participants were non exacerbators (Fig. 1), and 29.3% had a history of pneumonia. Comorbidities were frequent, with an age corrected Charlson index of 3.3 (SD: 1.9) and 26.1% had a cardiovascular disease (Table 1).

The mean FEV1(%) of PI*ZZ participants was 66.9% (SD: 30.7%) and mean KCO(%) 68% (SD: 23.2%). In general participants showed a moderate impairment in quality of life with a mean CAT score of 13.2 (SD: 9.3) and EQ-5D 0.82 (SD: 0.22) and VAS 59.3 (SD: 28.2). The remaining spirometric, quality of life and activity variables, as well as the results of the blood analysis are summarised in Table 2. Differences in LFTs and quality of life parameters between different genotypes are shown in Fig. 2.

Augmentation therapy: patterns of treatment and comparison of augmented versus non-augmented PI*ZZ individuals

A total of 190 (30%) PI*ZZ patients received augmentation therapy at the time of enrolment in the registry; of them 3 (1.5%) received infusions at home, 18 (9.5%) in Primary Care and the remaining 169 (88.9%) in the hospital. The treatment regimens most used were 120 mg/kg/biweekly in 93 (48.9%), 180 mg/kg/3 weekly in 55 (28.9%), 60 mg/kg/weekly in 35 (18.4%) and 2 patients (1%) at 250 mg/kg/monthly, in 5 cases the investigators indicate that they used a different regimen: 2 used 180 mg/kg/biweekly, and doses of 120 mg/kg/12 days, 140 mg/kg/biweekly and 60 mg/kg/biweekly were used by one patient each.

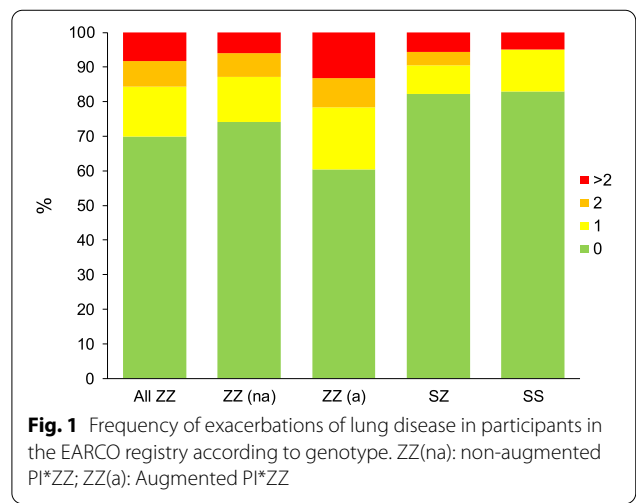


Table 1 Demographic and clinical characteristics of patients included in the EARCO registry and comparison between augmented and non-augmented PI*ZZ patients

| Variables | All ZZ (n = 629) | ZZ non-augmented (n = 436) | ZZ augmented (n = 190) | p value |
|---|------------------|----------------------------|------------------------|---------|
| Age, years | 55.6 (13.2) | 54.4 (14.0) | 58.4 (10.9) | 0.009 |
| Sex, male (%) | 324 (51.5) | 208 (47.7) | 114 (60) | 0.005 |
| BMI (kg/m ²) | 26 (4.8) | 26 (4.8) | 26.1 (4.8) | 0.629 |
| Smokers (%) | 11 (1.8) | 10 (2.3) | 1 (0.5) | 0.187 |
| Ex-smokers (%) | 356 (56.8) | 202 (46.3) | 152 (80.9) | <0.001 |
| Never smokers (%) | 260 (41.5) | 224 (51.4) | 35 (18.6) | <0.001 |
| Tobacco Exposure (Pack-years) | 17.8 (14) | 14.2 (12.2) | 22.7 (14.8) | <0.001 |
| Working status | | | | |
| Active | 338 (53.8) | 263 (60.5) | 72 (37.9) | <0.001 |
| Retired | 235 (37.4) | 135 (31) | 100 (52.6) | <0.001 |
| Unemployed | 30 (4.8) | 15 (3.4) | 15 (7.9) | 0.029 |
| Other | 25 (4.0) | 22 (5.1) | 3 (1.6) | 0.069 |
| Age at diagnosis of AATD | 44.7 (16.7) | 43.1 (17.9) | 48.3 (13.0) | 0.010 |
| Reason for diagnosis | | | | |
| Index case (%) | 457 (72.8) | 302 (69.4) | 152 (80.0) | 0.006 |
| Family screening (%) | 115 (18.3) | 100 (22.9) | 15 (7.9) | <0.001 |
| Clinical characteristics | | | | |
| Chronic respiratory disease (%) | 508 (81.4) | 317 (73.5) | 188 (98.9) | <0.001 |
| COPD (%) | 349 (55.9) | 180 (41.8) | 167 (87.9) | <0.001 |
| Emphysema (%) | 357 (57.2) | 187 (43.4) | 169 (88.9) | <0.001 |
| Bronchiectasis (%) | 137 (22) | 87 (20.2) | 49 (25.8) | 0.120 |
| Asthma (%) | 88 (14.1) | 74 (17.2) | 14 (7.4) | 0.001 |
| Liver disease (%) | 99 (16) | 69 (16.1) | 30 (16) | 0.981 |
| Charlson index (<i>age corrected</i>) | 3.3 (1.9) | 3 (1.9) | 4 (1.8) | <0.001 |
| Cardiovascular disease (%) | 163 (26.1) | 91 (20.9) | 72 (38.5) | <0.001 |
| Exacerbations previous year (%) | 189 (30.2) | 113 (25.9) | 75 (39.7) | <0.001 |
| History of pneumonia (%) | 173 (29.3) | 113 (28) | 57 (30.8) | 0.491 |

Data are presented as n (% of patients with non-missing data) or mean (Standard deviation)

BMI: Body mass index; COPD: Chronic obstructive pulmonary disease; AATD: Alpha-1 antitrypsin deficiency; cardiovascular disease includes hypertension, ischaemic heart disease, congestive heart failure and peripheral vascular disease

Augmented patients were older, more frequently male, former smokers and either unemployed or retired compared to non-augmented patients. They were more frequently index cases (79.9% versus 69.4%; $p=0.007$) and with a chronic respiratory disease (98.9% versus 73.5%; $p<0.001$). Only asthma was more frequent among non-augmented PI*ZZ patients (17.2% versus 7.4%; $p<0.001$) (Table 1).

Augmented patients had more impaired lung function and worse quality of life, both respiratory-specific and generic; however, there were no significant differences in physical activity between augmented and non-augmented PI*ZZ individuals (Table 2). Differences in lung function and quality of life variables between augmented and non-augmented PI*ZZ are also shown in Fig. 2.

The haemoglobin levels and white blood cell counts were significantly higher in augmented PI*ZZ subjects

versus non-augmented. Regarding liver function tests, only gamma-glutamyl transferase (GGT) (47.8 (SD: 40.1) IU/L vs 38.2 (SD: 45.2) IU/L; $p<0.001$) was significantly higher in augmented patients (Table 2).

Analysis of lung function of PI*ZZ individuals: concordance between FEV1(%) and KCO(%)

Of the 449 PI*ZZ participants with valid measurements of FEV1(%) and KCO(%), 343 (76.4%) had concordant values (248 (55%) both impaired and 95 (21.2%) both normal), whereas 106 (23.6%) were discordant (Fig. 3), the Kappa index was 0.47 (95% confidence interval 0.38 to 0.55).

Patients with impairment in lung function tests or FEV1(%) alone were older, more frequently male, active or former smokers and index cases, and more frequently diagnosed with a respiratory disease. Those who had

Table 2 Lung function, blood analysis, health related quality of life and physical activity of patients with PI*ZZ genotype and comparison between augmented and non-augmented subjects

| Variables | All ZZ (n = 629) | ZZ non-augmented (n = 436) | ZZ augmented (n = 190) | p value |
|--------------------------|------------------|----------------------------|------------------------|---------|
| Lung function | | | | |
| FVC, % | 91.8 (23.7) | 96.1 (21.3) | 81.8 (26.1) | <0.001 |
| FEV1, % | 66.9 (30.7) | 76.3 (29.4) | 45.5 (21.7) | <0.001 |
| FEV1/FVC, % | 0.54 (0.2) | 0.59 (0.2) | 0.44 (0.1) | <0.001 |
| KCO, % | 68 (23.2) | 75.1 (22.4) | 55.8 (19.1) | <0.001 |
| Quality of life | | | | |
| CAT | 13.2 (9.3) | 12.5 (9.7) | 14.8 (8.4) | 0.001 |
| BODEx | 2 (2.0) | 1.4 (1.8) | 3.3 (2.0) | <0.001 |
| EQ-5D | 0.82 (0.22) | 0.85 (0.20) | 0.73 (0.25) | <0.001 |
| VAS | 59.3 (28.2) | 62.9 (28.2) | 49.3 (25.7) | <0.001 |
| Exercise/activity | | | | |
| Active days in last week | 2.7 (2.4) | 2.7 (2.3) | 2.6 (2.4) | 0.717 |
| Active days usual week | 2.8 (2.4) | 2.9 (2.4) | 2.7 (2.4) | 0.440 |
| Minutes walked per day | 58.8 (63.9) | 59 (64.2) | 57.7 (63.0) | 0.924 |
| Blood analysis | | | | |
| Haemoglobin | 14.8 (2.4) | 14.5 (2.6) | 15.3 (1.7) | 0.001 |
| White blood cells | 7.0 (2.2) | 6.7 (2.0) | 7.6 (2.4) | <0.001 |
| Neutrophils | 4.5 (3.2) | 4.2 (2.5) | 5.1 (4.2) | 0.002 |
| Eosinophils | 0.25 (0.60) | 0.22 (0.41) | 0.30 (0.85) | 0.121 |
| Platelets | 237.8 (73.4) | 238.7 (70.9) | 237.0 (77.5) | 0.571 |
| AAT (mg/dL)* | 23.8 (8.3) | 23.8 (8.7) | 23.8 (7.5) | 0.571 |
| AST (UI/L) | 29.9 (17.4) | 30.8 (16.7) | 27.8 (13.1) | 0.202 |
| ALT (UI/L) | 29.7 (17.9) | 30.1 (17.5) | 28.7 (19.0) | 0.474 |
| GGT (UI/L) | 43.6 (44.1) | 41.5 (45.6) | 47.8 (40.8) | 0.001 |
| FIB-4 | 1.6 (2.5) | 1.6 (2.1) | 1.8 (3.3) | 0.103 |

Values are mean (Standard deviation) unless otherwise specified

FVC: Forced vital capacity; FEV1: Forced expiratory volume in 1 s; KCO: Carbon monoxide transfer coefficient; CAT: COPD assessment test; BODEx: Body mass index, obstruction, dyspnoea, exacerbations index; EQ-5D: Euro QoL 5 dimensions questionnaire; VAS: Visual analogue scale; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: Gamma-glutamyl transferase; FIB-4: Fibrosis 4

* AAT levels were obtained at diagnosis, before initiating augmentation therapy

impairment in FEV1(%) alone had more frequently bronchiectasis (40.5%) and asthma (24.3%). Up to 20.2% of individuals with normal lung function had asthma and 19.1% bronchiectasis. There were no significant differences in the prevalence of liver disease, although this was numerically higher in patients with impairment in KCO(%) alone (26.1%) (Table 3).

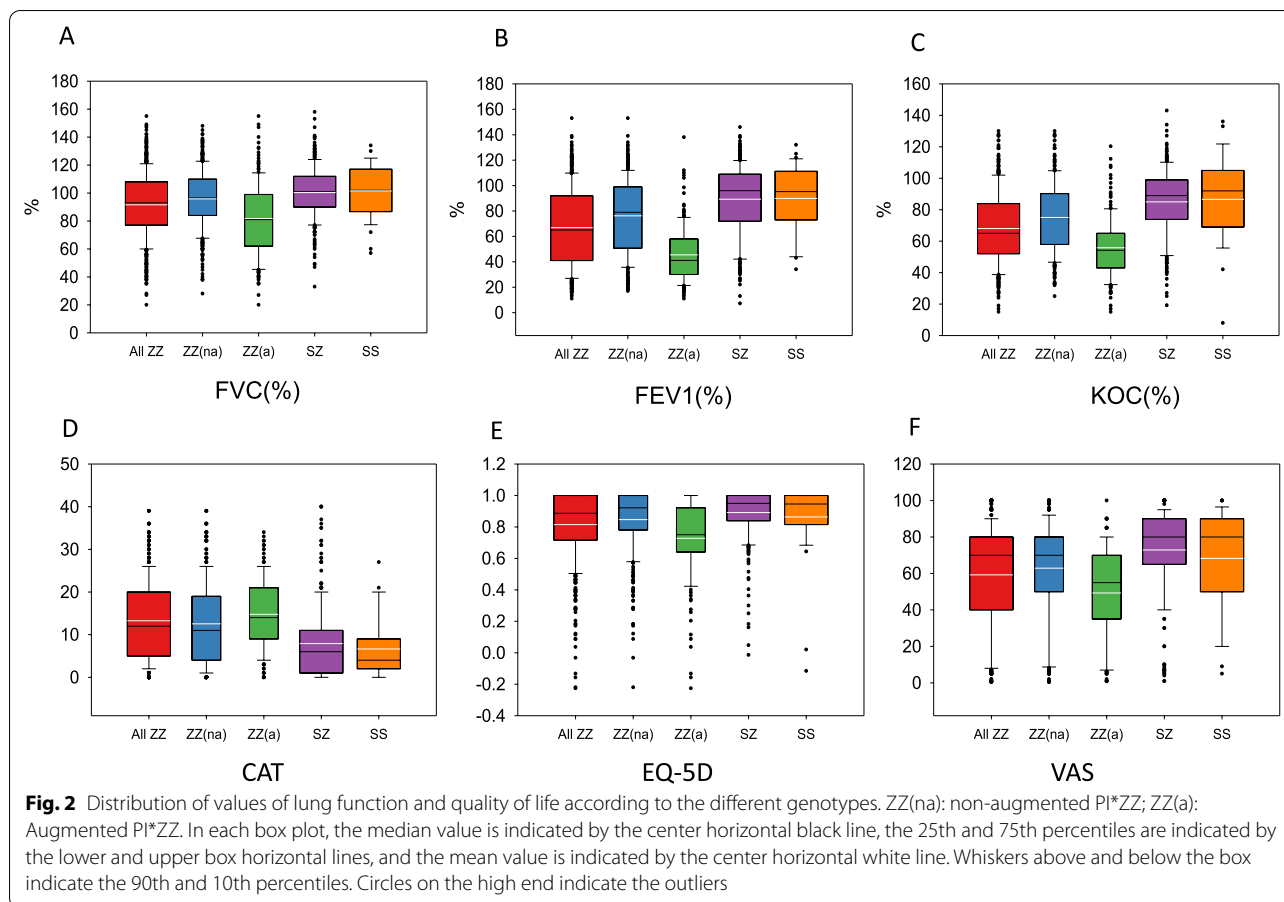
Regarding quality of life, CAT and EQ-5D scores were worse in patients with impaired lung function tests and impaired FEV1(%) compared with the other two groups. However, there were no significant differences in the patterns of physical activity, and patients with impaired FEV1(%) had a significantly longer time walking per day (77.3 min (SD: 76.4)) compared with the other groups (Table 4).

The analysis of blood parameters showed a significant difference in the plasma levels of AAT, with the highest levels in patients with impaired FEV1(%) and the lowest

in those with impaired KCO(%) (27.1 mg/dL (SD: 10) versus 22.1 mg/dL (SD: 9.2); $p < 0.05$). In contrast, FIB-4 was significantly higher in patients with impaired KCO(%) compared with the remaining groups and they also had numerically lower levels of platelets (Table 4).

Factors associated with impairment in FEV1(%) in multivariate analysis in PI*ZZ individuals

The multivariate analysis showed that advanced age, male sex, history of exacerbations, use of augmentation therapy and markers of inflammation (such as increased blood neutrophils and platelets) were associated with impaired FEV1(%). In contrast, increased serum levels of AAT were associated with better FEV1(%). When analysing these factors separately for augmented and non-augmented patients, the association of male sex and exacerbations remain for both groups, but markers



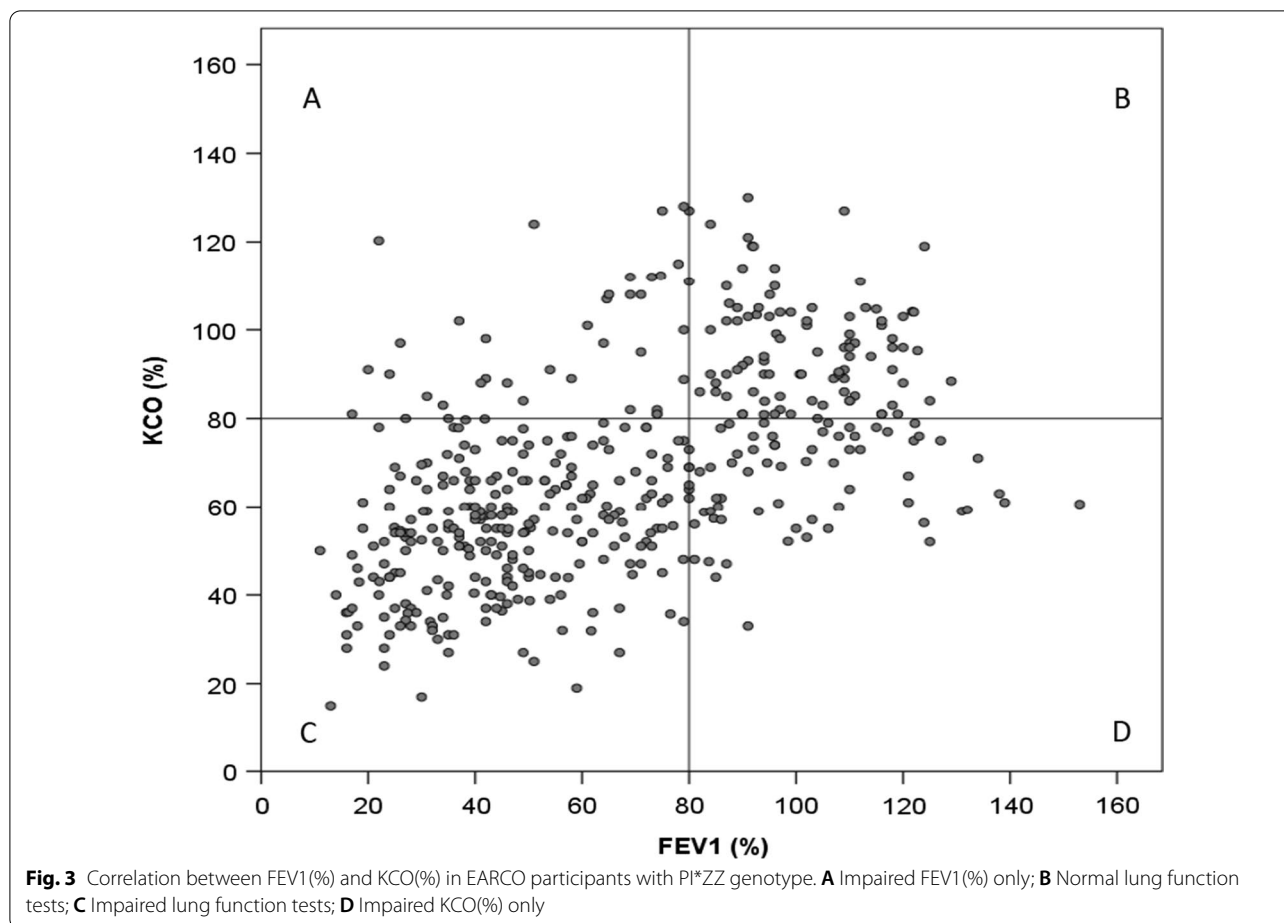
of inflammation were only significant for the non-augmented patients (Table 5).

Discussion

Despite the severe disruption caused by the COVID-19 pandemic, the EARCO registry has been able to recruit more than 1000 individuals with severe AATD from 15 countries over the course of its first 2 years. The clinical characteristics of the participants are similar to other previous series, with a mean age of 55 years and an even distribution between sex, with 71.8% suffering from with pulmonary disease and 14% from liver disease. The majority of PI*ZZ patients had a concordant impairment in FEV1(%) and KCO(%); however, those with impairment in FEV1(%) alone more frequently had asthma or bronchiectasis and those with impairment in KCO(%) alone more often had emphysema and liver involvement. As expected, PI*ZZ patients on augmentation therapy were more severely affected by lung disease and were more frequently index cases compared with non-augmented PI*ZZ cases. Increased age, male sex, more frequent exacerbations, and elevated markers of inflammation, such as blood neutrophils and platelets, were

associated with impaired FEV1(%), whereas higher levels of serum AAT were associated with better FEV1(%) in multivariate analysis.

The investigation about the characteristics and natural history of rare diseases, such as AATD, requires the development of registries to collect information about a large number of cases [12, 22]. National registries have been developed in Europe, United States (US) and Canada [5–7] and more than 20 years ago, the Alpha 1 International Registry was funded to harmonise data collection from several countries [8]. However, the greatest challenge has always been the collection of long-term follow up data in multicenter, international registries. At the end of the last century, the National Heart, Lung and Blood Institute (NHLBI) registry of patients with severe AATD recruited + 1000 individuals in the US and followed them for between 3.5 to 7 years to investigate the effectiveness of augmentation therapy in slowing the rate of decline of FEV1 [23]. In Europe, the Swedish, UK and German registries, among others, have generated relevant information about clinical phenotypes, comorbidities and factors influencing rate of decline of lung function [5, 6, 24–27]. However, despite these and



other examples, there is a clear unmet need of large series of severe AATD patients from different countries, with different genotypes and receiving different treatments to provide new information about the clinical and functional characteristics of the disease and its natural history.

Almost two thirds of the individuals recruited have the most frequent deficient genotype PI*ZZ, but up to 8% are carriers of rare deficient variants. Nearly 30% were non index cases, the mean FEV1(%) and KCO(%) were around 75% and participants showed a moderate impairment in quality of life.

Only 30% of the severe deficient PI*ZZ individuals received augmentation therapy; this percentage is influenced by the recruitment of patients from countries in which augmentation is not reimbursed [28]. Nevertheless, augmented patients were more frequently index cases, and had more severe impairment in lung function and more frequent exacerbations compared with non-augmented. Interestingly, most augmented patients were receiving regimens other than the approved dosage of weekly infusions of 60 mg/kg. The most frequent

regimen was biweekly administration of 120 mg/kg, followed by 180 mg/Kg every 3 weeks, and 5 patients were using other regimens, probably individual adjustments of dosage according to trough levels of serum AAT, a frequent practice that is not recommended by experts [12].

The usual pattern of lung disease in severe AATD is basal, bilateral, panlobular emphysema; however, different series have described other lung phenotypes, such as bronchiectasis, chronic bronchitis, asthma or even apical emphysema [25, 26]. Our population reflects this heterogeneity with 17.7% (22% of the PI*ZZ) having bronchiectasis and 15.1% (14.1% of the PI*ZZ) having asthma. The majority of our PI*ZZ patients (76%) had concordant impairment in FEV1(%) and KCO(%); interestingly, among the discordant subjects, those with impairment in FEV1(%) alone had more frequently bronchiectasis or asthma, and those with impairment in KCO(%) alone had signs of more liver involvement with a significantly higher index FIB-4, lower levels of platelets and a higher percentage of subjects with diagnosed liver disease. To the best of our knowledge, this observation of the possible link between a predominant impairment in diffusion

Table 3 Characteristics of PI*ZZ patients according to their impairment in FEV1(%), KCO(%) or both

| Variables | Impaired PFTs (n = 248) | Impaired KCO(%) (n = 69) | Impaired FEV1(%) (n = 37) | Normal PFTs (n = 95) | p value |
|---|-------------------------|--------------------------|---------------------------|----------------------|---------------------------|
| Age, years | 58.7 (10.7) | 55.2 (13.4) | 56.2 (12.4) | 45.2 (14.9) | < 0.001 ^{cef} |
| Sex, male (%) | 145 (58.5) | 33 (47.8) | 25 (67.6) | 43 (45.3) | 0.035 |
| BMI (kg/m ²) | 26.1 (5.0) | 25.8 (4.5) | 28 (5.2) | 26.1 (4.6) | 0.105 |
| Smokers (%) | 4 (1.6) | 2 (2.9) | 1 (2.7) | 2 (2.1) | 0.903 |
| Ex-smokers (%) | 193 (77.8) | 28 (40.6) | 22 (59.5) | 23 (24.2) | < 0.001 ^{acf} |
| Never smokers (%) | 51 (20.6) | 39 (56.5) | 14 (37.8) | 70 (73.7) | < 0.001 ^{acf} |
| Tobacco Exposure (Pack-years) | 21 (14.8) | 12.7 (10.8) | 14 (10.2) | 6.9 (7.6) | < 0.001 ^{ac} |
| Working status | | | | | |
| Active | 107 (43.1) | 40 (58) | 20 (54.1) | 74 (77.9) | < 0.001 ^{cef} |
| Retired | 121 (48.8) | 23 (33.3) | 16 (43.2) | 12 (12.6) | < 0.001 ^{cef} |
| Unemployed | 14 (5.6) | 2 (2.9) | 1 (2.7) | 2 (2.1) | 0.424 |
| Other | 6 (2.4) | 4 (5.9) | 0 (0) | 7 (7.4) | 0.077 |
| Age at diagnosis of AATD | 48.4 (12.8) | 45.7 (18.3) | 47.1 (12.7) | 31.4 (22.5) | < 0.001 ^{cef} |
| Reasons for diagnosis | | | | | |
| Index case (%) | 202 (81.5) | 40 (58.0) | 24 (64.9) | 48 (51.1) | < 0.001 ^{ac} |
| Family screening (%) | 24 (9.7) | 19 (27.5) | 6 (16.2) | 30 (31.6) | < 0.001 ^{ac} |
| Clinical characteristics | | | | | |
| Chronic respiratory disease (%) | 247 (99.6) | 48 (70.6) | 32 (86.5) | 43 (45.7) | < 0.001 ^{abcef} |
| COPD (%) | 214 (83.3) | 19 (27.9) | 25 (67.6) | 5 (5.3) | < 0.001 ^{abcdef} |
| Emphysema (%) | 203 (81.9) | 30 (44.1) | 27 (73.0) | 10 (10.6) | < 0.001 ^{acdef} |
| Bronchiectasis (%) | 45 (18.1) | 23 (33.8) | 15 (40.5) | 18 (19.1) | 0.002 ^{ab} |
| Asthma (%) | 27 (10.9) | 8 (11.8) | 9 (24.3) | 19 (20.2) | 0.036 |
| Liver disease (%) | 35 (14.5) | 18 (26.1) | 5 (13.5) | 19 (20.2) | 0.113 |
| Charlson index (<i>age corrected</i>) | 4 (1.9) | 2.8 (1.9) | 2.9 (1.3) | 1.5 (1.4) | < 0.001 ^{acef} |
| Cardiovascular disease (%) | 80 (32.7) | 13 (18.8) | 10 (27) | 12 (12.6) | 0.001 ^c |
| Exacerbations previous year (%) | 103 (41.5) | 13 (18.8) | 12 (32.4) | 8 (8.4) | < 0.001 ^{acf} |
| History of pneumonia (%) | 72 (31.2) | 18 (26.9) | 10 (30.3) | 18 (19.6) | 0.209 |

Impairment is considered when values are < 80% of reference

Data are presented as n (% of patients with non-missing data) or mean (Standard deviation)

LFT: Lung function tests; FEV1: Forced expiratory volume in 1 s; KCO: Carbon monoxide transfer coefficient; BMI: Body mass index; COPD: Chronic obstructive pulmonary disease; AATD: Alpha-1 antitrypsin deficiency; cardiovascular disease includes hypertension, ischaemic heart disease, congestive heart failure and peripheral vascular disease

Bonferroni ^ap < 0.05 for comparison between the groups "Impaired PFTs and Impaired KCO(%)". ^bp < 0.05 for comparison between the groups "Impaired PFTs and impaired FEV1(%)". ^cp < 0.05 for comparison between the groups "Impaired PFTs and normal PFTs". ^dp < 0.05 for comparison between the groups "Impaired KCO(%) and impaired FEV1(%)". ^ep < 0.05 for comparison between the groups "Impaired KCO(%) and normal PFTs". ^fp < 0.05 for comparison between the groups "Impaired FEV1(%) and normal PFTs"

capacity and more frequent or severe liver disease has not been previously reported and requires further investigation. Moreover, patients with impairment in KCO(%) also had significantly lower levels of serum AAT compared with patients with impairment in FEV1(%), suggesting a stronger relationship between lower levels of AAT and lung parenchymal disease instead of bronchial disease. Alternatively, patients with FEV1(%) impairment may be more severe and had higher levels of systemic inflammation which may result in elevated plasma levels of AAT. Concordance between FEV1/FVC and KCO was also observed by Ward et al. [29] in 70% of a group of

530 PI*ZZ patients from the UK. However, in their study the number of patients with impaired KCO alone was too small (only 8 subjects) and no description of clinical phenotypes were provided [29]. In a further study by the same group, a different rate of progression of impairment in airflow obstruction or in gas transfer in PI*ZZ according to impairment in FEV1 or KCO was demonstrated [6].

Increased serum levels of AAT in PI*ZZ individuals were significantly and independently associated with better FEV1(%) in multivariate analysis; this observation concurs with the results of the RAPID trial which

Table 4 Lung function, blood analysis, health related quality of life and physical activity of PI*ZZ patients according to their impairment in FEV1(%), KCO(%) or both

| Variables | Impaired PFTs (n = 248) | Impaired KCO(%) (n = 69) | Impaired FEV1(%) (n = 37) | Normal PFTs (n = 95) | p value |
|--------------------------|-------------------------|--------------------------|---------------------------|----------------------|--------------------------|
| Lung function | | | | | |
| FVC, % | 84.7 (22.3) | 111.8 (19.9) | 82.6 (21.3) | 103.9 (13.4) | < 0.001 ^{acdf} |
| FEV1, % | 44.9 (16.8) | 101.2 (17.8) | 54.6 (20.1) | 101.8 (12.3) | < 0.001 ^{acdf} |
| FEV1/FVC, % | 0.42 (0.12) | 0.72 (0.11) | 0.51 (0.13) | 0.80 (0.08) | < 0.001 ^{abcd} |
| KCO, % | 53.2 (13.9) | 65.5 (10.4) | 97.4 (14.4) | 96.7 (12.1) | < 0.001 ^{abcde} |
| Quality of life | | | | | |
| CAT | 16.7 (8.5) | 8.6 (7.1) | 12.9 (8.9) | 5.9 (6.7) | < 0.001 ^{acf} |
| BODEx | 3.1 (1.9) | 0.4 (0.7) | 1.9 (1.9) | 0.2 (0.4) | < 0.001 ^{abcd} |
| EQ-5D | 0.74 (0.24) | 0.9 (0.14) | 0.81 (0.18) | 0.93 (0.10) | < 0.001 ^{acf} |
| VAS | 53.6 (24.1) | 73.1 (17.0) | 61.6 (24.1) | 76.4 (26.6) | < 0.001 ^{acf} |
| Exercise/activity | | | | | |
| Active days in last week | 2.7 (2.4) | 2.7 (2.4) | 2.7 (2.3) | 2.6 (2.2) | 0.994 |
| Active days usual week | 2.8 (2.4) | 3.0 (2.3) | 3.1 (2.4) | 2.7 (2.1) | 0.822 |
| Minutes walked per day | 56.9 (67.7) | 60.2 (49.2) | 77.3 (76.4) | 64.6 (59.6) | 0.034 |
| Blood analysis | | | | | |
| Haemoglobin | 15.4 (1.6) | 14.7 (1.4) | 15.1 (1.9) | 14.1 (2.6) | < 0.001 ^{acf} |
| White blood cells | 7.5 (2.1) | 6.2 (1.7) | 6.8 (1.7) | 6.1 (1.8) | < 0.001 ^{ac} |
| Neutrophils | 4.8 (2.5) | 4.1 (4.7) | 5.2 (7.3) | 3.5 (1.3) | < 0.001 ^{ac} |
| Eosinophils | 0.23 (0.35) | 0.18 (0.22) | 0.27 (0.54) | 0.24 (0.59) | 0.175 |
| Platelets | 239.2 (75.7) | 216.8 (65.0) | 235.9 (56.0) | 235.8 (66.8) | 0.134 |
| AAT (mg/dL)* | 24.4 (7.6) | 22.1 (9.2) | 27.1 (10) | 23.3 (7.5) | 0.012 ^d |
| AST (UI/L) | 29.3 (14.3) | 36.3 (34.3) | 31.3 (13.8) | 27.5 (13.9) | 0.159 |
| ALT (UI/L) | 29.4 (18.6) | 30.3 (16.7) | 30.7 (15.2) | 29.3 (19.5) | 0.561 |
| GGT (UI/L) | 52.7 (52.1) | 42.2 (49.7) | 42.5 (39.3) | 30.3 (25.2) | < 0.001 ^f |
| FIB-4 | 1.7 (3) | 2.4 (4.2) | 1.4 (0.7) | 1.1 (0.7) | < 0.001 ^{ef} |

Impairment is considered when values are <80% of reference

Values are mean (Standard deviation) unless otherwise specified

FVC: Forced vital capacity; FEV1: Forced expiratory volume in 1 s; KCO: Carbon monoxide transfer coefficient; CAT: COPD assessment test; BODEx: Body mass index, obstruction, dyspnoea, exacerbations index; EQ-5D: Euro QoL 5 dimensions questionnaire; VAS: Visual analogue scale; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: Gamma-glutamyl transferase; FIB-4: Fibrosis 4

* AAT levels were obtained at diagnosis, before initiating augmentation therapy

Bonferroni ^ap < 0.05 for comparison between the groups "Impaired PFTs and Impaired KCO(%)". ^bp < 0.05 for comparison between the groups "Impaired PFTs and impaired FEV1(%)". ^cp < 0.05 for comparison between the groups "Impaired PFTs and normal PFTs". ^dp < 0.05 for comparison between the groups "Impaired KCO(%) and impaired FEV1(%)". ^ep < 0.05 for comparison between the groups "Impaired KCO(%) and normal PFTs". ^fp < 0.05 for comparison between the groups "Impaired FEV1(%) and normal PFTs"

described those patients with higher trough serum AAT levels had a reduced rate of decline of lung density, even in the placebo arm, in which the range of AAT trough levels was very limited [30].

Other independent variables associated with impaired lung function were male sex, exacerbations and some blood inflammatory markers. A faster decline in lung function in males has been already described [31, 32]; although the reason is unclear, among others, males are more often involved in "blue collar" occupations and exposed to environmental pollutants that may impact in lung function [24, 33]. The significant and strong

association of exacerbations with impaired lung function may be bidirectional: patients with more severe impairment in FEV1(%) have an increased risk of exacerbations and more frequent exacerbations accelerate FEV1(%) decline. Our results agree with previous findings in longitudinal studies that confirm the impact of exacerbations in the natural history of lung disease in AATD [27, 31, 34] and stress the importance of prevention of exacerbations in patients with AATD and lung disease.

Patients with COPD have increased lung and systemic inflammation, and since AAT is an acute phase protein, they also have increased serum levels of AAT compared

Table 5 Multivariate analysis of variables associated with FEV1(%) in individuals with PI*ZZ genotype in EARCO

| Variables | FEV1(%) | | | | | |
|-------------------|---------------|------------------|---------------------|-----------------|-------------------------|------------------|
| | All (n = 453) | | Augmented (n = 157) | | Non-augmented (n = 296) | |
| | Beta | 95% CI | Beta | 95% CI | Beta | 95% CI |
| Age | -0.366 | -0.543, -0.189 | NS | - | -0.577 | -0.792, -0.362 |
| Sex (male) | -10.414 | -15.087, -5.741 | -13.460 | -20.283, -6.638 | -8.004 | -14.006, -2.003 |
| Smokers | NS | - | NS | - | NS | - |
| Exacerbations | -15.741 | -20.781, -10.701 | -13.476 | -20.191, -6.761 | -16.985 | -23.870, -10.100 |
| Pneumonia | NS | - | NS | - | NS | - |
| Blood eosinophils | NS | - | NS | - | NS | - |
| Blood neutrophils | -0.060 | -0.092, -0.027 | NS | - | -1.158 | -2.261, -0.056 |
| Serum AAT | 27.077 | 22.949, 31.205 | NS | - | NS | - |
| Platelets | -0.565 | -0.859, -0.125 | NS | - | -0.068 | -0.112, -0.024 |
| Augmentation | -0.366 | -0.543, -0.189 | NS | - | NS | - |

AAT: alpha-1 antitrypsin; CI: Confidence interval; FEV1: Forced expiratory volume in 1 s; NS: non-significant

with healthy controls [35]. Some studies have suggested that there is a relationship between increased markers of systemic inflammation and the severity of lung and liver disease [36–38]. In our PI*ZZ patients, markers of systemic inflammation, such as increased neutrophils and platelets, were associated with more impaired FEV1(%), but this association was not observed in augmented patients. This may be a statistical effect due to a smaller sample size, but it may also be a consequence of the anti-inflammatory effect of the infused AAT that attenuates bronchial [39] and systemic inflammation [38, 40].

Our study has some limitations, the most important is the cross-sectional nature of data; however, there was a lack of information about the characteristics of large, international series of patients with severe AATD. On the other hand, it has the strength of a harmonised collection of data from many different countries with a single protocol and with close monitoring and quality control of the included data.

Conclusions

The EARCO registry has shown novel information about the clinical and functional characteristics of a large, international registry of patients with AATD. EARCO is a prospective study that will provide relevant information about the natural history of AATD in the future and is the platform for the development of other clinical studies in the field.

Abbreviations

AAT: Alpha-1 antitrypsin; AATD: Alpha-1 antitrypsin deficiency; AIR: Alpha-1 International Registry; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body mass index; BODEx: Body mass index, obstruction, dyspnoea, exacerbations index; CAT: COPD assessment test; CI: Confidence interval; COPD: Chronic obstructive pulmonary disease; CRC: Clinical Research

Collaboration; CRP: C-reactive protein; EARCO: European Alpha-1 antitrypsin Research Collaboration; eCRF: Electronic case report form; ERS: European Respiratory Society; EQ-5D: Euro QoL 5 dimensions questionnaire; FEV1: Forced expiratory volume in 1 s; FIB-4: Fibrosis 4; FVC: Forced vital capacity; GDPR: General Data Protection Regulation; GGT: Gamma-glutamyl transferase; IU: International units; KCO: Carbon monoxide transfer coefficient; NHLBI: National Heart, Lung and Blood Institute; NS: Non-significant; PAVS: Physical Activity Vital Sign; PI: Protease inhibitor; SD: Standard deviation; UK: United Kingdom; US: United States of America; VAS: Visual analogue scale.

Supplementary Information

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Additional file 1: Table S1. Description of rare variants identified in EARCO.

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Author contributions

MM and CFC drafting of the manuscript. CE performed the statistical analysis. All authors participated in the study concept, design and acquisition of data. All authors performed a critical revision and agree to be accountable for all aspects of the work. All authors read and approved the final manuscript.

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Availability of data and materials

The data that support the findings of this study are available from the EARCO group 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 the EARCO steering committee.

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

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