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Demographic and clinical characteristics of patients with alpha-1 antitrypsin deficiency genotypes PI*ZZ and PI*SZ in the Spanish registry of EARCO

María Torres-Durán, José Luis López-Campos, Juan Luis Rodríguez-Hermosa, Cristina Esquinas, Cristina Martínez-González, José María Hernández-Pérez, Carlota Rodríguez, Ana Bustamante, Francisco Casas-Maldonado, Miriam Barrecheguren, Cruz González, Marc Miravitlles

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Demographic and clinical characteristics of patients with alpha-1 antitrypsin deficiency genotypes PI*ZZ and PI*SZ in the Spanish registry of EARCO.

Authors: María Torres-Durán (1), José Luis López-Campos (2,3), Juan Luis Rodríguez-Hermosa (4,5), Cristina Esquinas (2,6), Cristina Martínez-González (7), José María Hernández-Pérez (8), Carlota Rodríguez (9), Ana Bustamante (10), Francisco Casas-Maldonado (11), Miriam Barrecheguren (2,6), Cruz González (12), Marc Miravitlles (2,6).

Center: 1. Servicio de Neumología. Hospital Álvaro Cunqueiro. NeumoVigo I+i Research Group, IIS Galicia Sur, Vigo, Spain. 2. Centro de Investigación Biomédica en Red de Enfermedades Respiratorias (CIBERES). Instituto de Salud Carlos III, Madrid, Spain. 3. Unidad Médico-Quirúrgica de Enfermedades Respiratorias. Instituto de Biomedicina de Sevilla (IBiS). Hospital Universitario Virgen del Rocío/Universidad de Sevilla, Spain. 4. Servicio de Neumología. Hospital Clínico de San Carlos. Departamento de Medicina, Facultad de Medicina, Universidad Complutense de Madrid, Madrid, Spain. 5. Research Institute of Hospital Clínico San Carlos (IdISSC), Madrid, Spain. 6. Pneumology Department, Hospital Universitari Vall d'Hebron; Vall d'Hebron Institut de Recerca (VHIR), Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain. 7. Pneumology Department, Hospital Universitario Central de Asturias, Instituto de Investigacion Sanitaria del Principado de Asturias. Oviedo, Spain. 8. Pneumology Department, Hospital Universitario Nuestra Señora de La Candelaria, Santa Cruz de Tenerife, Spain. 9. Servicio de Neumología, Complejo Hospitalario Clínico-Universitario de Santiago, Santiago de Compostela, Spain. 10. Pneumology Section. Hospital Sierrallana-TresMares. Cantabria. Spain. 11. Servicio de Neumología.

Hospital Clínico Universitario San Cecilio. Departamento de Medicina, Facultad de Medicina, Universidad de Granada, Granada, Spain. 12. Servicio de Neumología. Hospital Clínico Universitario. Instituto de Investigación INCLIVA, Valencia, Spain.

Correspondence: Marc Miravitlles

Pneumology Department. Hospital Universitari Vall d'Hebron, Vall d'Hebron Barcelona Hospital Campus.

Passeig Vall d'Hebron 119-129. 08035 Barcelona, Spain

Tel and fax: (34) 93 2746083. e-mail: marcm@separ.es

ABSTRACT

Background: The Spanish registry of alpha-1 antitrypsin deficiency integrated in the European alpha-1 antitrypsin deficiency research collaboration (EARCO) provides information about the characteristics of patients, in particular those with the PI*SZ genotype, which is frequent in Spain.

Method: Individuals with severe AATD defined as proteinase inhibitor (PI) genotypes PI*ZZ, PI*SZ and other rare deficient variants were included from February 1st, 2020, to February 1st, 2022. The analysis focuses on the comparison of the characteristics of Pi*ZZ and Pi*SZ participants.

Results: 409 individuals were included, 53.8% were men, mean age of 53.5 years (standard deviation (SD): 15.9). Genotypes were PI*ZZ in 181 (44.7%), PI*SZ in 163 (40.2%), PI*SS in 29 (7.2%) and others in 32 (7.9%). 271 (67.4%) had lung disease; 175 COPD (43.5%), 163 emphysema (40.5%) and 83 bronchiectasis (20.6%). Individuals with the PI*SZ genotype were younger, more frequently non-index cases and had a lower frequency of respiratory diseases except asthma compared with PI*ZZ. Among patients with respiratory diseases, PI*SZ individuals were significantly older both at onset of symptoms and at diagnosis, only asthma was more frequent in PI*SZ than in PI*ZZ subjects. Twelve (15.4%) PI*SZ patients received augmentation therapy compared with 94 (66.2%) with PI*ZZ ($p<0.001$).

Conclusions: There is a high prevalence of PI*SZ in Spain. Patients with the PI*SZ genotype were older at symptom onset and diagnosis and had less severe lung disease compared with PI*ZZ. The prevalence of asthma was higher in PI*SZ, and up to 15% of PI*SZ patients received augmentation therapy.

Keywords: alpha-1 antitrypsin; registries; genotype.

INTRODUCTION

Alpha-1 antitrypsin deficiency (AATD) is considered the most frequent potentially severe rare disease affecting adults, and its prevalence is around 2 /10,000 in Europe (1). AATD may predispose to liver disease in children and adults and pulmonary emphysema in adults (2).

The majority of patients with severe AATD are homozygous carriers of the Z mutation of the gene coding for the AAT protein (proteinase inhibitor (PI*ZZ)), but hundreds of variants have been identified, some of which are associated with low serum AAT levels (3,4). Among these variants, the most frequent is the S variant, which is particularly frequent in Western Spain (5). The risk of lung disease associated with the heterozygous PI*SZ genotype is controversial. Some carriers may have serum levels below those considered protective and may be candidates for augmentation therapy with intravenous AAT, if emphysema develops (6,7), while some studies suggest that the risk of lung disease associated with PI*SZ is significantly less than that of PI*ZZ (8).

The low prevalence of AATD and the extreme variability of its respiratory clinical manifestations implies that a single centre will never attend enough patients to acquire experience in the management of this condition. Therefore, the European Council (9) and the European Respiratory Society (ERS) (1) recommend organising the care of AATD patients in reference centres and developing prospective registries to better understand the natural history of the disease and the potential impact of different treatments (10). The Spanish registry of AATD was funded in 1992 (11) and in 2020 it was merged in the new European Alpha-1 antitrypsin Deficiency Research Collaboration (EARCO) International Registry (12). The EARCO registry is a prospective international registry developed by the EARCO Clinical Research

Collaboration (CRC) of the ERS (13), and the Spanish registry consists of the Spanish investigators, centres and participants included in the EARCO registry (14).

The current study presents the demographic and clinical characteristics of the participants in the Spanish registry in EARCO and, since Spain is one of the countries with the highest prevalence of the S allele, it provides a unique opportunity to investigate the differential characteristics of individuals with the PI*SZ genotype (15) and compare them with those of the PI*ZZ subjects.

METHOD

Structure of the Spanish registry of AATD

The Spanish registry of patients with AATD is constituted by the Spanish investigators and patients registered in the EARCO international registry (14). The registry is open to every clinician who manages AATD patients in Spain. The registry is observational and, therefore, patients are treated according to the attending physicians' criteria. The Spanish registry has one national coordinator (MT-D) designated by the Spanish Society of Pneumology and Thoracic Surgery (SEPAR), and a steering committee formed by clinicians and researchers with expertise in the disease. According to the data processor agreement signed between the national coordinator, representing the SEPAR and the Spanish registry, and the data controller of EARCO (Vall d'Hebron Research Institute, Barcelona, Spain), the Spanish registry is free to access fully anonymized data of the Spanish patients for analysis and evaluation.

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 the participating centres. All participants provided written

informed consent. The EARCO registry protocol has been registered in www.clinicaltrials.gov (ID: NCT04180319) 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 Spanish Organic Law 3/2018, of December 5th, Protection of Personal Data and Guarantee of Digital Rights (LOPDGDD) and its development regulations, and in accordance 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 regarding the protection of personal data.

Objectives of the Spanish AATD registry

The objectives of the Spanish AATD registry are linked to those of EARCO and have been described in detail in a previous publication (16). Briefly, the main objectives 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 analyse the baseline data of patients included in the Spanish registry in the first two years of EARCO, from February 1st, 2020, to February 1st, 2022.

Population and measurements.

The protocol of the study has been published previously (16). The inclusion criteria are: 1) individuals with diagnosed severe AATD; 2) deficiency is defined as AAT serum levels <11 μM (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 criterion is lack of patient consent.

The data collected include the following domains: demographics, proteinase inhibitor genotype and other laboratory analyses, comorbidities, lung function, respiratory symptoms, ultrasound-based elastography of the liver, exacerbations of respiratory disease, quality of life, physical activity, chest computed tomography (CT, 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

Qualitative variables were described with absolute frequencies and percentages. The description of quantitative variables was performed using the mean and standard deviation (SD), median and quartiles. The Kolmogorov–Smirnov test was used to assess the normality of distributions. The sociodemographic and clinical characteristics were compared according to the genotypes (PI*ZZ and PI*SZ). In the case of quantitative variables, the Student's t-test was carried out (Mann-Whitney U-test if normality was not assumed). The Chi-squared test (Fisher test for frequencies <5) was used for the comparison of categorical variables. The pack-years were transformed into an ordinal variable (0, <10, 10-20, 20-30 and >30) in order to compare the FEV1% between genotypes according to the degree of smoking consumption. 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

Population included

The Spanish registry included a total of 409 individuals with severe AATD from 17 centres distributed throughout the country; 218 (53.8%) participants were men, with a mean age of 53.5 years (SD: 15.9) and only 33 (8%) were active smokers. The distribution of genotypes was PI*ZZ in 181 patients (44.7%), PI*SZ in 163 (40.2%), PI*SS in 29 (7.2%) and others in 32 patients (7.9%). Up to 70.6% were index cases and the mean age at diagnosis was 46.4 years (SD: 17.3).

Characteristics of lung disease in participants in the Spanish registry.

Lung disease was present in 271 participants (67.4%); the most frequent pulmonary disease was COPD in 175 subjects (43.5%), followed by emphysema in 163 (40.5%) and bronchiectasis in 83 (20.6%). The most frequent respiratory symptoms at presentation were dyspnoea in 217 (53%), cough in 96 (23.5%) and sputum production in 68 (16.6%). Up to 77 (19.3%) had a history of pneumonia and spirometry showed a mean forced expiratory volume in 1 second (% predicted) (FEV1(%)) of 81.7% (SD: 31.3%) and the mean carbon monoxide transfer coefficient in percent predicted (KCO (%)) was 76.8% (SD: 23.4%).

Comparison of demographic and clinical characteristics between PI*ZZ and PI*SZ individuals.

Individuals with the PI*SZ genotype were younger, more frequently non-index cases and had a lower frequency of most respiratory diseases (COPD 25.9%, emphysema 24.7% and bronchiectasis 10% versus 60.3%, 59.8% and 32.4% in the PI*ZZ subjects; $p<0.001$ for all comparisons). However, there was no difference in the prevalence of asthma (13.6% versus 13.4%; $p=0.96$). Among PI*SZ subjects there were more active smokers (23.2% versus 2.8%; $p<0.001$), but they had better lung function and a lower frequency of exacerbations and previous pneumonia (Table 1). Never smokers showed no differences in FEV1(%), but significant differences in FEV1(%) were observed with

increased accumulated tobacco consumption in both genotypes (p for trend p<0.001 for PI*ZZ and PI*SZ), with smoking having a higher impact at lower cumulative doses in PI*ZZ subjects (Figure 1A). Significant differences between both genotypes were also observed for FVC(%); but not for FEV1/FVC (Figures 1B and 1C).

Comparison of characteristics and severity of lung disease between PI*ZZ and PI*SZ individuals.

The comparison of the 82 PI*SZ and 146 PI*ZZ subjects with respiratory disease is shown in Table 2. The distribution of age and sex was no different between the two genotypes, but PI*SZ patients were more frequently active smokers. The proportion of index cases, patients identified by family screening and patients with cardiovascular comorbidity did not differ between the two groups; however, the PI*SZ patients had a significantly older age both at symptom onset and diagnosis (49.9 (SD: 18.1) and 52.5 (SD:18) years versus 45.6 (SD:15) and 47.4 (SD:14.9) years for PI*ZZ; p=0.008 and p=0.003 respectively). The distribution of respiratory diseases was different between the two genotypes, with more emphysema, COPD and bronchiectasis in PI*ZZ individuals and more frequent asthma in subjects PI*SZ (Table 2 and Figures 2A and 2B). Both FEV1(%) and KCO(%) were significantly lower in Pi*ZZ compared to PI*SZ patients (61.1% (SD:28.2%) and 62.9% (SD:20.6%) versus 78.7% (SD:28.5%) and 84.7% (20.8%), respectively, p<0.001 for both comparisons). The COPD assessment test (CAT) score was also higher (worse) for PI*ZZ compared to PI*SZ individuals (10.9 (SD:7.9) versus 8.6 (SD:7), p<0.036). A total of 12 (15.4%) PI*SZ patients received augmentation therapy compared with 94 (66.2%) PI*ZZ patients (p<0.001).

Characteristics of lung diseases in patients with AATD

Patients with AATD and asthma had different characteristics from those with emphysema or bronchiectasis. Patients with asthma were younger, more frequently

female and with a higher proportion of never smokers. They also had better lung function and a lower prevalence of comorbidities but had a similar frequency of previous pneumonia compared to patients with emphysema. The demographic and clinical characteristics of patients with the most frequent chronic respiratory diseases are shown in Table 3. No statistical comparisons were performed because some patients could be included in more than one category due to the coexistence of respiratory diseases in some individuals.

DISCUSSION

The implementation of the EARCO international registry has been an opportunity for the Spanish AATD registry to join an international initiative and upgrade the database and take advantage of the structure and monitoring system of EARCO to improve the quality of data collection (14). During the first two years of recruitment, and despite the COVID-19 pandemic, a total of 17 centres included more than 400 patients in the EARCO registry, which constitutes the new Spanish AATD registry.

The characteristics of the patients included have changed from the previous reports of the Spanish registry. The first report made in 1998 included 223 subjects; 73% male, mean age 46 years and mean FEV1(%)= 53% (11). The second report in 2007 included 462 individuals; 63% male, mean age 51 years and mean FEV1(%)= 53% (17). Interestingly the percentage of males is now reduced to 54%, while the mean age has increased to 53 years and mean FEV1(%) to 81%. This increase in the mean FEV1(%) may, in part, be due to the improvement in population and family screening, earlier detection of carriers and early diagnosis of lung diseases in individuals affected (18-21). The inclusion of genotypes other than PI*ZZ may also explain the better lung function in the current analysis, although the influence is very limited because the mean

FEV1(%) in PI*ZZ subjects was 69.8%, which is still much better than in previous reports (11,17).

Several registries have evaluated the characteristics of individuals with the most common deficient PI*ZZ genotype (22-25), but there is limited information about the characteristics of subjects with the PI*SZ genotype. Since the S allele is especially frequent in Spain (5,15), the Spanish registry provides a unique opportunity to investigate the clinical manifestations of PI*SZ individuals and for comparison with PI*ZZ carriers. In general, individuals with the PI*SZ genotype were younger, more frequently non-index cases and with a lower frequency of most respiratory diseases, despite a higher prevalence of active smokers, but there were no differences in the prevalence of asthma. The possible influence of the S alleles in the prevalence and severity of asthma has been previously reported (26) and justifies the investigation of AATD in all adult asthmatics with non-fully reversible airflow obstruction, as indicated in guidelines. It is of note that we did not observe significant differences in lung function between never PI*SZ and PI*ZZ smokers. However, with increasing intensity of smoking, subjects with PI*ZZ presented more severely impaired lung function, while PI*SZ only showed a deteriorated lung function at smoking consumptions of more than 20 pack-years, highlighting again the increased susceptibility of homozygous Z subjects to the deleterious effect of tobacco smoking (27-29).

Considering only the individuals with diagnosed lung disease, we observed that PI*SZ carriers were older, both at onset of symptoms and at diagnosis, compared to PI*ZZ subjects and the severity of lung disease was milder in terms of FEV1(%) and KCO(%). Augmentation therapy was administered to two thirds of patients with the PI*ZZ genotype and lung disease. It is not possible to ascertain why the remaining third of patients were not treated. Two patients were active smokers and treatment was therefore

not indicated; but other reasons, including refusing treatment by the patient could explain the lack of augmentation for PI*ZZ subjects with lung disease. Although the indications for augmentation are clear, the opinions and attitudes about augmentation may vary greatly among specialists (30), and some may not indicate augmentation for very mild or very severe patients and others may not initiate augmentation if patients do not show clinical, functional, or radiological deterioration during follow-up (30,31).

On the other hand, 15.4% of PI*SZ patients with lung disease received augmentation. Treatment for PI*SZ patients is included in the indications described in the summary of product characteristics (SmPCs) of both brands of augmentation therapy available in Spain (32,33); nevertheless, there is no consensus among specialists about the efficacy of augmentation in PI*SZ patients with lung disease. While some studies demonstrated that they have a significantly increased risk of lung disease and augmentation would help to prevent its progression (7,29,34), others suggest that the risk of lung disease associated with the PI*SZ genotype is similar to that associated with PI*MZ and much less than the homozygous form of PI*ZZ (8,35).

An interesting observation derived from the data is the different distribution of lung diseases in PI*SZ and PI*ZZ patients. Emphysema and bronchiectasis were more frequent in PI*ZZ, but asthma was relatively more frequent in PI*SZ. Among the PI*ZZ subjects, only a minority had lung disease without emphysema, with 16 (11%) cases of bronchiectasis, 13 (9%) of asthma and 2 (1.3%) of both diseases combined. In contrast, 23.2% of PI*SZ subjects had asthma and no evidence of emphysema. We can compare our results with those of a similar cohort of 424 PI*ZZ unrelated patients in the UK. In this study, Wood et al (36) reported a higher prevalence of emphysema 65.8% vs 59.8% in our series) and lower prevalence of bronchiectasis (19.5% versus 32.4% in Spain). It is of note that 10% of their patients with bronchiectasis had no emphysema,

very similar to the 12% observed in our patients (x). Data from Wood et al (36) were published 16 years ago and it is not clear whether differences observed are due to real differences in phenotypes or due to a higher implementation of AATD screening and more frequent use of HRCT scans during the last years.

The demographic and clinical profiles of patients with emphysema or bronchiectasis in our group were quite similar, but that of asthmatics was clearly different. Patients with asthma were younger and diagnosed at a younger age, there was a lower prevalence of smokers and more women, a higher frequency of patients diagnosed by family screening and they had better lung function, lower symptom burden and higher serum AAT concentrations. History of pneumonia was also more frequent in PI*ZZ subjects compared to PI*SZ, both in the global population and in individuals with lung disease. These differences could in part be explained by the higher severity of lung disease in PI*ZZ patients, while other risk factors for pneumonia, such as age were no different between both genotypes.

Spain is only one of the 16 countries currently participating in the EARCO international registry. Some of the participating countries have joined EARCO through a unique national reference centre, but others, such as Portugal ~~(36)~~ (37) or the United Kingdom have followed the same structure as the Spanish registry with multiple centres contributing directly to the database and designating a national coordinator who has direct access to the anonymized national data. The international EARCO registry is the main research project of the EARCO initiative, but there are other research projects under development derived from the survey of unmet needs developed by academics, patients, and caregivers' representatives. The follow-up of patients included in the registry will provide relevant information about the natural history of the disease ~~(37)~~ (38).

CONCLUSIONS

The Spanish registry has shown the evolution of the baseline characteristics of the patients included, who now have an older age and have more preserved lung function, suggesting an improvement in early diagnosis and better management of the pulmonary disease. In general, patients with the PI*SZ genotype had a milder respiratory disease and were less susceptible to tobacco smoking but had a similar prevalence of asthma. Longitudinal follow-up is necessary to better understand the natural history of the disease.

Abbreviations

AAT: Alpha-1 antitrypsin; AATD: Alpha-1 antitrypsin deficiency; 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; CT: Computed tomography; eCRF: electronic case report form; EARCO: European Alpha-1 antitrypsin Research Collaboration; ERS: European Respiratory Society; FEV_1: Forced expiratory volume in 1 second; FVC: Forced vital capacity; GDPR: General Data Protection Regulation; GOLD: Global initiative for obstructive lung disease; HAD: Hospital Anxiety and Depression scale; ID: Identification; KCO: carbon monoxide transfer coefficient; LOPDGDD: Protection of Personal Data and Guarantee of Digital Rights Law; PI: Proteinase inhibitor; SD: Standard deviation; SEPAR: Spanish Society of Pneumology and Thoracic Surgery; SmPC: Summary of product characteristics; PR: Protocol registration.

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Authors' contributions

The study concept and design: MT-D, CE, MM. Data acquisition: MT-D, JLL-C, JLR-H, CM-R, JMH-P, CR, AB, FC-M, MB, CG, MM. Statistical analysis: CE. Drafting of the manuscript: MM, CE, MT-D. Critical revision and approval for submission: MT-D, JLL-C, JLR-H, EC, CM-R, JMH-P, CR, AB, FC-M, MB, CG, MM. All authors have read and approved the final manuscript.

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Availability of data and materials

Information on the EARCO data sharing commitments and requesting access to anonymized aggregated participant data and associated documents can be found at www.earco.org.

Competing interests

María Torres-Durán has received speaker fees from Chiesi, CSL Behring, Grifols and Resmed and consulting fees from CSL Behring and Grifols. 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, Boehringer Ingelheim, Chiesi, CSL Behring, Esteve, Ferrer, Gebro, GlaxoSmithKline, Grifols, Menarini, Novartis, Rovi, and Teva. Juan Luis Rodriguez-Hermosa has received speaker fees from Zambon, Bial, Gebro Pharma, GlaxoSmithKline, Chiesi, Boehringer Ingelheim, CSL Behring and Grifols. José María Hernández-Pérez has received speaker fees from Grifols, CSL Behring, Astra-Zeneca, GSK, Bial laboratory, Teva laboratory, support for attending meetings from Grifols, CSL Behring, and consulting fees from CSL Behring. Francisco Casas-Maldonado has received speaker fees from AstraZeneca, Bial, Boehringer Ingelheim, Chiesi, Gebro Pharma, GlaxoSmithKline, Laboratorios Esteve, Laboratorios Ferrer, Menarini, Novartis, Rovi, TEVA, VERTEX, Zambon, CSL Behring and Grifols and consulting fees from AstraZeneca, Chiesi, GlaxoSmithKline, CSL Behring and Grifols. Miriam

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REFERENCES

1. Blanco I, Bueno P, Diego I, Pérez-Holanda S, Casas F, Esquinas C, et al. Alpha-1 antitrypsin Pi*Z gene frequency and Pi*ZZ genotype numbers worldwide: an update. Int J Chron Obstruct Pulmon Dis 2017; 12: 561-569.

2. Miravitlles M, Dirksen A, Ferrarotti I, Koblizek V, Lange P, Mahadeva R, et al. European Respiratory Society Statement: Diagnosis and treatment of pulmonary disease in alpha-1 antitrypsin deficiency. Eur Respir J 2017; 50: 1700610.

3. Rodriguez-Frias F, Miravitlles M, Vidal R, Camos S, Jardi R. Rare alpha-1-antitrypsin variants: are they really so rare? Ther Adv Respir Dis. 2012; 6(2): 79–85.

4. López-Campos JL, Casas-Maldonado F, Torres-Duran M, Medina-Gonzálvez A, Rodriguez-Fidalgo ML, Carrascosa I, et al. Results of a diagnostic procedure based on multiplex technology on dried blood spots and buccal swabs for subjects with suspected alpha1 antitrypsin deficiency. Arch Bronconeumol 2021; 57(1): 42-50.

5. Blanco I, de Serres FJ, Fernandez-Bustillo E, Lara B, Miravitlles M. Estimated numbers and prevalence of PI*S and PI*Z alleles of alpha1-antitrypsin deficiency in European countries. Eur Respir J. 2006; 27: 77–84.

6. Alvarez-Granda L, Cabero-Perez MJ, Bustamante-Ruiz A, Gonzalez-Lamuno D, Delgado-Rodriguez M, Garcia-Fuentes M. PI SZ phenotype in chronic obstructive pulmonary disease. Thorax 1997; 52: 659-661

7. Seersholm N, Kok-Jensen A. Intermediate alpha 1-antitrypsin deficiency PiSZ: a risk factor for pulmonary emphysema? Respir Med 1998; 92: 241-245.

8. McElvaney GN, Sandhaus RA, Miravitlles M, Turino GM, Seersholm N, Wencker M, et al. Clinical considerations in individuals with Alpha-1 Antitrypsin PI*SZ genotype. Eur Respir J. 2020; 55: pii 1902410.

9. http://ec.europa.eu/health/archive/ph_threats/non_com/docs/contribution_policy.pdf [accessed 19.04.2022].

10. Miravitlles M, Nuñez A, Torres-Durán M, Casas-Maldonado F, Rodríguez-Hermosa JL, López-Campos JL, et al. The Importance of Reference Centers and Registries for Rare Diseases: The Example of Alpha-1 Antitrypsin Deficiency. COPD 2020; 17(4): 346-354.

11. Miravitlles M, Vidal R, Barros-Tizón JC, Bustamante A, España PP, Casas F, et al. Usefulness of a national Registry of alpha-1-antitrypsin deficiency. The Spanish experience. Respir Med 1998; 92: 1181-1187.

12. Miravitlles M, Chorostowska-Wynimko J, Ferrarotti I, McElvaney NG, O'Hara K, Stolk J, et al. The European Alpha-1 Research Collaboration (EARCO): a new ERS Clinical Research Collaboration to promote research in alpha-1 antitrypsin deficiency. Eur Respir J 2019; 53(2): pii: 1900138.

13. Brightling C, Genton C, Bill W, Welte T, Gaga M, Heuvelin E, et al. ERS Clinical Research Collaborations: underpinning research excellence. Eur Respir *J* 2018: 52(3).pii: 1801534.

14. Barrecheguren M, Torres-Duran M, Casas-Maldonado F, Miravitlles M. Spanish Implementation of the New International Alpha-1 Antitrypsin Deficiency International Registry: The European Alpha-1 Research Collaboration (EARCO). Arch Bronconeumol 2021; 57(2): 81-82.

15. Blanco I, Bueno P, Diego I, Pérez-Holanda S, Lara B, Casas-Maldonado F, et al. Alpha-1 antitrypsin Pi*SZ genotype: estimated prevalence and number of SZ subjects worldwide. Int J Chron Obstruct Pulmon Dis 2017; 12: 1683-1694.

16. Greulich T, Altraja A, Barrecheguren M, Bals R, Chlumsky J, Chorostowska-Wynimko J, et al. Protocol for the EARCO Registry: a pan-European observational study in patients with α_1-antitrypsin deficiency. ERJ Open Res 2020; 6(1). pii: 00181-2019.

17. Lara B, Blanco I, Martínez MT, Rodríguez E, Bustamante A, Casas F, et al. Spanish registry of patients with alpha-1 antitrypsin deficiency: Database evaluation and population analysis. Arch Bronconeumol 2017; 53: 13-18.

18. Torres-Durán M, Lopez-Campos JL, Barrecheguren M, Miravitlles M, Martinez-Delgado B, Castillo S, et al. Alpha-1 antitrypsin deficiency: outstanding questions and future directions. Orphanet J Rare Dis 2018; 13: 114.

19. Barrecheguren M, Monteagudo M, Simonet P, Llor C, Rodriguez E, Ferrer J, et al. Diagnosis of alpha-1 antitrypsin deficiency: a population-based study. Int J Chron Obstruct Pulmon Dis. 2016; 11: 999-1004.

20. Esquinas C, Barrecheguren M, Sucena M, Rodriguez E, Fernandez S, Miravitlles M. Practice and knowledge about diagnosis and treatment of alpha-1 antitrypsin deficiency in Spain and Portugal. BMC Pulm Med 2016; 16: 64.

21. López-Campos JL, Carrasco Hernandez L, Marquez-Martín E, Ortega Ruiz F, Martínez Delgado B. Diagnostic Performance of a Lateral Flow Assay for the Detection of Alpha-1-Antitrypsin Deficiency. Arch Bronconeumol. 2020;56(2):124-126.

22. Survival and FEV1 decline in individuals with severe deficiency of alpha-1 antitrypsin. The Alpha-1 Antitrypsin Deficiency Registry Study Group. Am J Respir Crit Care Med. 1998; 158: 49-59.

23. Piitulainen E, Tanash HA. The clinical profile of subjects included in the Swedish National Register on individuals with severe alpha-1 antitrypsin deficiency. COPD 2015; 12 (S1): 36-41.

24. Stockley RA. Antitrypsin deficiency assessment and programme for treatment (ADAPT): The United Kingdom registry. COPD 2015; 12(S1): 63-68.

25. Chorostowska-Wynimko J, Struniawski R, Sliwinski P, Wajda B, Czajkowska-Malinowska M. The national alpha-1 antitrypsin deficiency registry in Poland. COPD. 2015; 12 Suppl 1: 22-26.

26. Miravitlles M, Vilà S, Torrella M, Balcells E, Rodríguez-Frías, de la Roza C, et al. Influence of deficient alpha-1-antitrypsin phenotypes on clinical characteristics and severity of asthma in adults. Respir Med 2002; 96: 186-192.

27. Piras B, Ferrarotti I, Lara B, Martinez MT, Bustamante A, Ottaviani S, et al. Characteristics of Italian and Spanish patients with alpha-1-antitrypsin deficiency: Identifying clinical phenotypes. Eur Respir J 2013; 42: 54-64.

28. Choate R, Mannino DM, Holm KE, Sandhaus RA. Comparing Patients with ZZ Versus SZ Alpha-1 Antitrypsin Deficiency: Findings from AlphaNet's Disease Management Program. J COPD F 2019; 6: 29-39.

29. Green CE, Vayalapra S, Hampson JA, Mukherjee D, Stockley RA, Turner AM. PiSZ alpha-1 antitrypsin deficiency (AATD): pulmonary phenotype and prognosis relative to PiZZ AATD and PiMM COPD. Thorax 2015; 70: 939-945.

30. Greulich T, Albert A, Cassel W, Boeselt T, Peychev E, Klemmer A, et al. Opinions and attitudes of pulmonologists about augmentation therapy in patients with alpha-1 antitrypsin deficiency. A survey of the EARCO Group. Int J Chron Obst Pulm Dis 2022 Jan 5; 17: 53-64.

31. Stockley RA, Miravitlles M, Vogelmeier C. Augmentation therapy for alpha-1 antitrypsin deficiency: Towards a personalised approach. Orphanet J Rare Dis 2013; 8: 149.

32. Respreeza. Summary of Product Characteristics (SmPC). https://ec.europa.eu/health/documents/community-register/2015/20150820132594/dec_132594_es.pdf (accessed April 11th, 2022).

33. Prolastin. Summary of Product Characteristics (SmPC). http://grifols.com/documents/10192/27754341/ft-prolastin-es-en/786cce6a-effb-41b6-867f-59d7a34ca086 (accessed April 11th, 2022)

34. Dahl M, Hersh CP, Ly NP, Berkey CS, Silverman EK, Nordestgaard BG. The protease inhibitor PI*S allele and COPD: a meta-analysis. Eur Respir J 2005; 26: 67-76.

35. Franciosi AN, Carroll TP, McElvaney NG. SZ alpha-1 antitrypsin deficiency and pulmonary disease: more like MZ, not like ZZ. Thorax. 2021 Mar; 76(3): 298-301.

36. Wood AM, Simmonds MJ, Bayley DL, Newby PR, Gough SC, Stockley RA. The TNFalpha gene relates to clinical phenotype in alpha-1-antitrypsin deficiency. Respir Res. 2008 Jul 11; 9(1): 52.

37. Sucena M, Gomes J, Guimarães C, Miravitlles M. Implementation of European Alpha-1 Research Collaboration (EARCO) in Portugal: the future starts now. Pulmonology 2020; 26(4): 181-183.

38. Bilton D, Caine N, Cunningham S, Simmonds NJ, Cosgriff R, Carr SB. Use of a rare disease patient registry in long-term post-authorisation drug studies: a model for collaboration with industry. Lancet Respir Med. 2018 Jul;6(7):495-496.

Table 1. Demographic and clinical characteristics of the participants in the Spanish registry of EARCO and comparison between PI*ZZ and PI*SZ genotypes.

Variables	**Global (n=405)**	**ZZ (n=181)**	**SZ (n=163)**	**p value**
Age, years	53.5 (15.9)	55.4 (14.7)	51.0 (17.3)	0.015
Sex, male (%)	218 (53.8)	95 (52.5)	87 (53.4)	0.869
BMI (kg/m^2)	26.4 (4.8)	26.2 (4.9)	26.3 (4.9)	0.730
Smokers (%) Ex-smokers (%) Never smokers (%)	33 (8) 222 (54.4) 149 (36.8)	3 (2.8) 111 (61.3) 66 (36.7)	22 (23.2) 3 (44.9) 68 (41)	<0.001
Tobacco Exposure (Pack-years)	24.5 (21.9)	20.3 (13.8)	25.2 (25.1)	0.953
Chronic respiratory disease	267 (66.4)	146 (81.6)	82 (50.6)	<0.001

COPD (%)	175 (43.5)	108 (60.3)	42 (25.9)	<0.001
Emphysema (%)	163 (40.5)	107 (59.8)	40 (24.7)	<0.001
Bronchiectasis (%)	83 (20.6)	58 (32.4)	16 (10)	<0.001
Asthma (%)	55 (13.7)	24 (13.4)	22 (13.6)	0.963
Liver disease (%)	42 (10.6)	24 (13.4)	16 (10)	0.322
Age at onset of symptoms	46.1 (17.2)	44.2 (16.3)	47.9 (17.5)	0.063
Age at diagnosis of AATD	46.4 (17.4)	44.5 (17.2)	46.8 (18)	0.554
Index case (%)	286 (70.6)	135 (74.6)	106 (65)	0.053
Family screening (%)	98 (24)	39 (21.5)	45 (27.6)	0.121
Charlson index (*age corrected)*	3.1 (2.1)	3.2 (2)	2.9 (2)	0.347
Cardiovascular disease (%)	89 (22.5)	47 (26.4)	25 (15.7)	0.017
FVC, %	99.4 (22.6)	96.1 (26.2)	103 (17.4)	0.011
FEV1, %	81.7 (31.4)	69.8 (32.1)	93.2 (26)	<0.001
FEV1/FVC, %	65 (19)	57 (19)	72 (18)	<0.001
KCO, %	76.8 (23.4)	67.6 (22.5)	84.7 (20.8)	<0.001
Augmentation therapy (%)	114 (28.9)	95 (54)	13 (8.2)	0.001
AAT (mg/dL)	44.5 (24.4)	24.9 (17.6)	56.7 (11.8)	<0.001
Exacerbations previous year	0.44 (1)	0.66 (1.2)	0.28 (0.8)	<0.001
History of pneumonia (%)	77 (19.3)	44 (24.6)	21 (13.1)	0.007
CAT	7.4 (7.2)	9.4 (7.8)	5.6 (6.2)	<0.001
BODEx	1.2 (1.8)	1.8 (2)	0.6 (1.3)	<0.001

Variables	ZZ (n=146)	SZ (n=82)	p value
Age, years	58.6 (12.3)	57.6 (17.2)	0.692
Sex, male (%)	75 (51.4)	47 (57.8)	0.386
BMI (kg/m)	26.4 (4.8)	27.6 (5.3)	0.067
Smokers (%)	2 (1.4)	14 (17.1)	
Ex-smokers (%)	105 (71.9)	48 (58.5)	<0.001
Never smokers (%)	39 (26.7)	20 (24.4)	
Tobacco Exposure (Pack-years)	18.8 (9.7)	20.7 (13.5)	0.460
COPD (%)	108 (74)	42 (51.2)	0.001
Emphysema (%)	107 (73.3)	40 (48.8)	<0.001
Bronchiectasis (%)	38 (39.7)	16 (19.5)	0.002
Asthma (%)	24 (16.4)	22 (26.8)	0.061

Footnote: BMI: Body mass index; COPD: Chronic obstructive pulmonary disease; AATD: Alpha-1 antitrypsin deficiency; FVC: Forced vital capacity; FEV1: Forced expiratory volume in 1 second; KCO: Carbon monoxide transfer coefficient; AAT: Alpha-1 antitrypsin deficiency; CAT: COPD assessment test; BODEx: Body mass index, obstruction, dyspnoea, exacerbations index; Cardiovascular disease includes hypertension, ischaemic heart disease, congestive heart failure and peripheral vascular disease.

Table 2. Comparison of demographic and clinical characteristics of the participants in the Spanish registry of EARCO with chronic lung disease and PI*ZZ and PI*SZ genotypes.

Liver disease (%)	17 (11.8)	8 (9.8)	0.637
Age at onset of symptoms	45.6 (15)	49.9 (18.1)	0.008
Age at diagnosis of AATD	47.4 (14.9)	52.5 (18)	0.003
Index case (%)	25 (17.1)	15 (18.3)	0.824
Family screening (%)	21 (14.4)	12 (14.6)	0.959
Charlson index (*age corrected)*	3.5 (1.9)	4 (2.2)	0.105
Cardiovascular comorbidity (%)	43 (30.1)	22 (28.2)	0.771
FVC (%)	93.4 (26.6)	100.4 (20.7)	0.046
FEV1 (%)	61.1 (28.2)	78.7 (28.5)	<0.001
FEV1/FVC (%)	51 (17)	62 (19)	<0.001
KCO (%)	62.9 (20.6)	84.7 (20.8)	<0.001
Augmentation therapy (%)	94 (66.2)	12 (15.4)	<0.001
AAT (mg/dL)	25.8 (19.4)	57.5 (12.2)	<0.001
Exacerbations previous year	0.80 (1.3)	0.43 (1)	0.018
History of pneumonia (%)	39 (26.9)	10 (12.7)	0.014
CAT	10.9 (7.9)	8.6 (7)	0.036
BODEx	2.2 (2.1)	1.1 (1.7)	<0.001

Footnote: BMI: Body mass index; COPD: Chronic obstructive pulmonary disease; AATD: Alpha-1 antitrypsin deficiency; FVC: Forced vital capacity; FEV1: Forced expiratory volume in 1 second; KCO: Carbon monoxide transfer coefficient; AAT: Alpha-1 antitrypsin deficiency; BODEx: Body mass index, obstruction, dyspnoea and exacerbations index; CAT: COPD assessment test; BODEx: Body mass index, obstruction, dyspnoea, exacerbations index; Cardiovascular disease includes hypertension, ischaemic heart disease, congestive heart failure and peripheral vascular disease.

Table 3. Demographic and clinical characteristics of the participants in the Spanish registry of EARCO with different pulmonary diseases.

Footnote: The different subgroups are not mutually exclusive. BMI: Body mass index;

Variables	Emphysema (n=163)	Bronchiectasis (n=83)	Asthma (n=55)
Age, years	61.2 (11.7)	62.5 (11.5)	45.8 (16.4)
Sex, male (%)	96 (58.9)	41 (49.4)	24 (43.6)
BMI (kg/m^2)	26.7 (5.1)	26.8 (4.4)	26.4 (5.3)
Smokers (%)	11 (6.7)	4 (4.8)	6 (10.9)
Ex-smokers (%)	129 (79.1)	52 (62.7)	25 (45.5)
Never smokers (%)	23 (14.1)	27 (32.5)	24 (43.6)
Tobacco Exposure (Pack-years)	29.4 (22.5)	25.5 (22)	18.7 (19)
COPD (%)	128 (78.5)	53 (63.9)	14 (25.5)
Emphysema (%)	163 (100)	53 (63.9)	13 (23.6)
Bronchiectasis (%)	53 (32.5)	83 (100)	8 (14.5)
Asthma (%)	13 (8)	8 (9.6)	55 (100)
Liver disease (%)	18 (11.2)	8 (9.6)	5 (9.1)
Age at onset of symptoms	48.7 (15.4)	48.7 (14.9)	31.4 (17.3)
Age at diagnosis of AATD	51.7 (14.1)	52.9 (12.9)	38.8 (19)
Index case (%)	139 (85.3)	75 (90.4)	41 (74.5)
Family screening (%)	21 (12.9)	8 (9.6)	10 (18.2)
Charlson index (*age corrected)*	3.9 (1.7)	3.9 (1.6)	2.3 (2.1)
Cardiovascular comorbidity (%)	58 (36.7)	28 (34.1)	9 (17)
FVC (%)	94.3 (27.7)	90.7 (25.5)	101 (4)
FEV1 (%)	59.6 (27.5)	67.7 (28.7)	86.3 (27.9)
FEV1/FVC (%)	49 (15)	58 (16)	69 (17)
KCO (%)	60.9 (19.9)	70.4 (21.7)	81.8 (20.9)
Augmentation therapy (%)	95 (59.7)	38 (47.5)	8 (16)
AAT (mg/dL)	38.2 (26.9)	37.4 (22.3)	45.8 (21.9)
Exacerbations previous year	0.7 (1.2)	0.7 (1.3)	0.5 (1.2)
History of pneumonia (%)	34 (21)	27 (32.5)	12 (23.1)
CAT	11.5 (7.7)	11 (7.8)	7 (6.4)
BODEx	2.3 (2)	1.7 (2)	1 (1.5)

COPD: Chronic obstructive pulmonary disease; AATD: Alpha-1 antitrypsin deficiency; FVC: Forced vital capacity; FEV1: Forced expiratory volume in 1 second; KCO: Carbon monoxide transfer coefficient; AAT: Alpha-1 antitrypsin deficiency; BODEx: Body mass index, obstruction, dyspnoea and exacerbations index; CAT: COPD assessment test; BODEx: Body mass index, obstruction, dyspnoea, exacerbations index; Cardiovascular disease includes hypertension, ischaemic heart disease, congestive heart failure and peripheral vascular disease.

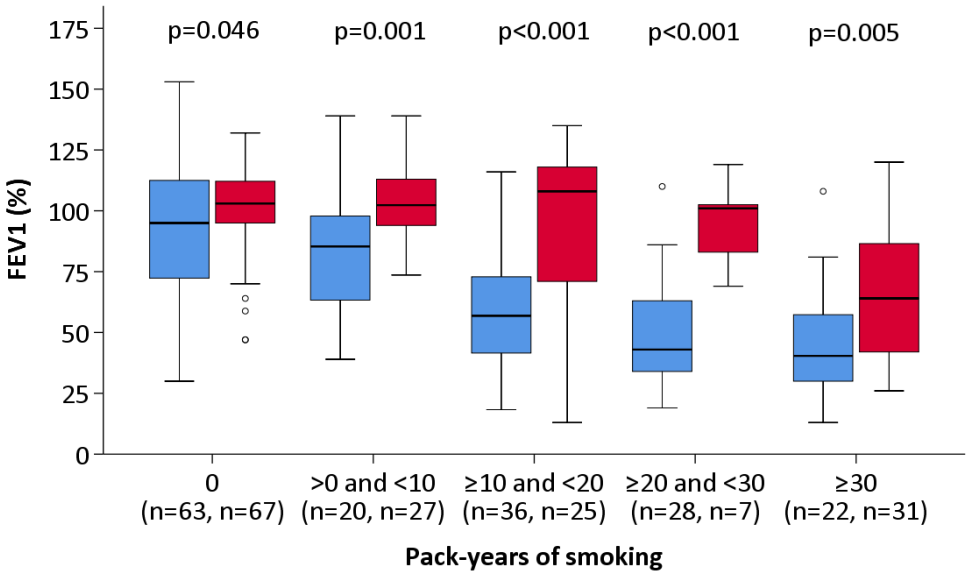
FIGURES

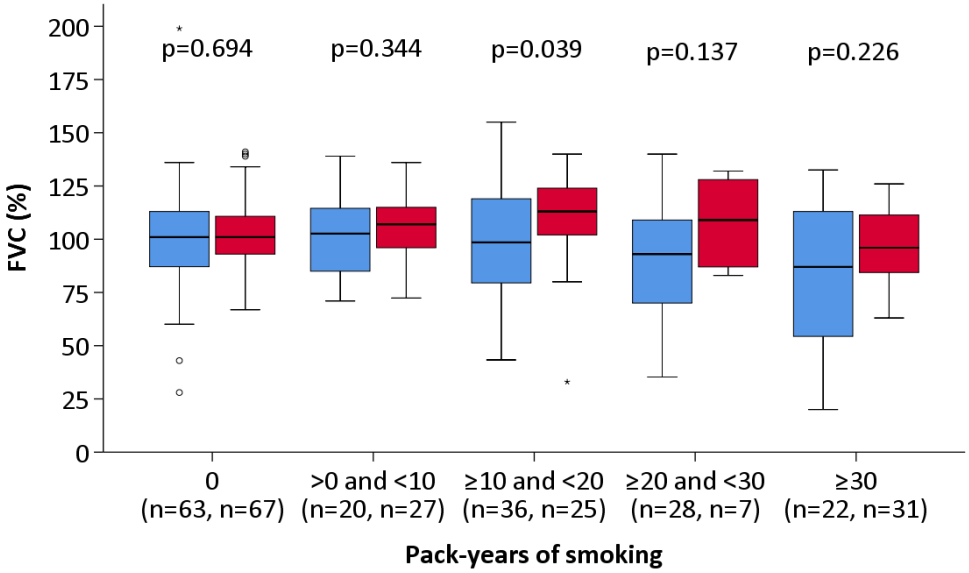
Figure 1. Comparison of FEV1(%) (1A), FVC (1B) and FEV1/FVC (1C) values of participants in the Spanish registry with the PI*ZZ and PI*SZ genotypes.

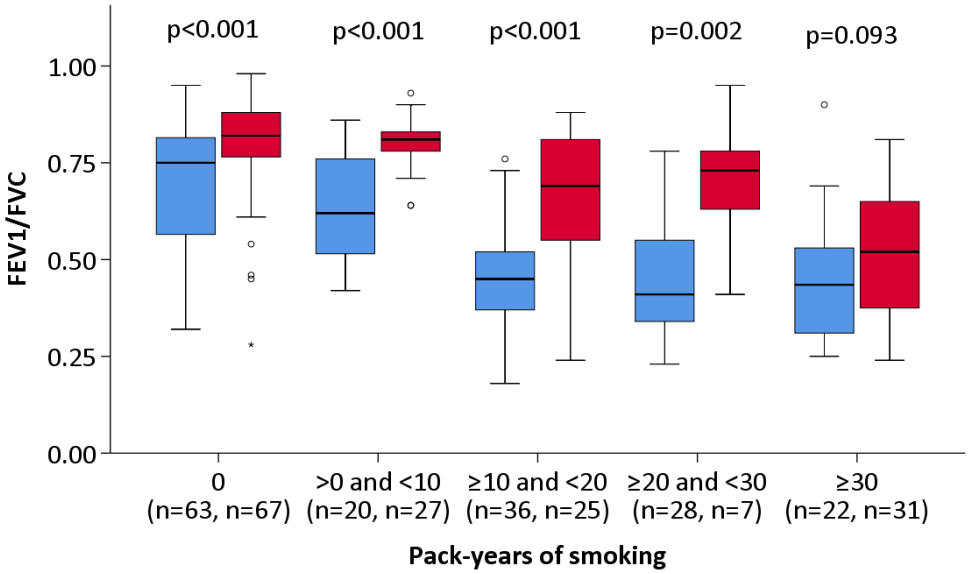
Footnote: Blue box plots represent the PI*ZZ and red box plots the PI*SZ genotypes. In each blox plot, the median value is indicated by the centre horizontal line, and the 25th and 75th percentiles are indicated by the lower and upper box horizontal lines. Circles on the high end indicate the outliers. P values according to the Student's T Test. There was a statistically significant difference between pack-years of smoking groups for FEV1(%) and FEV1/FVC for both PI*ZZ genotype (p for trend < 0.001) and PI*SZ genotype (p for trend < 0.001). For FVC(%) the p for trend was p=0.004 for PI*ZZ and p=0.29 for PI*SZ.

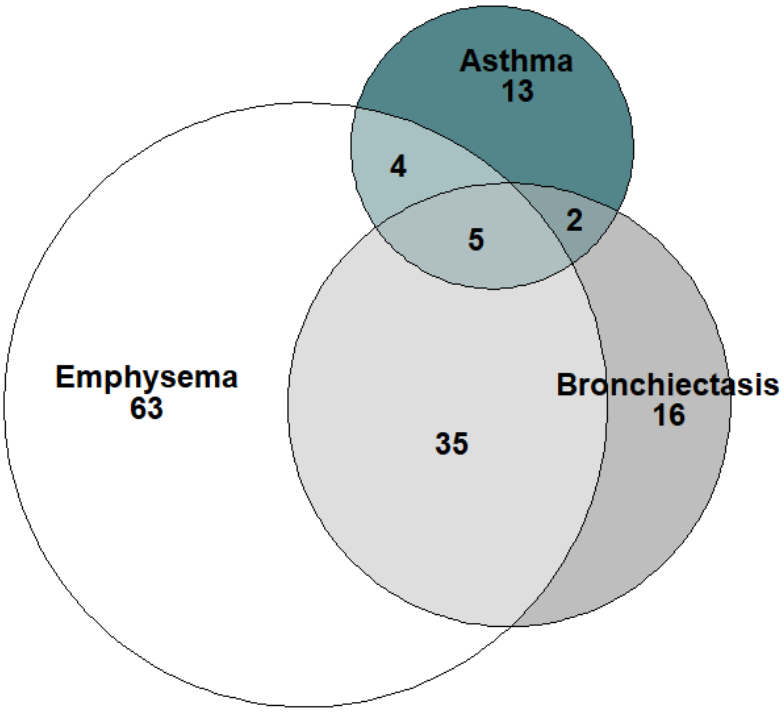
Figure 2. Distribution of lung diseases in participants of the Spanish registry with the PI*ZZ (2A) and PI*SZ genotypes (2B).

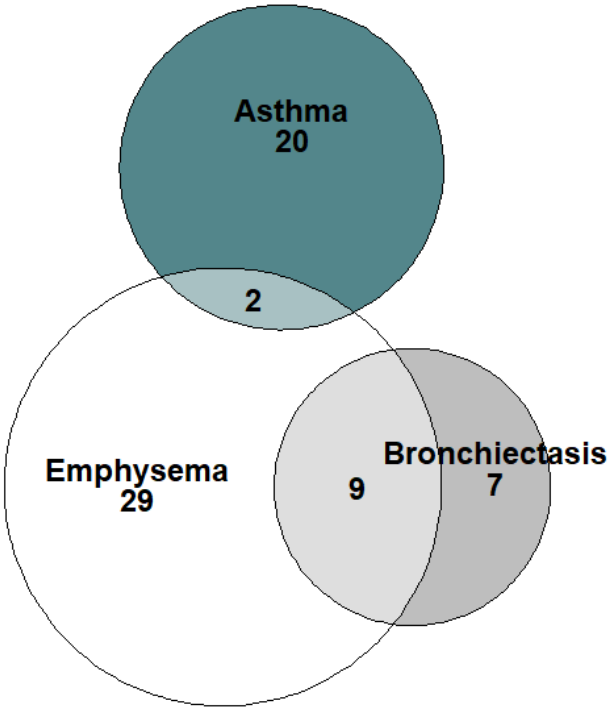
Footnote: The size of each circle is proportional to the number of individuals in each group


p=0.046
p=0.001
p<0.001
p<0.001
p=0.005
FEV1 (%)
175
150
125
100
75
50
25
0
0 (n=63, n=67)
>0 and <10 (n=20, n=27)
≥10 and <20 (n=36, n=25)
≥20 and <30 (n=28, n=7)
≥30 (n=22, n=31)
Pack-years of smoking


p=0.694
p=0.344
p=0.039
p=0.137
p=0.226
FVC (%)
200
175
150
125
100
75
50
25
0
0 (n=63, n=67)
>0 and <10 (n=20, n=27)
≥10 and <20 (n=36, n=25)
≥20 and <30 (n=28, n=7)
≥30 (n=22, n=31)
Pack-years of smoking


p<0.001
p<0.001
p<0.001
p=0.002
p=0.093
FEV1/FVC
1.00
0.75
0.50
0.25
0.00
0 (n=63, n=67)
>0 and <10 (n=20, n=27)
≥10 and <20 (n=36, n=25)
≥20 and <30 (n=28, n=7)
≥30 (n=22, n=31)
Pack-years of smoking


Asthma
13
4
2
5
Emphysema
63
Bronchiectasis
16
35


Asthma
20
2
Emphysema
29
Bronchiectasis
9
7