Clinical phenotypes of Italian and Spanish patients with α1-antitrypsin deficiency

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ABSTRACT   With the aim of providing better clinical characterisation of patients with α1-antitrypsin deficiency (AATD), we analysed the data of adult patients with severe AATD enrolled in the Spanish and Italian national registries.

We assessed 745 subjects, 416 of whom were enrolled in the Spanish registry and 329 in the Italian registry. 57.2% were male and 64.9% were smokers or former smokers with a mean±SD age of 49.9±13.8 years. Most (81.2%) were index cases, mainly having the PI*ZZ genotype (73.4%), and the mean±SD diagnostic delay was 9.0±12.1 years.

Patients with chronic bronchitis were younger, had better preserved lung function and lower tobacco consumption. Overlap patients (chronic obstructive pulmonary disease with asthma) were mainly females, more frequently never-smokers and received respiratory medications more often. 48% of emphysema, 27.5% of chronic bronchitis and 44.8% of overlap subjects were receiving augmentation therapy. Compared with PI*ZZ patients (n=547), the PI*SZ (n=124) subjects were older at diagnosis and had more preserved lung function, despite a higher mean smoking consumption.

Early diagnosis of AATD is still an unmet need. Augmentation therapy is administered to similar proportions of patients with different clinical phenotypes. PI*ZZ patients in both registries had more severe respiratory disease than those with PI*SZ, despite lower smoking levels.

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Introduction

Hereditary α_1-antitrypsin deficiency (AATD) is a rare condition associated with an increased risk of pulmonary and hepatic disease. This condition is inherited as an autosomal codominant condition and is characterised by reduced α_1-antitrypsin (α_1-AT) serum levels [1, 2], affecting approximately one in 2000–5000 individuals [3, 4].

There are >120 biochemical genetic variants of α_1-AT, which are classified into three major categories: 1) normal, with genotype M, characterised by α_1-AT within normal ranges; 2) deficient, characterised by reduced but detectable α_1-AT plasma levels with genotypes Z, S and M-like; and 3) null, currently designated Q0, with no detectable plasma levels [5, 6]. The main target of α_1-AT is neutrophil elastase, which is irreversibly bound and inactivated during a process that consumes the α_1-AT molecules as well [1].

The condition was first recognised in 1963 [7] and, as for other rare diseases, the difficulties in the diagnosis and management of these patients soon promoted the creation of different national registries [8, 9]. After a World Health Organization meeting [10] in 1997, the Alpha One International Registry (AIR) was founded in order to establish an international patient database and to encourage research and promote knowledge of the disease [11]. Despite the improvements achieved since then, the diagnosis of AATD is often delayed [12] and this time lag may affect the prognosis of affected individuals.

With the aim of better describing the clinical manifestations of patients with AATD, we compared the characteristics of patients from two large national registries and evaluated the differential aspects of individuals with different α_1-AT genotypes and clinical phenotypes.

Methods

This was an observational study in patients with severe AATD enrolled in the Spanish (Registro Español de Pacientes con Déficit de α_1-antitripsina (REDAAT)) and Italian (Registro Italiano per la Carenza Severa di α_1-antitripsina) national registries. The objectives of the study were: 1) to analyse the differences in the clinical and demographic characteristics of patients in both countries; 2) to compare index and nonindex cases; 3) to describe the characteristics of PI*ZZ patients with chronic obstructive pulmonary disease (COPD) according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) severity classes [13]; 4) to characterise the different clinical phenotypes of PI*ZZ patients with COPD: predominant emphysema, chronic bronchitis and overlap with asthma; and 5) to investigate the relationship between smoking consumption and impairment in lung function for PI*ZZ and PI*SZ subjects.

Participants and registries

We assessed AATD patients aged ⩾18 years enrolled in the REDAAT or the Italian registry of AATD from June 1993 to November 2011. REDAAT was founded in 1993 and became a part of AIR in 1999 [8, 14, 15]. This registry consists of an online questionnaire, which was first included in the website of the Sociedad Española de Neumología y Cirugía Torácica, and is now found on its own website (www.redaat.es) [14]. The criteria for inclusion are the presence of severe AATD (α_1-AT plasma concentrations <30% of the normal value) and being the carrier of a PI*ZZ genotype, PI*SZ genotype or some other rare deficient phenotypic variants of the deficiency [8, 14]. After a log-in procedure every accredited physician may access the system in order to enrol new patients or update the database. The database is registered at the Spanish Official Agency of Data Protection and has been accredited as a ''certified medical website'' by the College of Physicians of Barcelona (Collegi Oficial de Metges de Barcelona). Quality control of the data is regularly performed by the REDAAT coordinators.

The Italian registry of AATD was established in 1996 and became a member of AIR in 1999 [16]. Its inclusion criteria are the presence of severe α_1-AT deficiency, defined by the carriage of the PI*ZZ genotype, PI*SZ genotype or another rare severe deficient genotypic variant. The data are collected on forms sent by post or e-mail to the Italian Centre for diagnosis of AATD in Pavia, Italy, where the coordinators update the database.

Laboratory diagnosis of AATD

Laboratory diagnosis of AATD was performed in the two central laboratories in Barcelona (Spain) and Pavia (Italy), according to current diagnostic standards. These standards imply a flow chart that includes nephelometric plasma level, isoelectric focusing, rapid genotype and coding region sequencing, if needed. Both programmes use the dried blood spot method of blood collection and shipment. Technical details have been described elsewhere [17, 18]. Although similar in the main aspects (initial decision based on α_1-AT plasma level and genotyping for Z and S alleles), the algorithms used in Spain and in Italy have slight differences, which have recently been analysed [19]. All subjects entering the diagnostic procedure gave their written informed consent.

Data management and definitions

Since both national registries are members of AIR the same database is used, thereby allowing comparisons of the data collected [9]. The data analysed included demographical and physical information, smoking habits, reason for α$_1$-AT dosage and genotype, general and pneumological medical history, radiological features, pneumological and augmentation treatment, pulmonary function tests, liver function tests and quality-of-life assessment, as well as information related to the patient's work-life and death.

Both databases were first assessed for quality control and the frequency of missing data, then all the information included was coded in order to create a unique database. As a high-risk population, all subjects diagnosed with COPD, emphysema or chronic bronchitis by the registering physician or whose spirometry showed a post-bronchodilator forced expiratory volume in 1 s (FEV1) to forced vital capacity ratio of <70% were considered to have COPD. Diagnostic delay was calculated as the difference in years between the age at diagnosis and the age at symptom onset. All subjects diagnosed through familial screening were considered to be nonindex cases.

For the classification of clinical phenotypes, we used the reported respiratory diagnosis in the database provided by the physicians in charge of the patients (mainly respiratory specialists). Emphysema was considered when no other respiratory diagnosis was mentioned (n=267), with the same being performed for chronic bronchitis (n=40). The diagnosis of overlap asthma–COPD was based on the reporting of asthma together with either emphysema or chronic bronchitis (n=29).

The severity of COPD was based on the GOLD spirometric severity criteria [11]: I (mild) FEV1 ⩾80% predicted; II (moderate) FEV1 ⩾50–80% pred; III (severe) FEV1 ⩾30–50% pred; and IV (very severe) FEV1 <30% pred. For the objectives of the analysis, all patients with a clinical diagnosis of COPD, emphysema or chronic bronchitis by the attending physician were also included in the mildest category, even if spirometry did not show airflow obstruction.

Statistical analyses

Categorical variables were described by frequencies and percentages and compared using the Chi-squared test or Fisher's exact test when appropriate. Continuous variables were expressed as mean±SD and compared between groups using the t-test or one-way ANOVA where appropriate. All *post hoc* comparisons were made with the Bonferroni correction for multiple comparisons. Pearson's correlation analysis was performed to determine the relationship between continuous variables. The association between FEV1 (% pred) and pack-years in patients with the PI*ZZ and PI*SZ genotypes was studied by means of a logarithmic regression model. Data were processed using SPSS 17.0 (IBM SPSS, Inc., Chicago, IL, USA). The level of significance was set at 0.05 (two-tailed).

Results

Population characteristics of the Spanish and Italian patients

A total of 745 subjects was available in both databases, with 416 enrolled in the REDAAT and 329 in the Italian Registry. Of these, 426 (57.2%) subjects were male, the mean age at enrolment was 49.9±13.8 years and 483 (64.9%) subjects were active or former smokers, with a mean tobacco consumption of 23.4±17.7 pack-years. Dyspnoea was the principal symptom reported and the mean age at symptom onset was 39±14.8 years. The mean age at diagnosis was 47±14.7 years; therefore, the mean diagnostic delay was 9.0±12.1 years. Pulmonary disease was referred in 80.4% of all subjects and 72.5% were diagnosed with COPD. Respiratory medications were taken by 456 (61.2%) subjects, 13.2% needed oxygen therapy and 256 (34.4%) subjects were receiving augmentation treatment (table 1).

In the Spanish database there was a higher predominance of males (60.8% *versus* 52.6%; p<0.05), former smokers (60.8% *versus* 48.9%; p<0.01) and higher tobacco consumption (26.7 *versus* 19.2 pack-years; p<0.001) compared with Italian patients. The reasons for the diagnosis of AATD and the diagnotic delay were similar between the groups, even if Spanish patients were younger at symptom onset (36.9 years *versus* 43.5 years; p<0.001) and at diagnosis (45.4 years *versus* 49 years; p<0.01). Pulmonary diseases were more prevalent in the Spanish group (table 1). Despite a similar mean FEV1 % pred, there was a higher rate of use of respiratory medications in the Spanish registry (72.1% *versus* 47.4%; p<0.001). The frequency of rare alleles was higher in the Italian registry (18.5% *versus* 2.9%; p<0.001). The frequency of augmentation therapy was similar in the two countries (table 1).

Differential characteristics between index and nonindex cases

Patients diagnosed due to respiratory symptoms (index cases) were more frequently male and significantly older at inclusion and at the time of diagnosis (48.1±14.5 years *versus* 41.7±14.5 years). In general, the

TABLE 1 Clinical characteristics in patients with severe α₁-antitrypsin deficiency (AATD), stratified by the country of origin

	Global	Spain	Italy	p-value
Subjects	745	416	329	
Age years	49.9±13.8	50.5±13	49.1±14.6	
BMI kg·m⁻²	25.3±4.1	25.3±4.1	NR	
Male	426 (57.2)	253 (60.8)	173 (52.6)	*
Smoking				
Current	69 (9.3)	30 (7.2)	39 (11.9)	*
Former	414 (55.6)	253 (60.8)	161 (48.9)	**
Never	253 (34)	127 (30.5)	126 (38.3)	*
Missing	9 (1.2)	6 (1.4)	3 (0.9)	
Pack-years	23.4±17.7	26.7±19.1	19.2±15.2	***
AATD diagnosis				
Reason				
Lung disease	487 (65.4)	278 (66.8)	209 (63.5)	
Liver disease	62 (8.3)	35 (8.4)	27 (8.2)	
Family screening	138 (18.5)	75 (18)	63 (19.1)	
Other	56 (7.5)	26 (6.3)	30 (9.1)	
Phenotype				
Z	547 (73.4)	327 (78.6)	220 (66.9)	***
SZ	124 (16.6)	76 (18.3)	48 (14.6)	
Other	73 (9.8)	12 (2.9)	61 (18.5)	***
Age at diagnosis years	47±14.7	45.4±14.6	49±14.5	**
Main symptom dyspnoea	403 (54.1)	251 (60.3)	152 (45.9)	***
Age at symptom onset years	39±14.8	36.9±14.9	43.5±13.6	***
Diagnostic delay years	9.03±12.1	9.4±13.7	8.12±7.4	
Lung disease	599 (80.4)	365 (87.7)	234 (71.1)	***
Chronic bronchitis	181 (24.3)	150 (36.1)	31 (9.4)	***
Emphysema	427 (57.3)	276 (66.6)	151 (45.9)	***
Asthma	84 (11.3)	66 (15.9)	18 (5.5)	***
Bronchiectasis	126 (16.9)	113 (27.2)	13 (4)	***
COPD	540 (72.5)	317 (76.2)	223 (67.8)	*
Other	46 (6.2)	32 (7.7)	14 (4.3)	
Recurrent pneumonia	157 (21.1)	89 (21.4)	68 (20.7)	
Respiratory medication	456 (61.2)	300 (72.1)	156 (47.4)	***
Oxygen therapy	98 (13.2)	54 (13)	44 (13.4)	
Augmentation therapy	256 (34.4)	155 (37.3)	101 (30.7)	
Pulmonary function	709	401	311	
FEV1 L·s⁻¹	2.1±1.2	2±1.1	2.2±1.3	
FEV1 % pred	67.8±34.8	67.5±33.9	68.3±36.1	
FVC L	3.4±1.2	3.3±1.2	3.4±1.3	
FVC % pred	84.4±25.7	79.5±23	90.21±27.6	***
FEV1/FVC %	59.4±20	59±18.9	59.9±21.3	

Data are presented as n, mean±SD or n (%), unless otherwise stated. BMI: body mass index; NR: not reported; COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in 1 s; % pred: % predicted; FVC: forced vital capacity. *: $p<0.05$; **: $p<0.01$; ***: $p<0.001$.

prevalence of respiratory symptoms and respiratory diseases was lower in nonindex compared with index cases and their lung function parameters were significantly better preserved (table 2).

Comparison among GOLD stages

The PI*ZZ subjects diagnosed with COPD (n=412) were compared according to GOLD severity stages (table 3). To avoid variability generated by the different α₁-AT phenotypes, PI*SZ individuals were excluded from this analysis and the comparison of clinical phenotypes below. The mean age was similar in groups I, III and IV, but subjects in group II were older. In GOLD stage I patients and among patients with nonobstructive spirometry, females and nonindex cases prevailed. The percentage of never-smokers significantly decreased with the increase in the severity of COPD (from 55.7% in GOLD stage I to 11.4% in GOLD stage IV; $p<0.001$). The groups showed a similar age at symptom onset and a similar diagnostic delay. Cases of asthma and bronchiectasis were homogenously distributed among groups. Augmentation therapy was administered to 19.4% of GOLD stage I, 48.4% of GOLD stage II, 58.9% of GOLD stage III and 50.7% of GOLD stage IV patients.

TABLE 2 Clinical characteristics of patients with severe α1-antitrypsin deficiency (AATD), stratified by index and nonindex cases

	Index	Nonindex	p-value
Subjects	607	138	
Age years	50.9 ± 13.6	45.3 ± 13.7	***
BMI kg·m^{-2}	25.3 ± 4.2	25.5 ± 3.7	
Sex			***
Male	372 (61.3)	54 (39.1)	
Female	235 (38.7)	84 (60.9)	
Smoking			
Current	49 (8.2)	20 (14.7)	*
Former	367 (61.2)	47 (34.6)	***
Never	184 (30.7)	69 (50.7)	***
Pack-years	24.6 ± 18.3	15.1 ± 11.4	***
Country			
Spain	341 (56.2)	75 (54.3)	
Italy	266 (43.8)	63 (45.7)	
AATD diagnosis			
Age at diagnosis years	48.1 ± 14.5	41.7 ± 14.5	***
Phenotype			
Z	448 (73.8)	99 (71.7)	
SZ	94 (15.5)	30 (21.7)	
Other	64 (10.6)	9 (6.5)	
Lung disease	514 (85.1)	85 (62)	***
Chronic bronchitis	162 (27.5)	19 (14)	**
Emphysema	386 (62.5)	41 (30.1)	***
Asthma	62 (10.5)	22 (16.2)	
Bronchiectasis	109 (18.5)	17 (12.6)	
COPD	475 (78.3)	65 (47.1)	***
Other	43 (8.2)	3 (2.6)	
Symptoms			
Dyspnoea	361 (69)	42 (46.2)	***
Cough	81 (15.5)	16 (17.6)	
Other	11 (2.1)	2 (2.2)	
Asymptomatic	70 (13.4)	31 (34.1)	***
Age at symptom onset years	39.4 ± 14.7	35.9 ± 15.6	
Diagnostic delay years	9.5 ± 12	4.8 ± 13	**
Pneumonia	146 (24.1)	11 (8)	***
Respiratory medication	411 (74.1)	45 (36.6)	***
Oxygen therapy	94 (17.5)	4 (3.5)	***
Augmentation therapy	233 (38.4)	23 (16.7)	***
Pulmonary function	576	135	
FEV1 L·s^{-1}	1.9 ± 1.1	2.9 ± 1.2	***
FEV1 % pred	61.7 ± 32.5	94.5 ± 32	***
FVC L	3.2 ± 1.2	3.9 ± 1.3	***
FVC % pred	80.4 ± 24.7	101.1 ± 23.3	***
FEV1/FVC %	56.4 ± 19.6	72 ± 16.4	***

Data are presented as n, mean $\pm$ SD or n (%) unless otherwise stated. BMI: body mass index; COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in 1 s; % pred: % predicted; FVC: forced vital capacity. *: $p < 0.05$; **: $p < 0.01$ ***: $p < 0.001$.

Comparison among clinical phenotypes

We compared the subjects with emphysema (n=267), chronic bronchitis (n=40) and subjects with an overlap with asthma (n=29). Their general characteristics are summarised in table 4.

Patients with chronic bronchitis were younger, had more preserved lung function and lower tobacco consumption (17.3 ± 10.8 pack-years), despite the higher number of current smokers (25%). Overlap patients were mainly females (55.2%), were more frequently never-smokers (37.9%) and more often received respiratory medications (96.6%). Augmentation treatment was taken by 47.9% of the subjects with emphysema, 27.5% of those with chronic bronchitis and 44.8% of overlap subjects.

TABLE 3 Clinical characteristics of PI*ZZ homozygotes stratified by Global Initiative for Chronic Obstructive Lung Disease (GOLD) status

	GOLD I	GOLD II	GOLD III	GOLD IV	p-value
Subjects	62	128	151	71	
Age years	50.3±15.7	54.9±11	51.4±10	50.3±9.8	*
BMI$^{\#}$ kg·m^{-2}	24.5±4.4	25.3±3.5	25.1±4.1	23.6±4.1	
Male	25 (40.3)	66 (51.6)	100 (66.2)	58 (81.7)	***
Smoking					***
Current	10 (16.4)	13 (10.2)	9 (6)	5 (7.1)	
Former	17 (27.9)	76 (59.4)	121 (80.1)	57 (81.4)	
Never	34 (55.7)	39 (30.5)	21 (13.9)	8 (11.4)	
Pack-years	12.6±14.2	21±14.4	24.3±13.5	26.4±16.7	**
Reason for AATD diagnosis					
Lung disease	27 (44.3)	103 (80.5)	136 (90.1)	67 (94.4)	
Liver disease	7 (11.5)	1 (3.1)	4 (2.6)	0 (0)	
Family screening	23 (37.7)	17 (13.3)	11 (7.3)	4 (5.6)	
Other	4 (6.6)	4 (3.1)	0 (0)	0 (0)	
Age at diagnosis years	44.8±17.8	51.7±12.3	48.8±10.1	47.7±9.7	**
Main symptom dyspnoea %	46.41	74.8	79.9	77.1	
Age at symptom onset years	37.8±18.4	40.9±12.6	39.9±12.1	37.5±11.1	
Diagnostic delay years	9.9±17.8	9.5±13.7	8.1±9.4	9.5±9.3	
Lung disease					
Chronic bronchitis	15 (24.2)	49 (38.3)	56 (37.1)	16 (22.5)	*
Asthma	10 (16.1)	15 (11.7)	15 (10)	3 (4.2)	
Emphysema	41 (66.1)	101 (78.9)	127 (84.1)	61 (85.9)	*
Bronchiectasis	14 (23.3)	33 (25.8)	34 (22.5)	10 (14.1)	
Others	6 (12.8)	3 (3)	16 (12.2)	4 (6.3)	
Pneumonia	12 (19.4)	38 (29.7)	38 (25.2)	19 (26.8)	
Respiratory medication	32 (52.5)	107 (88.4)	131 (92.9)	64 (98.5)	***
Oxygen therapy	3 (5.4)	12 (10.3)	30 (21.3)	24 (37.5)	***
Augmentation therapy	12 (19.4)	62 (48.4)	89 (58.9)	36 (50.7)	***
Pulmonary function					***
FEV1 L·s^{-1}	2.8±0.8	1.8±0.5	1.2±0.3	0.8±0.2	***
FEV1 % pred	98.7±16.3	62.7±8.3	36.9±5.7	23.4±4	***
FVC L	3.9±1	3.3±1.2	3±1	2.3±0.9	***
FVC % pred	104.8±15.7	86.6±18.2	71.7±18.2	50.7±15.6	***
FEV1/FVC %	71.1±11.1	55.2±110.8	43.6±10.6	36.9±9	***

Values are given as n, mean±SD or n (%), unless otherwise stated. BMI: body mass index; AATD: α$_1$-antitrypsin deficiency; FEV1: forced expiratory volume in 1 s; % pred: % predicted; FVC: forced vital capacity. $^{\#}$: not available for patients from the Italian registry. *: $p<0.05$; **: $p<0.01$; ***: $p<0.001$.

Comparison between α$_1$-AT genotypes

A total of 547 (73.4%) subjects carried the PI*ZZ genotype and 124 (16.6%) the PI*SZ. The groups were similar in age, body mass index and sex distribution. The PI*SZ subjects were older at the time of diagnosis, less symptomatic and had a lower prevalence of lung disease compared to those with PI*ZZ. They also had more preserved lung function (mean FEV1 89.9% *versus* 63.2% for PI*ZZ; $p<0.001$). Respiratory medications were more frequent among PI*ZZ subjects (66.2% *versus* 41.9%; $p<0.001$) and the rate of augmentation therapy was higher in this group (39.7% *versus* 8.1%) (table 5).

We observed a significant association between FEV1 % pred and pack-years in patients with the PI*ZZ genotype ($R^2=0.26$; $p<0.001$) as well as in patients with the PI*SZ genotype ($R^2=0.32$; $p<0.001$) (fig. 1).

Discussion

Research on rare diseases is hampered by the difficulties in collecting enough individuals for clinical and epidemiological studies. The World Health Organization has acknowledged the need for large population-based registries of AATD in order to foster basic and clinical investigations as well as to conduct clinical trials of new treatments [10]. Registries provide a unique opportunity to compare large enough populations from different countries to explore the characteristics of patients and the patterns of medical care. In this study, we compared the characteristics of Spanish and Italian patients included in their national registries.

TABLE 4 Clinical characteristics of PI*ZZ homozygotes, stratified by obstructive lung disease phenotype

	Emphysema	Chronic bronchitis	Asthma overlap	p-value
Subjects	267	40	29	
Age years	53 $\pm$ 11.3	47.7 $\pm$ 14.3	51.9 $\pm$ 12.8	*
BMI# kg·m^{-2}	24.6 $\pm$ 3.6	24.5 $\pm$ 4.1	27.1 $\pm$ 5.4	*
Male	174 (65.2)	19 (47.5)	13 (44.8)	*
Smoking				***
Current	19 (7.1)	10 (25)	1 (3.4)	
Former	192 (72.2)	16 (40)	17 (58.6)	
Never	55 (20.7)	14 (35)	11 (37.9)	
Pack-years	23.7 $\pm$ 15.6	17.3 $\pm$ 10.8	24.9 $\pm$ 18.3	
Reason for AATD diagnosis				
Lung disease	277 (85)	29 (74.4)	25 (86.2)	
Liver disease	7 (2.6)	1 (2.6)	2 (6.9)	
Family screening	26 (9.7)	3 (7.7)	2 (6.9)	
Other	7 (2.6)	3 (7.7)	0 (0)	
Genotype				*
Z	210 (78.9)	25 (62.5)	22 (75.9)	
SZ	20 (7.5)	6 (15)	6 (20.7)	
Other	36 (13.5)	9 (22.5)	1 (3.4)	
Age at diagnosis years	50.4 $\pm$ 12.3	46.3 $\pm$ 14.2	49.8 $\pm$ 15.8	
Main symptoms dyspnoea	204 (80.6)	16 (45.7)	25 (89.3)	
Age at symptom onset years	40.6 $\pm$ 13.5	39.1 $\pm$ 14.8	37.6 $\pm$ 13.3	
Diagnostic delay years	9.5 $\pm$ 13.4	6.2 $\pm$ 6.1	10 $\pm$ 12.9	
Bronchiectasis	40 (15.1)	9 (22.5)	5 (17.9)	
Pneumonia	69 (25.8)	11 (27.4)	4 (13.8)	
Respiratory medication	210 (84.7)	17 (50)	28 (96.6)	***
Oxygen therapy	58 (23.4)	0 (0)	6 (20.7)	**
Augmentation treatment	128 (47.9)	11 (27.5)	13 (44.8)	
Pulmonary function				
FEV1 L·s^{-1}	1.5 $\pm$ 0.8	2.3 $\pm$ 1.1	1.5 $\pm$ 0.7	***
FEV1 % pred	49.6 $\pm$ 25.6	72.9 $\pm$ 31.8	55.4 $\pm$ 23.8	***
FVC L	3.1 $\pm$ 1.2	3.4 $\pm$ 1.1	2.9 $\pm$ 1.2	
FVC % pred	76.8 $\pm$ 24.7	87.9 $\pm$ 21.1	75.9 $\pm$ 26.1	*
FEV1/FVC %	47.9 $\pm$ 14.9	66.1 $\pm$ 18.1	55 $\pm$ 17.8	***

Data are presented as n, mean $\pm$ SD or n (%), unless otherwise stated. BMI: body mass index; AATD: α_1-antitrypsin deficiency; FEV1: forced expiratory volume in 1 s; % pred: % predicted; FVC: forced vital capacity. #: not available for patients from the Italian registry. *: p<0.05; **: p<0.01; ***: p<0.001.

Since both registries are included in the AIR [11], they share the same database, thereby allowing direct comparisons of data and pooling of data for further analysis.

The characteristics of the patients were somewhat different to those described 15 years ago for the large National Heart, Lung and Blood Institute (NHLBI) Registry in the USA [20]. The mean age in the USA registry was 46 years, 55.5% were males and the mean FEV1 was 46.7% pred, compared with 49.7 years, 56.9% males and a mean FEV1 of 63.2% pred in our series. This difference in mean FEV1 % pred indicates the larger number of nonindex cases in our study, which may be a positive consequence of the family screening programmes developed in both Spain and Italy [16, 18].

Spanish patients were significantly younger at the onset of symptoms and diagnosis; however, the diagnostic delay did not significantly differ between the two countries. Diagnostic delay continues to be an important hurdle to achieve appropriate care of patients with AATD. In the USA there was an improvement in the length of diagnostic delay from 7.2 years in 1994 to 5.6 years in 2003 [21], similar to the 6-year delay observed in Germany and Austria [22]. Unfortunately, the situation in Spain and Italy is worse with a mean delay of 9 years. More awareness campaigns are needed, especially among primary care physicians who care for most patients with COPD, particularly in early stages of the disease [23]. Another interesting difference is the higher prevalence of rare genotypes in Italy compared with Spain, which is in accordance with previous reports [24, 25] and could be related to the differences between the two nationwide diagnostic algorithms [19]. A list of the rare genotypes reported in the two registries is available as online supplementary material.

TABLE 5 Clinical characteristics stratified by α₁-antitrypsin genotype

	ZZ	SZ	p-value
Subjects	547	124	
Age years	49.7 ± 13.4	51.1 ± 16.2	
BMI# kg·m⁻²	25 ± 4	26.1 ± 4.2	
Male	311 (56.9)	67 (54)	
Smoking			
Current	49 (9)	13 (10.5)	
Former	311 (56.9)	57 (46)	*
Never	179 (32.7)	53 (42.7)	*
Missing	8 (1.5)	1 (0.8)	
Pack-years	21.6 ± 15	34 ± 27.5	***
Reason for AATD diagnosis			
Lung disease	381 (69.7)	57 (46)	***
Liver disease	36 (6.6)	22 (17.7)	***
Family screening	99 (18.1)	30 (24.2)	
Other	29 (5.3)	15 (12.1)	*
Age at diagnosis years	46.3 ± 14.3	49.5 ± 16.7	*
Main symptom dyspnoea	316 (57.8)	42 (33.9)	***
Age at symptom onset years	38.6 ± 13.8	41.3 ± 20.1	
Diagnostic delay years	9.1 ± 12.1	9.5 ± 13.3	
Lung disease	466 (85.2)	76 (61.3)	***
Chronic bronchitis	142 (26)	28 (22.6)	
Emphysema	345 (63.1)	42 (33.9)	***
Asthma	60 (11)	22 (17.7)	
Bronchiectasis	104 (19)	16 (12.9)	
COPD	429 (78.4)	54 (43.5)	***
Other	32 (5.8)	10 (8.1)	
Recurrent pneumonia	122 (22.3)	19 (15.3)	
Respiratory medication	362 (66.2)	52 (41.9)	***
Oxygen therapy	71 (13)	14 (11.3)	
Augmentation treatment	217 (39.7)	10 (8.1)	***
Pulmonary function	523	117	
FEV1 L·s⁻¹	1.9 ± 1.1	2.7 ± 1.3	***
FEV1 % pred	63.2 ± 32.4	89.9 ± 36.2	***
FVC L	3.3 ± 1.2	3.6 ± 1.3	*
FVC % pred	82.7 ± 25	91.4 ± 26.7	**
FEV1/FVC %	56.6 ± 19.2	71.8 ± 18.2	***

Data are presented as n, mean ± SD or n (%), unless otherwise stated. BMI: body mass index; AATD: α₁-antitrypsin deficiency; FEV1: forced expiratory volume in 1 s; % pred: % predicted; FVC: forced vital capacity. #: not available for patients from the Italian registry. *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$.

When patients with criteria for COPD were analysed, we observed that the mean age was very similar across all the GOLD severity stages from I to IV. In contrast, as the severity of COPD increased, the proportion of males and ever smokers also rose. The prevalence of other respiratory conditions, such as bronchiectasis or episodes of pneumonia, was not related to the severity of COPD. Up to 19.4% of the patients in the GOLD I severity group were receiving augmentation therapy, although guidelines do not recommend the initiation of therapy in individuals with preserved lung function [2, 26, 27]. Similarly, in the NHLBI registry 11% of patients with FEV1 >80% pred were receiving augmentation therapy [20]. It is important to consider that nonindex cases without augmentation therapy may have the same survival as the general population if they do not smoke [28].

According to the predominance of symptoms, AATD is a very heterogeneous disease [29], and patients may be classified into different clinical phenotypes [30, 31]. Most of the patients were classified by their physicians as having pulmonary emphysema, whereas a smaller number presented a predominance of other phenotypes. 9% had also been diagnosed with asthma, which has been described as an overlap COPD–asthma phenotype [32]. This 9% is somewhat lower than the 13% of overlap phenotype described in the COPDGene cohort composed of COPD smokers [32]. Compared to other series of patients with AATD, the percentage found in our study is much lower than the 31% of prevalence of asthma in the NHLBI registry [20] and the 38.6% reported in the Alpha One Foundation Research Network Registry [9]. Our patients
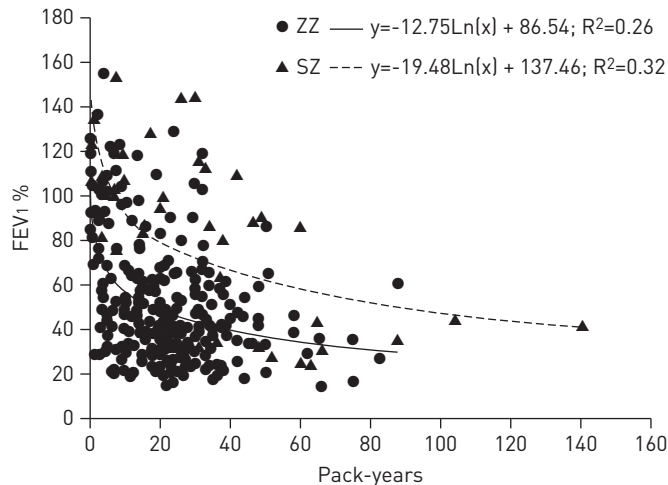
FIGURE 1 Logarithmic regression model of forced expiratory volume in 1 s (FEV1) % predicted and pack-years of smoking for Pi*ZZ and Pi*SZ individuals included in the Spanish and Italian registries.

with overlap COPD–asthma were more frequently female, never-smokers; the mean age at diagnosis was 37.6 years and 45% were under augmentation therapy.

The prevalence of bronchiectasis in our series was 16.9%, being higher in Spain (27.2%) than in Italy (4%). It is not possible to ascertain whether this difference is real or due to the different frequency of assessment of patients using computed tomography (CT). Interestingly, in a well-characterised series of patients with AATD studied using CT scans, PARR *et al.* [33] found exactly the same 27% prevalence of clinically significant bronchiectasis as that in the Spanish cohort. Patients with bronchiectasis had a greater impairment in physiology and health status [33], underlining the importance of the identification of bronchiectasis in this population. The identification of clinical phenotypes may have an impact in the selection of respiratory medications [34].

There is controversy about the susceptibility of the protease inhibitor SZ genotype (PI*SZ) to develop pulmonary emphysema. A meta-analysis of case–control and cohort studies suggested that patients with PI*SZ have an odds ratio of 3.26 (95% CI 1.24–8.57) for the development of COPD [35]. However, if one unusually positive study is discounted [36], no increased risk was observed. In an attempt to investigate their natural history, the AIR also included Pi*SZ individuals [11]. We observed that PI*SZ subjects had more preserved lung function, despite a higher mean smoking consumption, which is in agreement with previous studies describing less emphysema on CT scans and less abnormal respiratory physiology test results in PI*SZ compared with matched subjects with PI*ZZ [37]. On plotting the smoking consumption with the FEV1 % pred in both groups of individuals with PI*SZ and PI*ZZ, we observed the same type of curve, demonstrating a significant relationship between a higher smoking consumption and a lower FEV1 % pred for the two genotypes. However, the curve of PI*SZ individuals was displaced by 20–30%, meaning that for any given quantity of smoking consumption a PI*SZ subject had an FEV1 % pred that was between 20% and 30% better than a Pi*ZZ subject. If we bear in mind the marked difference in confidence intervals of α₁-AT serum level values in PI*ZZ and PI*SZ individuals [38], this would further support the concept that the risk for lung impairment is inversely related to serum α₁-AT levels. Another interesting observation from the curve was that the impact of smoking is greater at the beginning of the habit. There was steeper decline in lung function with the first 20 pack-years of smoking compared with consequent consumption for both genotypes. It is possible that a survivor effect accounted for the mild decline in FEV1 % pred at the end of the curve, but it is difficult to accept a significant survivor effect influencing the results obtained at the beginning of the curve at low levels of smoking, when the curve is steeper. These results highlight the importance of early identification of subjects with AATD, particularly at an age when they have not started smoking. Family screening is one of the best strategies to detect early cases and prevent the evolution of the disease by vigorous counselling against smoking.

The indication of augmentation therapy in PI*SZ is not clear [2, 26]; however, 8% of our PI*SZ subjects were on augmentation (mean FEV1 58.8% pred). It is not possible to ascertain which criteria were used for starting therapy in this particular subgroup. Augmentation therapy is a limited and expensive resource and must be prescribed under strict criteria based on the best evidence available. The observation of augmentation therapy in patients with the PI*SZ genotype and in patients with normal lung function requires further investigation.

Data derived from large AATD registries have provided information about different aspects of the disease, including its natural course [20, 39]. However, no information on the characteristics of COPD and its different clinical phenotypes in AATD individuals has been available. The current data provide new information that helps to better characterise patients with this rare disease [40].

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