Universitat Autònoma de Barcelona

LONGITUDINAL STUDY ON THE DIAGNOSIS AND TREATMENT OF COPD AND ALPHA-•ONE ANTITRYPSIN DEFICIENCY IN CATALONIA

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TESIS DOCTORAL

LONGITUDINAL STUDY ON THE DIAGNOSIS AND TREATMENT OF COPD AND ALPHA-ONE ANTITRYPSIN DEFICIENCY IN CATALONIA

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BARCELONA, 2016

A mis padres

Index

PRESENTATION

This doctoral thesis aims to extend the knowledge of the management of COPD in Primary Care in Catalonia.

The study focuses on the treatment patterns of newly-diagnosed COPD patients and their adherence to current guidelines and also provides in depth knowledge of the screening of alpha-1 antitrypsin deficiency.

The presentation of this doctoral thesis is done as a compendium of publications according to the regulations of the Autonomous University of Barcelona (UAB).

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LIST OF ABBREVIATIONS

ACOS	Asthma-COPD Overlap Syndrome
AAT	Alpha-1 antitrypsin
AATD	Alpha-1 antitrypsin deficiency
BMI	Body Mass Index
COPD	Chronic obstructive pulmonary disease
CT	Computed Tomography
DBS	Dried blood spots
DM	Diabetes Mellitus
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
ICS	Inhaled corticosteroids
IQR	Inter quartile range
LABA	Long-acting β2 agonists
LABD	Long-acting bronchodilators
LAMA	Long-acting antimuscarinics
OSA	Obstructive Sleep Apnea
PC	Primary Care
PDE4	Phosphodiesterase-4
Pi	Protease inhibitor
RCT	Randomized clinical trial
SABA	Short-acting bronchodilators
SABD	Short-acting β2 agonists
SAMA	Short-acting antimuscarinics

SIDIAP	System for the Development of Research in Primary Care
WHO	World Health Organization

INDEX OF TABLES AND FIGURES

Tables:

Figures:

1. INTRODUCTION

1. INTRODUCTION

1.1. Chronic obstructive pulmonary disease

1.1.1. Definition and Diagnosis

Chronic obstructive pulmonary disease (COPD) is a respiratory disease characterized by a non fully reversible airflow obstruction. This airflow limitation is progressive and related to an abnormal response of the lungs to noxious particles and gases, primarily tobacco smoke[1].

The main symptoms of the disease are dyspnea, cough and sputum production. The presence of exacerbations and related comorbidities are also common during the natural history of the disease.

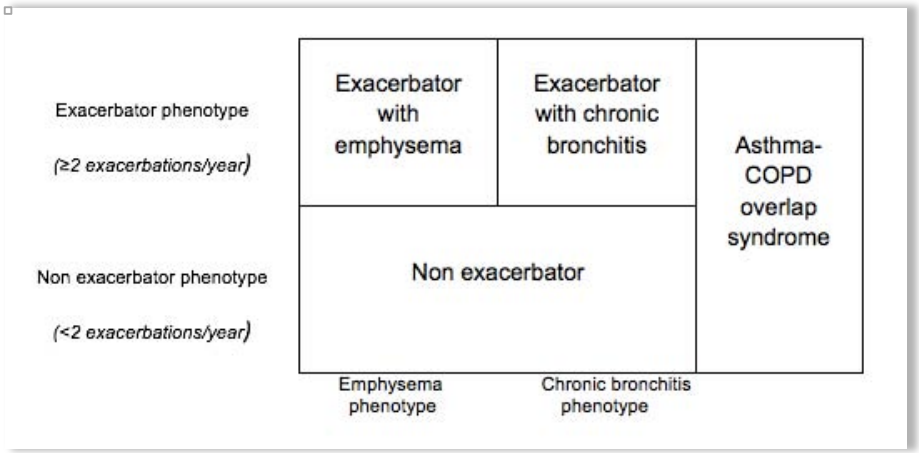

Figure 1. GesEPOC COPD phenotypes. Adapted from Miravitlles et al. [2]

COPD should be ruled out in every individual with a history of smoking older than 40 years of age who presents with respiratory symptoms such as cough or shortness of breath. Diagnosis of the disease should be confirmed by spirometry: a **forced expiratory volume in one second** (FEV1) to **forced**

vital capacity (FVC) ratio post bronchodilator < 0.7 demonstrates chonic airflow obstruction[1].

Airflow obstruction measured by the FEV1 is used to define the grade of severity of the disease. However, COPD is very heterogeneous and can not be described based on only one measure. To better describe COPD patients, the Spanish Guideline of COPD (GesEPOC) defines four clinical phenotypes aiming to identify subgroups with prognostic value and to determine the most accurate treatment for each subgroup[2]. These clinical phenotypes are: the **asthma-COPD overlap syndrome** (ACOS), exacerbators with emphysema, exacerbators with chronic bronchitis and non exacerbators (Figure 1). In this guideline, frequent exacerbator patients are defined by two or more exacerbations in the previous year, whilst ACOS patients are identified based on the presence of some major and minor criteria. To be diagnosed with ACOS a patient must fulfil two major criteria or one major and two minor criteria (Table 1).

Major criteria
Positive post-bronchodilator test with an increase of FEV_1 >15% and >400 ml
FENO > 40 ppb
Personal history of asthma
Minor criteria
Elevated IgE in blood
Personal history of atopy
Positive post-bronchodilator test with an increase of FEV_1 > 12% and >200 ml in at least 2 different measurements

Table 1. Major and minor criteria to establish a diagnosis of ACOS. Adapted from Soler-Cataluña et al.[3] FeNO: Fraction of exhaled nitric oxide; ppb: parts per billion.

1.1.2. Epidemiology

Prevalence

The **World Health Organization** (WHO) estimates that up to 328 million people around the world have COPD with a global prevalence of 1%[4]. This prevalence increases to 8-10% for individuals above 40 years old[5]. In Europe, the results of a systematic review showed that the prevalence of COPD varies from 2.1% to 26.1% depending on the country, the definition used and the population groups studied[6]. A study conducted in Spain in 1997 observed a prevalence of COPD in individuals between 40 and 69 years old of 9.1% (14.3% in men and 3.9% in women)[7]. More recently, the EPI-SCAN study raised this prevalence to 10.2% in individuals between 40 and 80 years old (15.1% in men and 5.7% in women)[8]. Both studies described a remarkable underdiagnosis of the disease, being of up to 73% in the EPI-SCAN study[9].

Mortality and disease burden

COPD is the third leading cause of mortality worldwide after ischemic heart disease and cerebral vascular disease, with a mortality rate for COPD adjusted for the global population in 2008 of 449.22 in men and 238.47 in women[10]. Mortality rates vary widely among the different countries in Europe and surprisingly, there was a trend to a fall in COPD mortality between 1994 and 2010, with a marked reduction in the mortality rates in men (from 90.07 deaths/100,000 inhabitants to 61.33 deaths/100,000 inhabitants)[11]. In Spain, the mortality rate adjusted by age decreased for both genders.

COPD has a high economic burden, both in the utilization of health resources and in the loss of quality of life. Respiratory diseases generate 6% of the costs of health resources in Europe, and more than half are due to COPD. In Spain the costs related to COPD are 759-1000 million Euros/year (between 1712 and 3228 Euros/year per patient)[12].

1.1.3. Etiology

Tobacco smoking

Exposure to tobacco smoking is the most important risk factor for the development of COPD and also the most studied to date. Prospective cohort studies have estimated a risk to develop COPD in smokers of 25-30%[13]. The risk is proportional to accumulated tobacco consumption and can increase to 51% in smokers of more than 30 packs-year[9]. Although smoking cessation reduces the slope of FEV1 loss, baseline values are never recovered (Figure 2).

Observational studies have shown that the involuntary inhalation of the tobacco smoke, known as passive smoking, is also a risk factor to develop COPD[14-16].

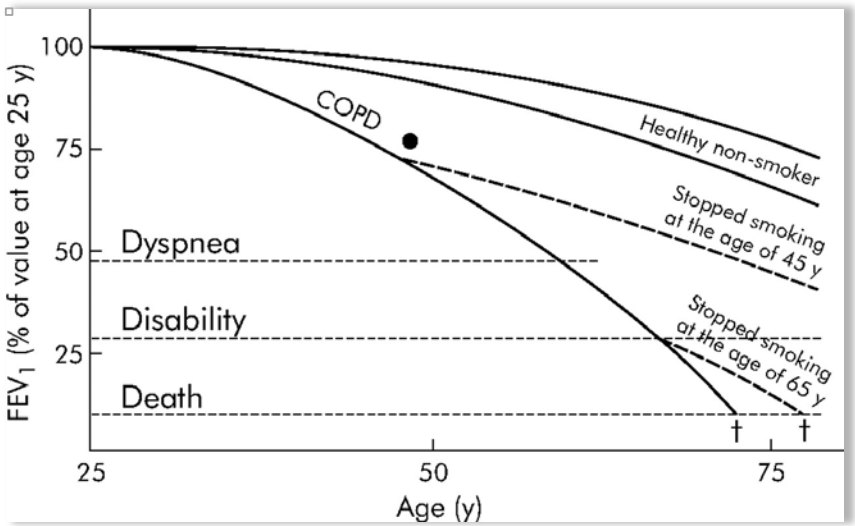

Figure 2. Evolution of COPD based on smoking history. Adapted from Fletcher C and Peto R[17]

Biomass smoking

Biomass is organic matter that can be used as a source of energy, such as wood, charcoal or manure. Some epidemiological studies have demonstrated

an association between the inhalation of smoke obtained from the combustion of biomass and COPD[18,19].

This proportion is higher in underdeveloped countries but can also be found in rural areas of developed countries. Although some authors have found that biomass can be the cause of COPD in almost one quarter of the patients[20], a recent cross sectional study showed that in Spain only 2.6% of the COPD cases are related to biomass exposure[21].

Other risk factors

Occupational exposure to dust (organic or inorganic), chemical agents and toxic smoke can contribute to the development of COPD[21-23].

Congenital AATD predisposes to the development of emphysema in the presence of other risk factors such as tobacco smoking[24]. A previous history of tuberculosis is also related to COPD[25]. Conversely, high levels of ambiental contamination are noxious for individuals with lung diseases but are not considered to be a relevant risk factor of COPD.

1.1.4 Management of the COPD patient: healthcare pathways

The Spanish National Health System provides universal health coverage for every individual. This service is centralized by **Primary Care** (PC) physicians, who are the first and main contact with the health system and also act as a filter of access to more complex services. COPD is diagnosed mostly in PC, and due to its high prevalence the patient if also often managed in the PC setting. Severe or complicated patients are referred to a pneumologist for further evaluation. Referrals are mostly made from PC, but sometimes COPD patients access pneumology clinics through the emergency departments.

In most of the Spanish regions coordination between primary and tertiary care has been established, mainly through protocols, committees, and clinical and teaching sessions.

Even when a patient is managed in a tertiary level of care, the PC physician is usually the only medical professional allowed to prescribe long term prescriptions and therefore, treatments prescribed by a pneumologist must be validated afterwards in PC.

In Catalonia, all the general practitioners in the Catalan Health Institute use the same specific software called ECAP to record the clinical information of their patients.To facilitate multidisciplinary management, this information is accessible by the different specialists whilst also allowing PC physicians to review the specialists' notes.

1.1.5. COPD treatment based on GesEPOC

The main objectives of pharmacological treatment of COPD are: to reduce the chronic symptoms of the disease, to reduce the frequency and severity of exacerbations and to improve the prognosis of the disease[1,26]. Besides pharmacological treatment, there are some general measures that should be implemented in every patient such as smoking cessation, physical activity, an adequate nutrition, management of comorbidities and vaccination[26].

Inhaled bronchodilators

The cornerstones of the treatment of COPD patients are **long-acting bronchodilators** (LABD). There are two classes of LABD: **long-acting beta-2 adrenergics** (LABA) and **long-acting muscarínic antagonists** (LAMA). LABD allow a better control of respiratory symptoms, help to reduce the frequency of exacerbations and improve lung function and quality of life[27-29]. They have a direct impact on the exercise capacity by reducing dynamic hyperinflation and improving cardiac function[30].

Short-acting bronchodilators (SABD; **short-acting beta-2 adrenergics**, SABA, and **short-acting muscarínic antagonists**, SAMA) are used in patients with intermittent symptoms or as a rescue therapy; there is no indication to use SABD as a maintenance treatment in the COPD patient.

For patients that remain symptomatic or have exercise limitations in spite of treatment, the alternative choice is the combination of two bronchodilators with a different mechanism of action (LABA+LAMA). The combination of two LABD improves lung function, dyspnea and quality of life compared to one LABD in monotherapy, without significantly increasing possible adverse events[31-33]. A recent **randomized clinical trial** (RCT) has also showed that a combination of two LABD can reduce the number of exacerbations compared to a LABA and **inhaled corticosteroids** (ICS) in COPD patients with at least one exacerbation the previous year[34].

Inhaled corticosteroids

Treatment with ICS is beneficial in COPD patients with frequent exacerbations despite optimal bronchodilator therapy, although benefits in terms of a reduction in mortality have not been demonstrated[35]. More recent studies have shown that treatment with ICS improves symptoms and is more efficient in preventing exacerbations in patients with a high peripheral eosinophil count[36].

Others

Other treatments can be added to the inhaled therapy to optimize results.

Roflumilast is an oral phosphodiesterase-4 inhibitor (PDE-4) with anti-inflammatory effect that reduces the number of exacerbations in patients with severe COPD, symptoms of chronic bronchitis and frequent exacerbations[37]. During the first 4 weeks, adverse events such as weight loss of gastrointestinal effects are common.

The administration of long term high dose N-acetylcysteine has shown to reduce the number of exacerbations and improve the quality of life of patients with COPD, although evidence of its efficacy is modest[38].

Long term macrolides at low doses have shown to reduce the number of exacerbations in severe COPD patients with frequent exacerbations and multiple previous treatments with antibiotics or hospital admission. Due to the risk of side effects and increase of bacterial resistance, this treatment is reserved for very selected cases under close supervision in reference centers[39-40].

Theophylline is a less effective bronchodilator with an additive effect to other inhaled bronchodilators. Its toxicity is dose-dependent and theophylline levels should be monitored when administered long term.
COPD patients with chronic hypoxemia may benefit from the use of long term oxygen therapy[41].

Non pharmacological treatment includes respiratory rehabilitation. A systematic review showed that respiratory rehabilitation improves muscular strength and resistance, exercise capacity, dyspnea and quality of life[42]. Respiratory rehabilitation is recommended in COPD patients with dyspnea ≥2 of the modified Medical Research Council dyspnea scale, deconditioning or poor tolerance to exercise capacity.

Finally, every active smoker COPD patient should be encouraged to stop smoking. Smoking cessation measures include cognitive behavioral therapy and pharmacological treatment. Specific guidelines have been published for smoking cessation in patients with COPD[43].

Pharmacological treatment by COPD phenotypes

Nowadays, the tendency in treatment recommendations in COPD guidelines is to adapt treatment to the patient characteristics or phenotype.

Non exacerbator phenotype
Patients with this phenotype are treated with LABD alone or in combination. There is not enough evidence to recommend the use of LAMA over LABA in

these patients. There is no indication for the use of anti-inflammatory drugs in patients with this phenotype.

Exacerbator with emphysema

The main goal of treatment in patients with frequent exacerbations is the prevention of these episodes. Long-acting bronchodilators (LAMA and LABA) have demonstrated to reduce exacerbations; but LAMA have shown to be more effective than LABA in the prevention of exacerbations[44,45]. Therefore, GesEPOC recommends the use of LAMA in monotherapy in the less severe or symptomatic patients. In the next step, the combination of LABA/LAMA has shown to be more effective compared to LAMA in monotherapy in preventing exacerbations, particularly mild and moderate, in patients with poor lung function and at least one exacerbation during the previous year[46].

When LABD are insufficient to control symptoms and exacerbations, the use of anti-inflammatory drugs is recommended. A combination of LABA/ICS has shown to decrease the rate of exacerbations in COPD patients compared with LABA alone[47].

Exacerbators with chronic bronchitis

In patients with COPD and chronic bronchitis, other anti-inflammatories in addition to ICS can provide benefits. Roflumilast has shown to reduce exacerbations in patients with chronic bronchitis. In patients with contraindications or intolerance to any of the previous drugs, high dose N-acetylcysteine can be used as second line treatment. In patients with severe COPD and frequent bacterial exacerbations despite optimal bronchodilator and anti-inflammatory therapy, the use of long term macrolides has demonstrated to reduce the rate of exacerbations[39].

Phenotypes	Severity			
	I	II	III	IV
Non Exacerbator	LAMA or LABA	LAMA or LABA	LAMA + LABA	LAMA + LABA + theophylline
	SABA or SAMA	LAMA + LABA		
ACOS	LABA + ICS	LABA + ICS	LABA + LAMA + ICS	LABA + LAMA + ICS
Exacerbator with emphysema	LAMA or LABA	LABA + ICS	LABA + LAMA + ICS	LABA + LAMA + ICS (theophylline can be added)
		LAMA + LABA		
		LAMA or LABA		
Exacerbator with chronic bronchitis	LAMA or LABA	LABA + ICS	LABA + LAMA + (ICS or IPE4)	LABA + LAMA + (ICS or IPE4)
		LAMA + LABA	(LAMA or LABA) + ICS + IPE4	LABA + LAMA + ICS + IPE4 (carbocisteine can be added)
		LAMA or LABA		Theophylline
		(LAMA or LABA) + IPE4		Antibiotics

Table 2. Pharmacological treatment of COPD base don phenotypes and severity. Adapted from Miravitlles et al (2).

Asthma-COPD overlap syndrome

Patients with ACOS have been excluded from pharmacologic clinical trials for not being pure asthma or COPD patients. Consequently, there is no clear information about the response of these patients to the therapies currently available. Some studies have demonstrated that patients with COPD and eosinophilic inflammation treated with ICS present a significant improvement in bronchial inflammation with clinical and spirometric improvement. Two small, randomized trials have demonstrated that the prescription of corticosteroids (oral or inhaled) according to the intensity of bronchial eosinophilic inflammation in patients with COPD was significantly superior in preventing exacerbations and improving health-related quality of life compared with the prescription of ICS according to the current guidelines[48,49]. Therefore, ACOS patients should be treated with ICS combined with LABA from early stages of the disease. More severe patients can be treated with triple therapy with LAMA+LABA/ICS.

1.2. Alpha one antitrypsin deficiency

1.2.1. Definition

Alpha-1 antitrypsin deficiency (AATD) is a genetic condition that is associated with low levels of **alpha-1 antitrypsin** (AAT) and predisposes to the development of certain diseases, mainly liver diseases (including neonatal cholestasis, juvenile hepatitis, cirrhosis in children and adults, and carcinoma) and pulmonary emphysema. Emphysema secondary to AATD is the most common congenital life-threatening disease in adult life. AATD is an underdiagnosed condition and is usually detected in advanced stages of pulmonary disease[24].

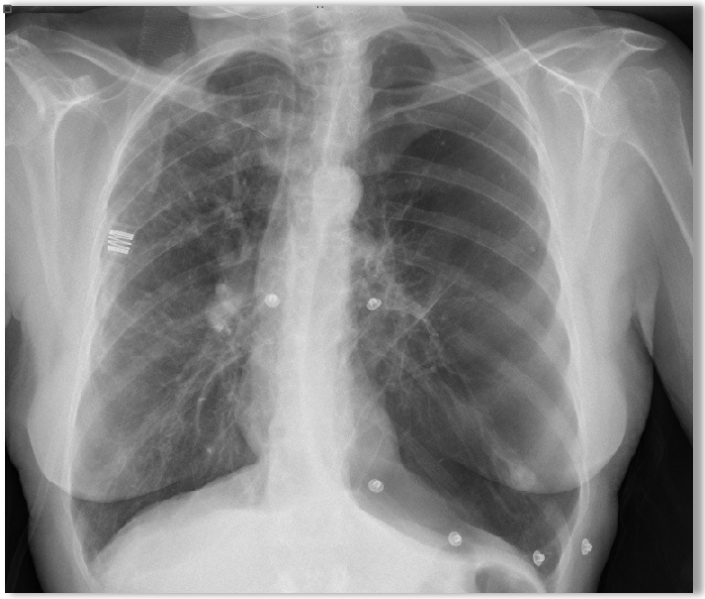

Figure 3. Chest radiography showing emphysema in a patient with AATD

The AAT gene is transmitted by simple autosomal codominant inheritance. The gene is located in chromosome 14 and is characterised by its high polymorphism. More than 100 variants have been identified, 30 of which are

of clinical significance[50]. The group of variants is known as the Pi (**protease inhibitor**) system. The normal allele, present in 85-90% of normal individuals, is called PiM. The most common deficient alleles are PiS and PiZ, which are present in 10% and 2% of the population, respectively[50]. These alleles codify abnormal proteins that polymerize in the liver and only a small percentage of the protein reaches the bloodstream. Liver disease is caused by accumulation of this intrahepatic polymer and emphysema develops as a result of insufficient AAT concentrations in blood and lung tissue to protect the lungs (Figure 4).

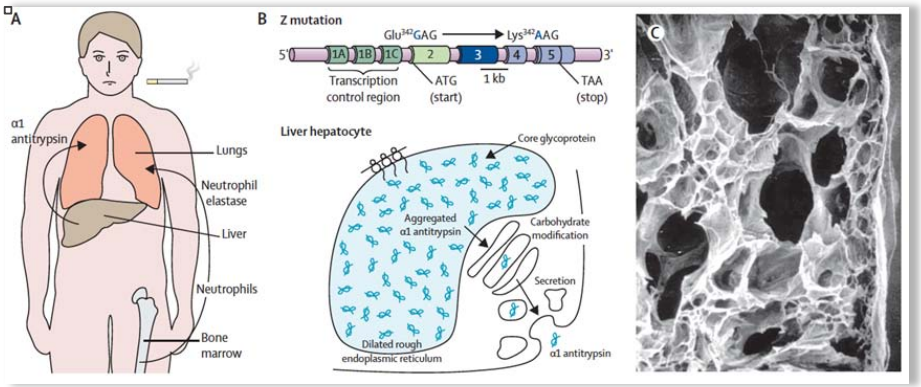

Figure 4. Clinical manifestations of AATD. Adapted from Crystal et al[51]

1.2.2. Epidemiology

The prevalence of AATD has been estimated from some large population studies. In a Swedish study that screened all newborns from 1972–1974, the authors found a prevalence of 1 in 1,600 among the 200,000 newborns tested[52].

In Europe there is a high variation in the prevalence of the Z allele among countries. This allele is more frequent in the northwest of the continent while the S allele is more prevalent in the Iberian Peninsula. In Spain the prevalence of the S and Z alleles is 104 per 1000 inhabitants and 17 per 1000 inhabitants, respectively, and it has been estimated that there may be 12,000 ZZ and

436,000 SZ individuals[53]. A recent review of the information gathered in the Spaish Registry of AATD (REDAAT) showed that only 511 deficient individuals had been diagnosed to date, 348 of whom were homozygotes for the Z allele[54]. These numbers highlight the significant underdiagnosis of AATD.

1.2.3. Clinical evolution and natural history

Although AATD predisposes to the development of certain diseases, in clinical practice this risk is limited to the phenotypes ZZ and less frequently to the phenotypes SZ, rare deficient variants and null phenotypes[50].

Infants and children may develop liver diseases, but respiratory symptoms rarely appear in individuals younger than 25 years of age. Up to 60% of ZZ individuals may develop chronic airflow obstruction[50] and tobacco smoke is the most important risk factor and also a key element in the natural history of the disease[55]. In smokers with AATD, respiratory symptoms appear between 35-40 years of age while in non smokers the onset can take place one decade later[56]. Both mortality and FEV loss are directly influenced by the tobacco consumed[57]. Therefore, the importance of early diagnosis lays in the opportunity to quit smoking, which is determinant in the prognosis of the disease, and the possibility to start early specific treatment if needed.

1.2.4. Diagnosis

AATD should be suspected in the presence of several clinical presentations, such as a young adult with respiratory symptoms or individuals with emphysema. Moreover, the WHO recommends the testing of all COPD patients[58]. AATD is sometimes diagnosed due to a history of liver disease or family studies (Table 3).

The diagnosis can be made by the determination of AAT levels in serum. This test is not expensive and is accessible at all levels of care, and yet it is not widely used. There is a generalized lack of knowledge in the medical community regarding AATD and how to diagnose it, and this, in part, determines the high level of underdiagnosis of the disease.

Since PC physicians attend most COPD patients, and this is usually the first point of contact of patients with health care providers, several screening initiatives have been previously developed in PC, with modest results[59]. However, the initial diagnosis can be suspected with the determination of AAT in serum by nephelometry, a test that is readily accessible in most

Patients with chronic obstructive pulmonary disease
Adults with bronchiectasis
Patients with partially reversible adult asthma
Blood relatives of individuals with known AAT deficiency
Dyspnea and chronic cough in many members of the same family
Liver disease of unknown cause
Reduction in the α_1 protein peak in the proteinogram

Table 3. Candidates for AAT determination. Adapted from Vidal et al[60].

clinical laboratories and a very reduced cost, making it widely available in PC in Spain. The complete algorithm of diagnosis of AATD includes phenotyping by iso electrophocusing and genotyping[60].

1.2.5. Treatment

The treatment of patients with emphysema due to AATD must include all the pharmacological and non pharmacological measures considered to be effective for the treatment of COPD as described previously. Since 1987 a purified preparation of AAT from donor plasma is available for intravenous administration[60].The aim of this treatment is to raise AAT levels in plasma and lung tissue to thereby prevent the destruction of the lung and to slow the progression of emphysema.

Augmentation therapy has demonstrated to have biochemical efficacy for achieving and maintaining AAT levels in both blood and lung tissue[62]. Large observational studies have shown that patients treated with augmentation therapy have a slower decline in FEV1 and a reduction in mortality compared to those not receiving this treatment[61,62]. Placebo-controlled RCT using lung density measured by **computed tomography** (CT) as the primary outcome showed a reduction in lung density decline in treated and untreated patients[63,64].

The recent RAPID RCT included 180 patients with emphysema secondary to AATD recruited in 28 centers in 13 countries[65]. Patients were randomized to receive either augmentation therapy or placebo and were followed for over 2 years by CT densitometry, followed by an extension period in which all patients received active treatment and were followed for 2 additional years. The results showed that augmentation therapy was effective in reducing the annual loss of lung tissue. Moreover, patients initially in the placebo arm who agreed to extend the study and, subsequently, received active treatment for the next two years, showed a reduction in the rate of decline in lung density that was similar to the decline observed in the patients initially included in the active arm of the study[65].
However, the initial excess loss of lung tissue during the 2 years on placebo was not recovered. This finding underscores the importance of early diagnosis and treatment to prevent the development of emphysema in individuals with AATD.

2. RATIONALE

2. RATIONALE

COPD is a chronic respiratory disease with a notable morbidity and mortality as well as high economic burden. COPD is frequently diagnosed and managed in PC due to its high prevalence.

Clinical guidelines recommend the treatment of all COPD patients with persistent symptoms with LABD and the adjustment of treatment to the patient´s characteristics or phenotype. Previous studies have shown that some COPD patients remain untreated or are undertreated after the diagnosis of the disease. In contrast, the use of some anti-inflammatory drugs, such as the ICS is widespread and frequently used off-label with the associated risk of side effects. However, there is a lack of large real life studies based on data collected from the usual clinical practice that reflect the COPD treatment patterns of COPD in PC in our country.

Most of COPD patients are controlled in PC, which is also the first point of contact among the patients seeking health care. Unfortunately, there is a lack of knowledge in the medical community about AATD. The diagnostic test to detect AATD is not expensive and can be easily performed in PC, However, despite of previous initiatives to improve the detection rates of AATD in PC, the impact of these initiatives in increasing the diagnosis and improving the management of AATD-related COPD is still unknown.

3. OBJECTIVES

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3.1 General objective

To investigate the diagnosis of and treatment approaches to COPD in PC in Catalonia through analysis of the **System for the Development of Research in Primary Care** (SIDIAP) database.

3.2 Specific Objectives

To describe the initial treatment patterns in patients with newly diagnosed COPD in Catalonia.

To evaluate the adaptation of the initial treatment patterns to the patients´ clinical characteristics and severity.

To quantify the number of AAT determinations performed in PC in Catalonia.

To describe the characteristics of all the individuals tested.

To describe the management and outcomes of the individuals with deficient values during a 6 month follow-up.

4. METHOD

4. METHOD

This doctoral thesis has led to two publications. The first was on a study performed in a population of newly-diagnosed COPD patients to answer the two first specific objectives of the study. The aim of the second study was to answer the two objectives regarding AATD.

The two studies had a similar methodology. Both were epidemiological, population-based, observational studies with information obtained from the SIDIAP database.

VARIABLES	SOURCE OF INFORMATION	AVAILABILITY
Sociodemographic data (date of birth, country of origin, PC centre)	SIAP (Catalan Health Service Database)	>2000 year
Clinical data (visits, referrals, vaccines, smoking, drinking, BMI, blood pressure, ICD-10 codes, sick leaves, etc)	e-CAP (Primary Care e-records)	>2005 year
Drugs dispensed in community pharmacies	Pharmacy Official Invoice Database (Catalan Health Service)	>2005 year
Laboratory tests	Primary Care Lab Database	>2006 year
Socioeconomic status	Census data	>2001 year
Hospital Admissions	Inpatient Care MBDSS (Catalan Health Service)	>2004 year
Date and cause of death	National Office of Statistics	>2003 year
Other external databases	Cancer registries, the Catalan Registry of Arthoplasties etc	

Table 4. Information included in SIDIAP database. Adapted from Bolívar et al[66]

SIDIAP was created in 2010 under the auspices of the Institute for Research in Primary Care IDIAP Jordi Gol and the Catalan Health Institute. SIDIAP is a functional unit the main objective of which is to generate a large database with all the information collected from the electronic clinical files (e-CAP) and other

complementary sources providing valid and reliable information for research in PC[66].

All the PC physicians in the public Catalan Health System use the same electronic clinical records program called e-CAP, which was fully implemented in 2005. SIDIAP gathers the following information for each individual controlled in a PC center (more than 5.8 million inhabitants distributed in 279 PC centers, Figure 5):

- Information from the e-CAP: demographic data (age, gender), health problems (using CIE-10 codification), date and number of visits to the PC physician, clinical information (e.g blood pressure measures, spirometries or **body mass index**, BMI) or referrals.
- Laboratory results: the results of every laboratory test requested in PC since 2006 is available.
- Information of the medication dispensed in pharmacies with Catalan Health System prescriptions.

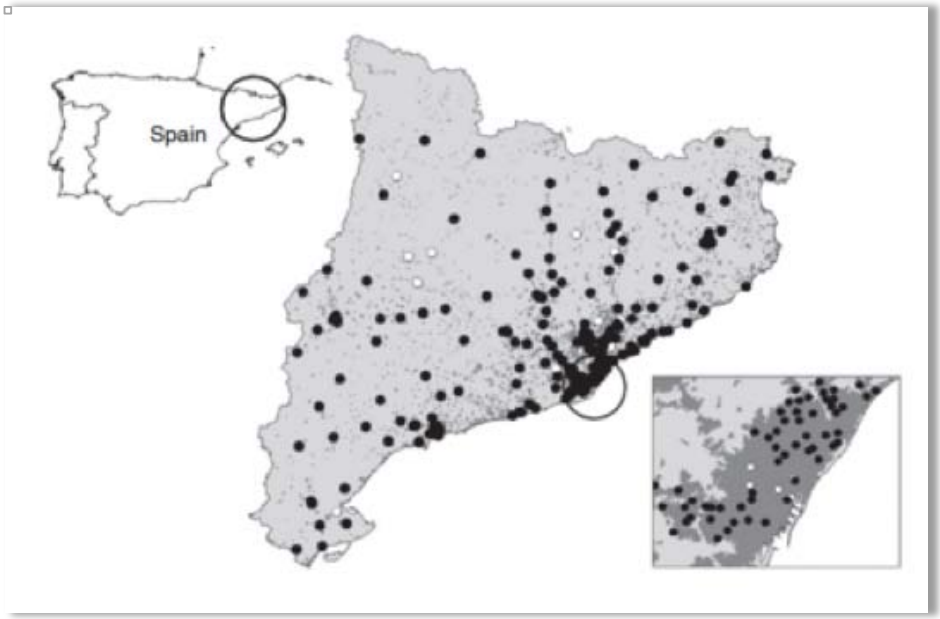

Figure 5. Primary Care centers participating in SIDIAP: geographic distribution. Adapted from Bolívar et al[66].

Additionally, SIDIAP is linked to other databases such as the Hospital Discharge database or the National Mortality Registry. (Table 4)

4.1 Specific methodology for Study 1

In this study we included all patients diagnosed with COPD from 2007 to 2012. For the correct identification of the COPD patients we elaborated an algorithm based on previous studies with similar characteristics (Table 5).

AUTHOR/COUNTRY (Database)	DIAGNOSIS OF COPD
Smidth M[67]. Denmark	> 35 years of age and at least one of the following: -Hospital contact: An ICD-10 codified diagnosis of COPD, chronic bronchitis, etc during a hospital admission or outpatient visit -Treatment: Two or more prescriptions of bronchodilators over the following 12 months -Spirometry: Two spirometries performed within the following 12 months
Price D[68]. UK (GPRD)	>35 years of age -A codified diagnosis of COPD -One year of practice data prior to last extraction date -Spirometry compatible with COPD within5 years of the last data registry
Wurst K[69]. UK (GPRD)	-At least 40 years of age -At least one COPD-related medical code -Diagnosis of COPD confirmed by spirometry
Bilde L[70], Denmark	->40 years of age - At least one case of admission to a hospital with a diagnosis of COPD
Soriano JB[71], UK (GPRD)	-One or more records indicating OXMIS codes compatible with COPD (OXMIS codes)
Mullerova H[72], UK (GPRD)	->45 years of age -A codified diagnosis of COPD - Prescriptions of COPD-related medications (i.e. bronchodilators, inhaled or oral corticosteroids) within 1 year after the first medical diagnosis of COPD

	Excluded if other serious lung diseases codified
Miller D[73], UK (GPRD)	->45 years of age - A diagnosis of COPD, chronic bronchitis, chronic obstructive airway disease, or emphysema Cystic Fibrosis and lung cáncer excluded
Griffin J[74], UK (GPRD)	->35 years of age -A clinical record of the diagnosis of COPD
Penning van Beest F[75], Netherlands (PHARMO)	->55 years of age - Patients receiving their first COPD therapy in the study period Excluded if hospital admission for asthma, lung cancer, lung surgery, tuberculosis, sarcoidosis, lung fibrosis or pneumoconiosis or inhaled treatment prior to the inclusion.
Gershon AS[76], Canada	-A hospital admission or outpatient visit codified as COPD (ICD-9, ICD-10)
Kim C[77], Korea (KHIRA)	->40 years of age - ICD-10 codes for COPD or emphysema - Use of more than one of the following COPD drugs at least twice per year: LAMAs, LABAs, ICS, SAMAs, SABAs or methylxanthine
Quint JK[78], UK (CPRD GOLD)	-8 diagnostic algorithms tested: 1. COPD Code+spirometry+COPD medication 2. COPD Code+spirometry 3. COPD Code+COPD medication 4. COPD Code only 5. Non specific Bronchitis code+COPD medication 6. Non-specifi c bronchitis code only 7. Symptoms +spirometry 8. symptoms only
Raluy-Callado M[79], UK (CPRD)	->40 years of age -A codified diagnosis of COPD, chronic bronchitis or emphysema.

Table 5. Criteria used for the selection of a COPD population in previous database studies. UK: United Kingdom

The inclusion criteria in our study were (Figure 6):

a) Patients older than 40 years of age with a diagnosis of COPD, emphysema or chronic bronchitis, smoking history and FEV1/FVC < 0.7.
b) When the smoking history was unknown; patients were included if treatment was initiated after the diagnosis of COPD
c) When spirometry was not available, we excluded patients with a diagnosis codified as asthma and/or who received no treatment after diagnosis and/or were treated with a leukotriene inhibitor or

chromoglicates in order to rule out patients with asthma or a miscodified diagnosis.

d) Patients with a FEV1/FVC < 0.7 but not codified as COPD, emphysema or chronic bronchitis were included if: they had a significant smoking history or received treatment for COPD after spirometry but not during the previous year, and there was no other codified diagnosis that could present with obstructive spirometry, such as bronchiectasis, asthma or cystic fibrosis.

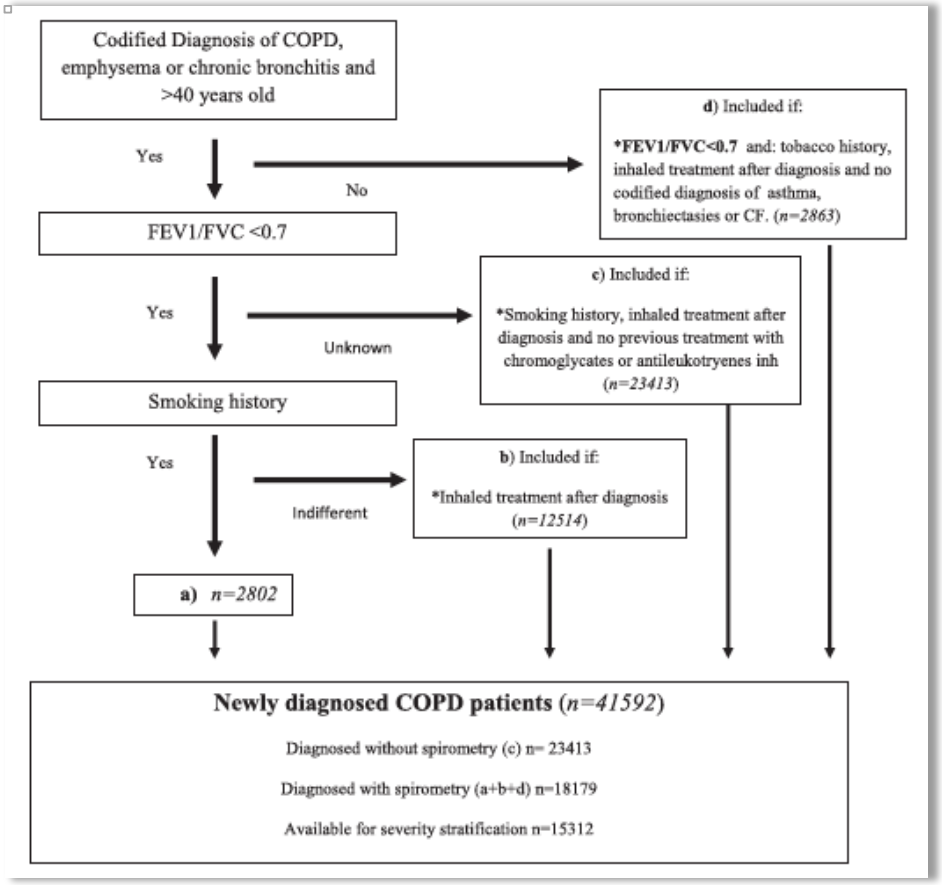

Figure 6. Diagnostic criteria for newly diagnosed COPD patients. Adapted from Barrecheguren et al[107].

Basal demographic and clinical characteristics were collected, including smoking history, comorbidities, exacerbations and treatment. The initial

treatment was collected from the pharmacy registry when used for a minimum of three months after the diagnosis of COPD. The treatment patterns were described as all the possible combinations of inhaled treatments.

Severity was assessed based on GOLD severity stages in the patients for whom a FEV1 value was available (stage 1 mild, FEV ≥ 80% predicted, stage 2 moderate 50% ≥ FEV1 < 80% predicted; stage 3 severe, 30% ≥ FEV1 < 50% predicted; stage 4 very severe FEV < 30% predicted)[1].

Exacerbations were identified by diagnostic codes and by treatment (patients receiving antibiotic and/or oral corticosteroids in the absence of another codified infectious event such as tonsillitis or urine infection).

Patients with two or more exacerbations during the previous year were classified as having a frequent exacerbator phenotype, while those with a previous history of asthma were included in the asthma COPD overlap (ACOS) phenotype, and the remaining COPD patients were considered non exacerbators.

Statistical analysis

A descriptive analysis of each yearly cohort (2007-2012) and of the whole sample was performed. For qualitative variables, absolute frequencies and corresponding percentages were calculated. Quantitative variables following a normal distribution were described by mean and standard deviation, while those that did not follow a normal distribution were expressed using the median and 25-75 percentiles. The same descriptive analysis was performed according to GOLD severity and phenotype.

4.2 Specific methodology for Study 2

In this study we included all individuals with an AAT determination during the years 2007-2008 and 2010-2011.

Individuals were classified as follows based on the results of the AAT determination: no deficiency: AAT > 100 mg/dL; intermediate deficiency: AAT between 50 mg/dL and 100 mg/dL; and severe deficiency: AAT < 50 mg/dL[80].

Individuals with 15 years old or less were considered children and analysed separately.

The demographic and clinical characteristics were recorded for all the study populations. For individuals with intermediate and severe deficiencies, we collected data on referrals to a specialist, complementary tests (spirometry and CT scans), pharmacologic treatment, and number of respiratory infections during the 6 months following the determination.

Statistical analysis

A descriptive analysis of each period (2007–2008 and 2010–2011) and of the whole sample was performed separately for children and adults. For qualitative variables, absolute frequencies and corresponding percentages were calculated. Quantitative variables following a normal distribution were described by mean and standard deviation, while those not following a normal distribution were described using the median and 25–75 percentiles. Differences between groups were performed using the chi-square test for categorical variables, while continuous variables were tested using the Student's *t*-test (or the Mann–Whitney *U*-test, if the variables were not normally distributed). All tests were two-tailed, and significance was set at 5%. All statistical analyses were performed using a statistical software package (SPSS Version 20.0; IBM Corporation, Armonk, NY, USA).

4.3 Ethics

The study was approved by the IDIAP Jordi Gol Ethics Committee (Barcelona, Spain).

5. RESULTS

5. RESULTS

5.1. Treatment patterns in COPD patients newly diagnosed in primary care.

During the study period (2007-2012) 41,592 patients with a new diagnosis of COPD were identified (Fig. 6). In total, 33,102 (79.6%) of patients were men with a mean age of 66.7 years (SD 11.6). Diagnosis was established without spirometry in 56.3% of the cases. The distribution of patients diagnosed by year was homogeneous, with the lowest number of patients being diagnosed during the summer months (July to September). Of these newly diagnosed patients, 10,888 (26.2%) were frequent exacerbators, with 2152 (5.2%) being classified as ACOS and the remaining 28,552 (68.6%) as non exacerbator COPD patients. The most common comorbidities were hypertension (51.8%), dyslipidemia (43%) and diabetes mellitus (22.4%). Aside from asthma, the most frequent respiratory comorbidities were **obstructive sleep apnoea** (OSA) (3.1%) and bronchiectasis (2.6%). The baseline characteristics are shown in Table 6.

	2007 (n= 7,069)	2008 (n= 6,335)	2009 (n= 7,244)	2010 (n= 7,098)	2011 (n= 6,706)	2012 (n= 7,140)	Total (n= 41,592)
Age	67.4 (11.5)	67.3 (11.6)	66.5 (11.7)	66.3 (11.6)	66.1 (11.5)	66.7 (11.5)	66.7 (11.6)
Gender (male)(%)	79.8	80.8	79.5	79.1	79.3	79.2	79.6
Current smoker (%)	37.6	40.1	42.1	45.5	45.1	44	42.6
Ex smoker (%)	28.9	30.8	32.6	35.2	39.7	43.7	35.2
Non smoker (%)	6.7	7.5	6.8	6.1	7	4.9	6.5
Unknown (%)	26.9	21.6	17.5	13.1	8.2	7.4	15.7
BMI	28.5 (5.2)	28.5 (5.1)	28.5 (5.3)	28.6 (5.5)	28.6 (5.2)	28.4 (5.2)	28.5 (5.3)
FEV1 %	58.6 (18.7) (n=2291)	58.7 (18.1) (n=2440)	59.8 (18.7) (n=2798)	59.7 (18.1) (n=2850)	60.3 (18.6) (n=2652)	60.5 (19.4) (n=2281)	59.6(19.6) (n=15312)
GOLD 1(%)	12.2	12.3	14.4	13.8	15	15.8	13.9
GOLD 2(%)	54.5	56.1	55	55.8	55.4	54.3	55.2

GOLD 3(%)	28	26.4	25.7	26	25.5	24.7	27
GOLD 4(%)	5.3	5.2	5	4.5	4	5.2	4.8
Phenotype							
ACOS (%)	5	4.8	5.2	5.2	5.1	5.6	5.2
Non Exacerbator(%)	67.9	67.7	68	69.4	70	68.8	68.6
Exacerbator(%)	27.1	27.4	26.8	35.4	24.9	25.6	26.2
Comorbidities							
Asthma (%)	5	4.8	5.2	5.2	5.1	5.6	5.2
Bronchiectasis(%)	2.2	2.5	2.5	2.9	2.6	2.7	2.6
Ischaemic Heart Disease (%)	9.7	10.3	10	10	10.4	10.9	10.2
Neoplasia (%)	4.2	4.9	5.2	5.4	5.5	6.5	5.3
OSA (%)	2.9	2.9	3.1	2.9	3.2	3.1	3.1
Anaemia (%)	12.3	10.9	9.4	9.5	9.2	7.9	9.8
DM (%)	24.3	23.1	21.5	21.9	21.5	22.2	22.4
Dyslipidemia (%)	41.6	42.1	42.4	42.4	45.2	44.4	43
Hypertension (%)	55.4	53.7	50.2	50.7	50.3	51	51.8
Atrial Fibrillation (%)	12	10.7	9.1	9.4	7.7	8.1	9.5
Exacerbations (median, IQR)	1 (2)	1 (2)	1 (2)	1 (2)	1 (2)	1 (2)	1 (2)
Pneumonia (%)	2.6	3.1	3	2.9	2.6	3.3	2.9

Table 6. Baseline characteristics of patients with newly diagnosed COPD during the years 2007-2012.

5.1.1 Initial treatment pattern during the study period

After the diagnosis of COPD, 32,655 (78.8%) patients received treatment for their disease. Considered individually, ICS and LABA were the most frequently prescribed drugs (45.2% and 42.8%, respectively). The most frequently prescribed treatment pattern was a short-acting b2 agonist (SABD) in monotherapy (17.7%), with this pattern increasingly slightly from 16% to 19.5% from 2007 to 2012 at the expense of the increased use of short-acting antimuscarinics (SAMA, from 9.5% to 13.2%). This was followed by LABA/ICS (17.3%) and triple therapy with LABA/LAMA + ICS (12.2%), both with similar frequencies over the years. The number of patients receiving ICS in monotherapy decreased from 6.5% in 2007 to 2.7% in 2012. The number of untreated patients also decreased from 24.4% to 15.1% during the study period. The initial treatment patterns are shown in Table 7 and Fig. 7.

Treatment	2007 (n=7,069)	2008 (n=6,335)	2009 (n=7,244)	2010 (n=7,098)	2011 (n=6,706)	2012 (n=7,140)	TOTAL (n=41,592)
By drug							
SABA	31.9	29.4	28.5	26.6	27.8	27.8	28.7
SAMA	23.4	25.5	24.5	25.3	24.4	26.9	25
LABA	41.5	43.7	42.5	41.4	42.4	46.2	42.8
LAMA	19.3	22.4	22.5	23.6	25.1	28.2	23.5
ICS	48.2	48.4	47.2	44.6	41.3	41.5	45.2
Theophylline	1.1	0.9	0.7	0.6	0.4	0.6	0.7
Mucolítics	22.5	22.4	22.2	22.2	19.9	13.6	20.4
Bypattern							
SABD	16	16.5	17.6	18.1	18.8	19.5	17.7
LABA	3.2	3.1	2.5	3.4	5.6	7.5	4.2
LAMA	5.8	7.4	7.9	8.9	10	11.3	8.6
LABA+LAMA	1	1	0.9	1	2.2	3.7	1.7
LABA+SAMA	1.4	1	1.1	1.2	1.7	1.4	1.3
LABA+ICS	18.6	18.6	18.8	16.9	15.4	15.6	17.3
LAMA+ICS	1.1	1.1	1.2	1.1	0.9	1.2	1.1
SAMA+ICS	4.8	5	3.7	3.9	3.6	4	4.2
LABA+LAMA+ICS	11.3	12.6	12.5	12.6	11.9	12	12.2
LABA+SAMA+ICS	5.9	7.1	6.6	6.3	5.6	6	6.2
ICS	6.5	4.1	4.4	3.8	3.9	2.7	4.2
No treatment	24.4	22.3	22.7	22.7	20.4	15.1	21.2

Table 7. Initial treatment patterns

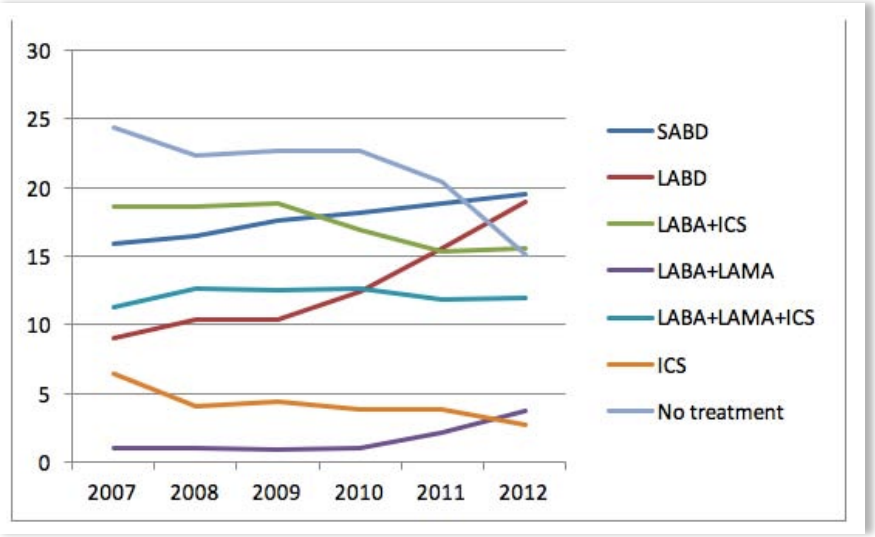

Figure 7. Initial treatment patterns

5.1.2 Initial treatment pattern by phenotype

Inhaled corticosteroids were frequently prescribed in the ACOS (69.2%) and in patients with the exacerbator phenotype (52.4%). In contrast, the use of ICS decreased from 43.8% in 2007 to 35.8% in non exacerbator patients in 2012.

The most frequent prescription pattern after diagnosis in the ACOS and exacerbator phenotypes was LABA/ICS (30.5% and 17.8%), while non exacerbators most frequently received SABA (18.8%). Non exacerbators were more likely to receive no treatment at all after diagnosis (23.5% versus 17.4% in exacerbators and 11.2% in ACOS) (Fig. 8). Most of the patients that received mucolytics after diagnosis (20.4%) were non exacerbators (60.4%).

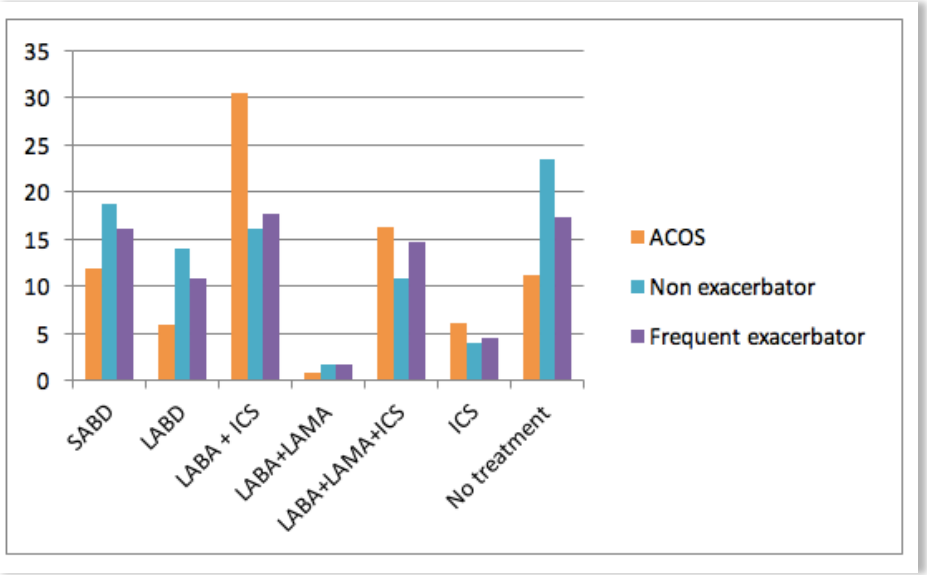

Figure 8. Treatment pattern by phenotype

5.1.3 Initial treatment pattern by severity

FEV1 was available in 15,312 (36.8%) patients, and they were classified based on GOLD severity stages: stage 1 13.9%, stage 2 55.2%, stage 3 26% and stage 4 4.8%. The frequency of the different phenotypes was similar in all severity stages. Less severe patients most frequently received SABD in monotherapy (21% in stage 1 versus 14.8% in 4) or no treatment at all after diagnosis (38.7% stage 1 versus 13.6% in 4). Compared with less severe stages, patients in stage 4 were usually treated with triple therapy (36.6% versus 5.7% in stage 1) or theophylline (2.5% of stage 4 versus 0.4% in 1).

The percentage of patients treated with ICS was higher in the most severe GOLD stages (28.3%, 37.3%, 51.3%, 59.3% for stages 1-4, respectively) while the number of patients that received ICS alone was lower (5%, 4%, 3.8%, 2.3% from stage 1-4, Fig. 9).

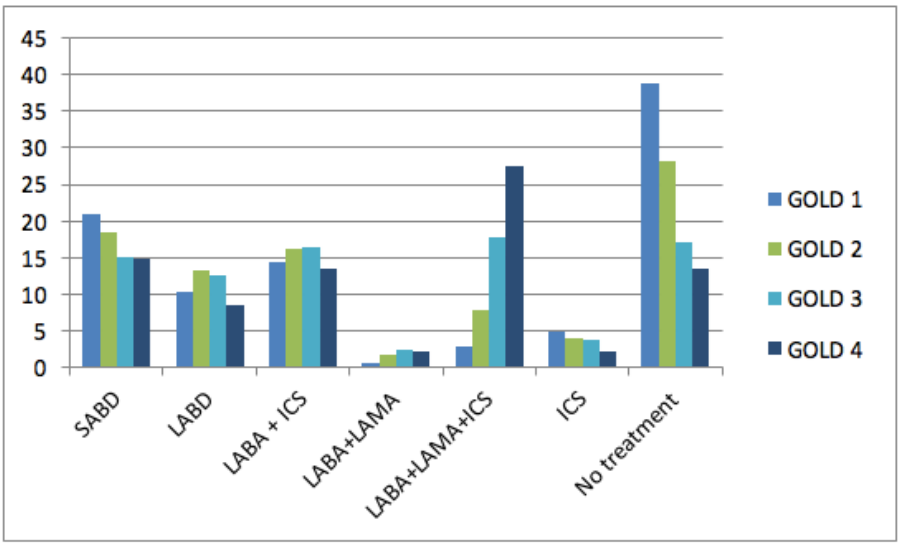

Figure 9. Treatment pattern by severity

5.2 DIAGNOSIS OF ALPHA-1 ANTITRYPSIN DEFICIENCY

5.2.1 Frequency of AAT determination

In total, 12,409 determinations of serum AAT were performed during the 4 years of the study, of which 1,335 (10.7%) were children. The number of determinations was higher in the second period (5,559 determinations in 2007–2008 and 6,850 determinations in 2011–2011) due to the low number of individuals tested in 2007. Nonetheless, the rate of individuals tested per year did not increase significantly after 2008 (Table 7). Figure 1 shows the number of determinations performed by age groups.

Period	Children	Adults	Total	n/10,000 inhabitants
2007	331	1998	2329	4.33
2008	382	2848	3230	6.85
2007-2008	713	4846	5559	
2010	325	3351	3676	6.77
2011	297	3676	3174	5.82
2010-2011	622	6228	6850	

Table 8. Number of AAT determinations performed by year.

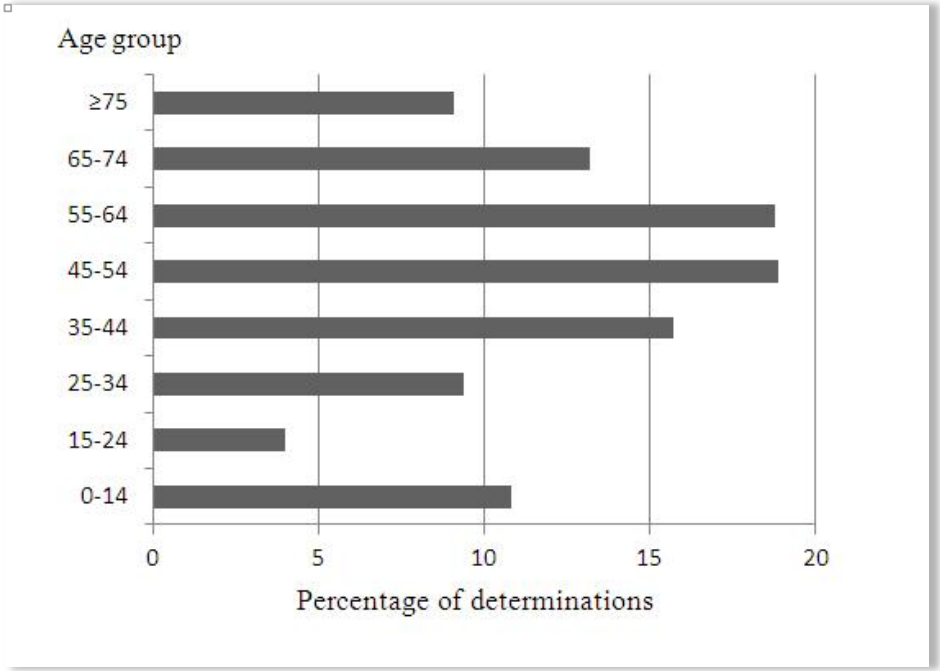

Figure 10. Determinations performed by age

5.2.2 Characteristics of the individuals tested

The mean age of the individuals tested was 52.6 (SD 16.3) years in adults and 4.6 (SD 4.1) years in children, with an equal distribution between sexes. Among adults, 37.1% were smokers or former smokers. The most frequent comorbidities in adults were dyslipidemia (27.6%), hypertension (27.4%), diabetes

mellitus (11.7%), depression (10.1%), and ischemic heart disease (4%). Up to 41% of children and 18.5% of adults were receiving treatment for a respiratory disease at the time of the determination. The majority of the determinations were performed in urban areas. Demographic characteristics are shown in Tables 8 and 9.

Variables	Children (n=1335)
Mean age (SD)	4.61 (4.1)
Sex (men)	769 (57.6)
Urban setting	868 (65)
Smokers	12 (0.9)
Former smokers	2 (0.1)
Bronchiectasis	2 (0.1)
Asthma	298 (22.3)
Hepatitis	7 (0.5)
Cirrhosis	0
Hepatocarcinoma	0
High transaminase levels	236 (17.7)

Table 9. Demographic characteristics and diseases related to AATD of children individuals tested for AAT during the study period

5.2.3 Indications for AAT determinations, AAT concentrations, and follow-up

As a possible indication for AAT determination, 3,195 (28.9%) adults and 393 (29.4%) children had a previous diagnosis of a disease related to AATD. Up to 17.7% of children and 47.1% of adults had transaminase levels above normal (Tables 2 and 3). Nine percent of children were between the age 0 year and 1 year, suggesting neonatal jaundice as the most likely indication. During the previous year, 31.3% of individuals had had at least one respiratory infection and 1.3% had had pneumonia.

Variable	Normal AAT levels (n=10445)	Intermediate deficiency (n=607)	Severe deficiency (n=22)	Total (n=11074)
Age (mean, SD)	52.9 (16.3)	48.0 (14.4)**	42.5 (15.7)**	52.6 (16.3)
Sex (men)	5756 (55.1)	377 (62.1)**	14 (63.6)	6147 (55.5)
Smoker	2219 (21.2)	113 (18.6)	7 (31.8)	2339 (21.1)
Former smoker	1668 (16)	101 (16.6)	3 (13.6)	1772 (16)
AAT mg/dl (mean, SD)	150.9 (34.2)	87.6 (10.8)	27.6 (11.6)	147.2 (36.7)
Previous diseases related to AATD				
COPD	937 (9)	34 (5.6)*	6 (27.3)*	977 (8.8)
Emphysema	193 (1.8)	14 (2.3)	4 (18.2)**	211 (1.9)
Chronic bronchitis	293 (2.8)	14 (2.3)	0	307 (2.8)
Bronchiectasis	284 (2.7)	11 (1.8)	0	295 (2.7)
Asthma	794 (7.6)	45 (7.4)	3 (13.6)	842 (7.6)
Hepatitis	768 (7.4)	32 (5.3)	1 (4.5)	801 (7.2)
Cirrhosis	127 (1.2)	3 (0.5)	0	130 (1.2)
Hepatocarcinoma	4 (0)	0	0	4 (0)
High transaminase levels	5430 (52)	313 (51.6)	8 (36.4)	5751 (51.9)
Previous respiratory infections	3486 (33.8)	162 (26.6)*	9 (40.9)	3657 (33.02)
Previous pneumonia	136 (1.6)	5 (0.8)	1 (4.5)	142 (1.3)
Hypertension	2908 (27.8)	126 (20.8)**	2 (9.1)*	3036 (27.4)
Dyslipidemia	2901 (27.8)	158 (26)	2 (9.1)*	3061 (27.6)

DM	1247 (11.9)	44 (7.2)**	1 (4.5)	1292 (11.7)
Depression	1070 (10.2)	51 (8.4)	2 (9.1)	1123 (10.1)
Ischemic heart disease	428 (4.1)	13 (2.1)**	0	441 (4)

Table 10. Comparison of the characteristics of adult patients tested for AAT during the study period according to AAT levels.

The mean AAT plasma level was 147.2 (36.7) mg/dL in adults and 154.1 (37.2) mg/dL in children. In total, 663 (5.3%) individuals (56 children) had an intermediate AAT deficiency, while 24 (0.2%) individuals (two children) had a severe deficiency, with a prevalence of 0.19 cases of severe deficiency per 100 determinations. Patients with severe deficiency were younger than individuals with normal AAT levels (42.5 years vs 52.9 years, *P*=0.003) and were more likely to have a previous diagnosis of COPD or emphysema (45.5% vs 10.8%, *P*,0.05) (Table 10).

During the 6-month follow-up, four of the patients with severe deficiency (18.1%) were newly diagnosed with COPD or emphysema, two (9.1%) following diagnostic spirometry and one (4.2%) after a computerized tomography scan. Only three patients (13.6%) were referred to a pneumologist and another patient was referred to internal medicine (Table 10).

Diagnosis after AAT determination	Normal AAT levels (n=10,445)	Intermediate deficiency (n=607)	Severe deficiency (n=22)
COPD	106 (1)	5 (0.8)	2 (9.1)*
Emphysema	36 (0.3)	1 (0.2)	2 (9.1)**
Chronic bronchitis	18 (0.2)	2 (0.3)	0
Respiratory infections	3090 (29.5)	148 (24.4)**	10 (45.5)*
Pneumonia	58 (0.6)	3 (0.5)	0
Spirometry	407 (2.9)	24 (4)	2 (9.1)
Referrals			
Pneumology	229 (2.2)	22 (3.6)*	3 (13.6)*
Gastroenterology	489 (4.7)	42 (6.9)*	0
Internal Medicine	73 (0.7)	2 (0.3)	1 (4.5)

Table 11. Six-month follow-up of adults tested for AATD according to AAT levels. *p<0,05 and *p<0,01 compared to individuals with normal AAT levels. Data are expressed as n(%).

6. DISCUSSION

6. DISCUSSION

The results of this study show that in many cases the management of a COPD patient in PC in Catalonia, Spain, do not comply with current guidelines. The main issues observed were that the use of ICS was widespread, but has decreased in recent years in non exacerbator patients. Moreover, many COPD patients still remain untreated after diagnosis although this frequency has decreased, and some GOLD 4 patients are still receiving SABD or no treatment at all after diagnosis. Regarding AATD screening, the number of AAT determinations performed in PC in Catalonia, is low and has not increased in the last years. In addition, in most cases, we could not identify the reason for requesting the test, and after detection of a severe deficiency, some individuals were not tested further or referred to a specialist.

The problem of undertreatment of COPD

Undertreatment of COPD still remains a challenge in Spain, although prevalence studies have shown a significant decrease in this disease in recent years. The IBERPOC study performed in 1998 showed that 81% of COPD patients were undiagnosed and untreated while in 2007 this number had fallen to 54%, with the decrease being more notable in patients with severe COPD[8]. Undertreatment of COPD has shown to be similar in other countries: in the US, up to 59% of COPD patients were not treated[81] while in Denmark a similar percentage of undertreatment (57.8%) has been described for COPD patients with a FEV1 < 60%[82]. Obviously, the frequency of undertreatment is significantly reduced in patients with an established diagnosis of COPD. In our study up to 38.9% of patients were treated either with a SABD or without any inhaled treatment, which was consistent with similar studies performed in the UK that showed that the number of untreated newly diagnosed COPD patients varied from 15% to 25.1%[68,69]. Similarly, Price et al reported 17% of untreated patients in a cohort of COPD in PC also in the UK[68]. However, we found a marked, progressive reduction of undertreatment over our study period,

especially in the number of patients that did not receive inhaled treatment, which decreased 9.3% in 6 years.

Some authors have observed that patients treated only with SABD in monotherapy have lower levels of airflow limitation and milder dyspnea[69]. Conversely, frequent exacerbations, a low FEV1 and dyspnea have been described as predictors of the need for treatment in COPD[83]. Nonetheless, we found that 17% of frequent exacerbators and 13.6% of GOLD 4 patients remained untreated, and 16.2% and 14.8% respectively were only treated with SABD. Similar findings have been described in two incident cohorts of COPD patients in the UK, in which 23.8% of GOLD C and D and 37% of COPD patients with a FEV1 < 50% did not received any maintenance treatment, thereby demonstrating that undertreatment in PC is common in all stages of the disease and in different countries[69.79].

Patterns of initial treatment of COPD

In our study, the most frequent treatment pattern was the use of SABD in monotherapy, which has surprisingly increased to become the most commonly prescribed treatment pattern in 2012 and was even found to be frequent in GOLD 3 and 4 patients and in frequent exacerbators. The use of a SABD in monotherapy is also the most prescribed treatment after the diagnosis of COPD in the UK[69,79] and similar to our results, 7.9% of GOLD C and D patients received only a SABD after diagnosis. Although still common, this treatment pattern is less used in prevalent COPD patients[68]. These results disagree with guidelines, which recommend the use of LABD as maintenance treatment in symptomatic COPD, whilst treatment with SABD is only recommended for mild patients with few intermittent symptoms[1,84]. In our study population, most of the treatments with SABD corresponded to the use of SAMA, which may be explained by the recommendations of our health care authorities at the time of the study and the associated restrictions in the prescription of new LABD.
One of the most frequent patterns throughout the years was the combination of LABA/ICS, and any ICS containing regime was prescribed in almost half of the population, a number observed by other authors in similar cohorts[79,83]. Price et

al. [68] described that in patients with COPD in PC the combination of LABA/ICS was the most frequently prescribed treatment, followed by triple therapy. Again, approximately 50% of patients received ICS, including half of the patients with frequent exacerbations or concomitant asthma. (Table 11, Figure 10).

In contrast to these results, the Spanish guidelines of COPD recommend the use of ICS in the ACOS and frequent exacerbator phenotypes[2,26]. While it is true that most of our data are prior to the publication of GesEPOC, the previous guidelines of the Spanish society (published in 2001 and 2007) also recommended the use of ICS in severe COPD patients with more than 1 exacerbation per year[85,86], while the initial GOLD document recommended ICS in COPD patients with a FEV1 < 50% and frequent exacerbations[87].

Despite the recommendations of the use of ICS, previous studies have shown that up to 30% of ICS prescriptions in PC do not have a clear indication[88.89]. We observed that ICS were prescribed more frequently for the more severe patients or in ACOS or frequent exacerbator patients. Nonetheless, one third of the non exacerbators and GOLD 1 patients received ICS, indicating an over prescription of these drugs. In contrast, one third of ACOS patients and half of the frequent exacerbators did not receive ICS after diagnosis. Similar to our results, a more recent study with five-year data (2009-2013) also in the UK[79] showed that up to 20% of patients in categories GOLD A and B received ICS, while Brusselle et al described that almost all patients with COPD, irrespective of their level of severity or GOLD group, will eventually receive triple therapy at some point during the 10-year period after the diagnosis of COPD[90].

A recent Spanish consensus document on the use of ICS has agreed on the indication of ICS in exacerbator and ACOS patients and has aslo agreed with the withdrawal of ICS in patients that do not fulfil these criteria[91].

While the use of ICS is widespread, LABD alone represents a low percentage of new treatments. Although its use has increased in the last years, few patients are treated with a LABD or with dual LABA/LAMA. Furthermore, a recent study

has shown that only 35% of COPD patients are continuously treated with LABD[92].

Treatment of COPD by phenotypes

We identified only 5% of patients with the ACOS phenotype in our cohort, although the real prevalence of ACOS in our study might be underestimated due to our inclusion criteria. We aimed to exclude asthma patients that were miscoded as COPD, therefore, we excluded patients with a coexisting diagnosis of COPD and asthma when we were not able to verify the presence of chronic airflow obstruction or the smoking history. In contrast, due to these restrictive criteria for ACOS, we believe our patients with a concomitant diagnosis of COPD and asthma to be truly ACOS. Moreover, the presence of a previous diagnosis of asthma has proved to be a good indicator to suspect ACOS in COPD patients[93]. In our study, patients with ACOS were more likely to receive maintenance treatment after diagnosis.

Two thirds of our COPD patients were non exacerbators, being consistent with previous studies performed in Catalonia[94]. Non exacerbators were more likely to be treated with SABD or to remain untreated and surprisingly, most of the patients that received mucolytics belonged to this phenotype.

Compliance with existing guidelines

Our results indicate that initial treatment for COPD very often does not comply with existing guidelines. Knowledge of these guidelines in PC is variable. In a physician survey performed in 12 countries worldwide in 2013, 85% of GPs reported awareness of COPD guidelines, including local guidelines[95].

Treatment pattern	Price et al[68] (n=24,957)	Wurst et al[69] (n=7,881)	Raluy-Callado et al[79] (n=27,224)	Brusselle et al[90] (n=3,505)	Barrecheguren et al[107] (n=41,592)
SABD	11.1	22.9	29.6	12	17.7
LABA	1.8	3.1	4.9	1.1	4.2
LAMA	7.9	12.5	12.1	3.1	8.6
LABA + ICS	26.7	22.1	13.5	24.8	17.3
LAMA + ICS	1.7	1.5	0.4	1.3	1.1
LABA + LAMA	0.8	0.7	1.8	-	1.7
LABA + LAMA + ICS	23.2	10.6	7.5	9.7	12.2
ICS	5.9	9.2	1.8	12.2	4.2
No treatment	17	15	25.1	20.6	21.2

Table 12. Comparison between COPD treatment patterns in different cohorts.

However, in the US, only 13.3% and 28.7% of GP's were very familiar with the ATS/ERS guidelines or the GOLD document, respectively[96]. In Italy, almost a quarter of the 1864 GPs participating in a national survey declared not to use any guideline in their clinical practice[97]. In a previous smaller study in Spain, adherence to treatment recommendations was assessed in 1365 COPD patients in PC, and only 18% of the patients were treated according to guidelines, with the cost per patient per year being higher in the non adherence group, particularly in moderate patients who represent the majority of patients attended in PC[98].

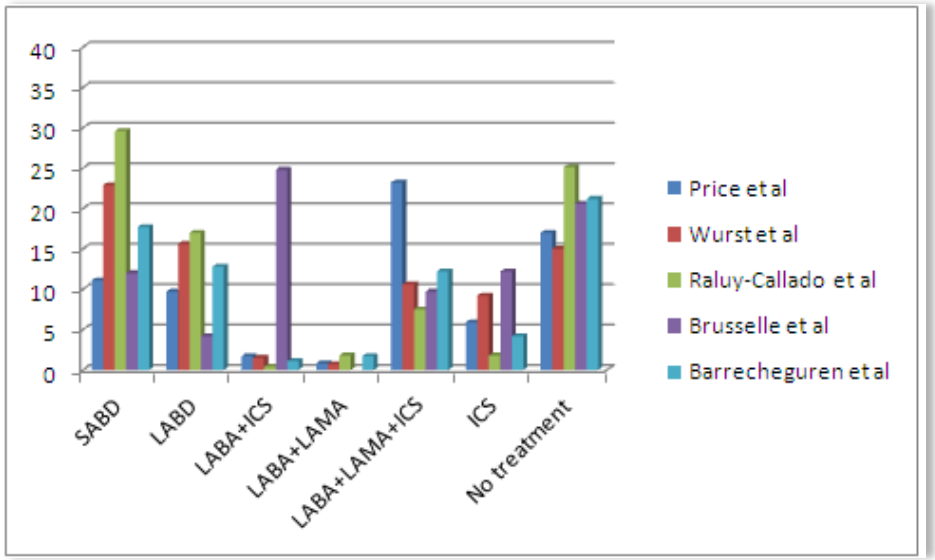

Figure 11. Comparison between COPD treatment patterns in different cohorts

Relationship between alpha-1 antitrypsin deficiency and COPD

One of the risk factors to develop COPD is AATD, which is a relatively common congenital disorder. The AAT protein is the most abundant proteinase inhibitor that targets mainly the neutrophil elastase. Low levels of AAT in the blood and tissues produce an imbalance between proteases and anti-proteases that predisposes to the development of pulmonary emphysema[50,60]. The first step in the diagnostic algorithm of AATD is the measurement of AAT levels in serum by nephelometry. This test can be performed in a routine blood test and therefore, is accessible to most PC physicians. After the determination, individuals with low AAT levels or uncertain results should be referred to a specialist outpatient clinic for further evaluation[60].

The problem of underdiagnosis of AATD

As COPD, AATD remains significantly underdiagnosed despite the recommendations of national and international guidelines[50,60] (Table 3). Moreover, there is still a large delay between the onset of symptoms and diagnosis[99] with no significant improvement in this delay having been observed during the last decades[100]. In Spain, it is estimated that 12,026 patients have a severe deficiency[60], with ~1,700 of these cases corresponding to Catalonia alone[101]. Nonetheless, only 511 cases from all over the country have been diagnosed to date and included in the Spanish registry for AATD[102].

Possible explanations for the underdiagnosis of AATD have been addressed in previous studies. Knowledge of AATD is generally poor even among trainees with special interest in respiratory medicine[103]. Awareness of AATD among non pulmonologists is low in comparison with other respiratory diseases[104], with the consequent low rate of testing for AATD[99.100,105]. A survey carried out in Spain and Portugal showed that the main reasons for not testing for AATD are the referral of patients to other specialists for testing or the erroneous perception of

the high cost of the test[106]. Interestingly, only 15% of the physicians reported to test all COPD patients and bronchiectasis and asthma patients were more frequently tested.

AAT testing in primary care in Catalonia

Despite the current recommendations of testing symptomatic adults with persistent airway obstruction and individuals with unexplained liver disease[50,60], the rate of AAT determinations observed in our study along the years varied from 4.33 determinations per 10,000 inhabitants in 2007 to 6.85 determinations per 10,000 inhabitants in 2008, with intermediate values for 2010 and 2011. Data from our previously described COPD cohort[107] indicated that a mean of 6,932 new patients were diagnosed with COPD per year between 2007 and 2012, being a figure well above the mean number of 375 COPD patients tested yearly for AATD during the 4 years of our study.

Although underdiagnosis of the deficiency has been reported in many countries, to our knowledge, this low rate of AAT determinations in the general population and in COPD patients has not been previously reported, thereby not allowing comparison of our findings with data from other countries or geographical areas.

Regarding the reasons for requesting AAT determination, we observed that only 13% of the adults tested had COPD, chronic bronchitis, or emphysema and half had high transaminase levels, which could justify the request for AAT determination. These results concur with the observation that 70% of PC physicians in Spain were aware of liver complications of AATD, but very few decided to test all COPD patients[106].Similarly, only 0.5% of children had a codified liver disease at the time of AAT determination, and interestingly, the number of children tested for elevated transaminase levels and asthma was similar, although AATD is not a recognized cause of respiratory diseases in childhood[108].

Screening initiatives for AATD

In an attempt to improve the rate of diagnosis of AATD in COPD, several screening initiatives or case detection programs have been developed[102-107], some of which are carried out in PC[109-114]. In the IDDEA of AATD case detection project in COPD patients, volunteer PC physicians were provided with filter paper to collect **dried blood spots** (DBS), together with information about AATD and a Web tool[111]. The ratio of recruitment only reached 6.6 patients per participant over the 9-month collection period, being somewhat low considering that the estimated prevalence of COPD in Spain is 10.2% of adults older than 40 years[9]. However, among the individuals tested, 4% were carriers of the severe deficient allele Z, and 0.34% were diagnosed with severe homozygous PiZZ deficiency[111].

Case detection programs including COPD patients from Pneumology clinics have achieved a higher number of AAT determinations. De la Roza et al conducted a nationwide case detection program in Spain that tested 2137 COPD patients[113] and one single center in Argentina collected DBS samples from 1002 COPD patients and found 1.2% of deficient ZZ individuals[109]. More recently, Greulich et al published the results of a large targeted screening program in Germany. During 12 years, 18,638 individuals were tested for AATD and the study identified 6.92% of ZZ individuals[114]. The highest AATD detection rate was observed by Bals et al, but in their study AAT serum levels were prescreened by the physician before sending the sample and hence, the study population was very selected[115] (Table 13). In an attempt to increase screening in COPD patients, Jain et al[112] implemented an electronic alert to encourage guideline-based testing for AATD. This alert was displayed for patients with obstructive spirometry results, and this tool was associated with an increase in the frequency of testing.

Study	Level of care	Target population	Nº of tests performed	% deficient values
Barrecheguren et al	PC	General population	12,409	0.2
Bals et al	PC, pediatricians, pneumologists	General population	2,722	8.2
Wencker et al	PC, pneumologists	Respiratory disease	1,156	0.26
Rodriguez et al	Pneumologists	COPD	50	0
Luisetti et al	Pneumologists	Respiratory disease/family screening	1,841	12
De la Roza et al	Pneumologists	COPD	2,137	0.37
Molina et al	PC	COPD	596	0.5
Sorroche et al	Pneumologists	COPD	1,002	1.2
Greulich et al	All physicians	General population	18,638	6.9

Table 13. Frecuencies of deficient values observed in screening programs and epidemiological studies.

Other strategies, such as programs to educate respiratory physicians[116] and the combination of an awareness program with the offer of free diagnostic testing[117] resulted in higher rates of detection of individuals with severe AATD. Population screening programs in areas of high prevalence or protocols to measure and the AAT phenotype in selected patients were found to be effective at detecting AATD patients[117-119].

Case detection programs are key to early diagnosis. Smoking plays an essential role in the development of emphysema due to AATD and early diagnosis allows the implementation of anti-smoking measures as well as early treatment when necessary.

7. STRENGHTS AND LIMITATIONS

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Our study has some limitations related to database studies that have to be addressed.

First, studies based on large clinical databases are subjected to possible diagnostic and miscoding bias and invalid data[120]. Previous studies identified their population using a codified diagnosis of COPD[70,73,76,79,121-124] (Table 5) which has proven to be an accurate method to identify these patients from databases[71,78]. This was verified in our study, since on using the accepted criteria based on age, smoking history and obstructive spirometry we only identified a further 6.9% of individuals with COPD among those without any respiratory code registered in the clinical records. On the other hand, in about half of our patients codified as COPD spirometry was not available, which is consistent with previous clinical studies in PC in Spain[125] and other European countries[126-128]. To avoid misdiagnosis in individuals without spirometry codified as COPD, we used criteria based on age, smoking exposure, and the use of treatment for COPD, similar to previous studies[67,72,74,75,77]. It should be noted that the prevalence of COPD in the SIDIAP database is 2.70% (CI 95% 2.68-2.72) in individuals of all ages and 10.56% (CI 95% 10.45-10.66) in individuals >65 years old, which is very similar to the estimated prevalence of COPD in Spain[8].

In an attempt to avoid the inclusion of asthma patients, we excluded subjects with codified asthma but not COPD, even if they fulfilled criteria for COPD. Furthermore, we excluded patients who despite having a code for COPD were treated with asthma medications and had no spirometry confirmatory of chronic airflow limitation. With these restrictive criteria, the real prevalence of ACOS in our area may have been underestimated. In fact, we identified 5.2% patients with ACOS, while epidemiological studies estimate the prevalence of ACOS as between 15 and 20% of COPD patients[94-129].

Another possible bias related to the use of administrative data is the under-reporting of exacerbations. To minimize this, we identified exacerbations in two ways: using a codified diagnosis and collecting treatment with oral corticosteroids and/or antibiotics in the absence of another codified infection. This criterion has been used in previous studies[68,69,74] and, moreover, the frequency of exacerbator patients in our study agrees with a recent study performed in our area[94]. Lastly, the Pharmacy Registry did not allow us to identify the origin of the prescription. However, in our health system the diagnosis of COPD is mainly made in PC and furthermore, prescriptions for chronic diseases are only managed by PC physicians.

One limitation regarding the diagnosis of AAT is that the reason to request a complementary test is not recorded in the SIDIAP database, and we cannot be completely certain of the indication leading to the AAT determination. We can only assume the reason based on the codified diagnosis or the results of liver function tests. Second, although databases are also subject to possible diagnostic and miscoding biases, considering that our main objective was to quantify the number of AAT determinations performed, we believe that this possible bias had little impact, if any, on the main objective of the second study.

The main strength of our study is the large coverage of the database, including more than 80% of the population of Catalonia (Spain), thereby ensuring the representativeness of our data. In addition, complementary sources included in SIDIAP provide quality information. The Pharmacy registry includes only prescriptions that the patient has picked up from the pharmacy, thus, the information regarding treatment patterns is accurate. Also, the laboratory results are collected from the laboratory records, which prevent errors in the introduction of data.

8. CONCLUSIONS

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Initial treatment patterns in newly diagnosed COPD patients often do no comply with guidelines.

The use of ICS is excessive but has decreased mainly in non exacerbator patients.

Many COPD patients still remain untreated after diagnosis, although this trend has decreased over time. Some GOLD 4 patients are still receiving SABD or no treatment at all after diagnosis.

The number of AAT determinations in PC is low in relation to the prevalence of COPD but increased slightly along the study period.

The indication to perform AAT determination is not always clear, and patients detected with deficiency are not always referred to a specialist.

9. APPLICABILITY

9. APLICABILITY

This is the first study on COPD with data obtained from SIDIAP database. It has shown that SIDIAP is a good source of information for epidemiological research in COPD. This population database provides real-life information of the COPD patients controlled in PC, and the results have demonstrated that the quality of the data is accurate.

The present study has allowed the identification of gaps in the prescription of treatment for newly diagnosed COPD patients. It has demonstrated poor implementation of the guidelines, which suggests the need to improve the dissemination of the COPD guidelines as well as to monitor the management and treatment patterns in PC.

Our results confirm the contention that the first reason for the underdiagnosis of AATD is the low number of AAT determinations performed in PC. This suggests that the dissemination of information regarding AATD among PC physicians could help to increase awareness of the disease. The incorporation of AATD screening to the current COPD protocols in PC could also help to reduce underdiagnosis.

Our study has also pointed out the need to improve the referral circuits and the communication between PC and the different specialists to prevent individuals diagnosed not receiving a definitive diagnosis. The international guidelines recommend the referral of every patient diagnosed with AATD for assessment in a reference center.

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ANNEX I

ANNEX I. Publications

Publication 1:

Barrecheguren M, Monteagudo M, Ferrer J, et al. Treatment patterns in COPD patients newly diagnosed in primary care. A population-based study. Respir Med 2016; 111:47-53.

Article with copyright:

http://www.ncbi.nlm.nih.gov/pubmed/26758585

Publication 2:

Barrecheguren M, Monteagudo M, Simonet P, et al. Diagnosis of Alpha-one antitrypsin deficiency: a population-based study. Int J Chron Obstruct Pulmon Dis. 2016: 10;11:999-1004.

http://www.ncbi.nlm.nih.gov/pubmed/27274221

International Journal of COPD

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ORIGINAL RESEARCH

Diagnosis of alpha-1 antitrypsin deficiency: a population-based study

This article was published in the following Dove Press journal:
International Journal of COPD
10 May 2016
Number of times this article has been viewed

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Introduction: Alpha-1 antitrypsin deficiency (AATD) remains an underdiagnosed condition despite initiatives developed to increase awareness. The objective was to describe the current situation of the diagnosis of AATD in primary care (PC) in Catalonia, Spain.

Methods: We performed a population-based study with data from the Information System for Development in Research in Primary Care, a population database that contains information of 5.8 million inhabitants (80% of the population of Catalonia). We collected the number of alpha-1 antitrypsin (AAT) determinations performed in the PC in two periods (2007–2008 and 2010–2011) and described the characteristics of the individuals tested.

Results: A total of 12,409 AAT determinations were performed (5,559 in 2007–2008 and 6,850 in 2010–2011), with 10.7% of them in children. As a possible indication for AAT determination, 28.9% adults and 29.4% children had a previous diagnosis of a disease related to AATD; transaminase levels were above normal in 17.7% of children and 47.1% of adults. In total, 663 (5.3%) individuals had intermediate AATD (50–100 mg/dL), 24 (0.2%) individuals had a severe deficiency (<50 mg/dL), with a prevalence of 0.19 cases of severe deficiency per 100 determinations. Nine (41%) of the adults with severe deficiency had a previous diagnosis of COPD/emphysema, and four (16.7%) were diagnosed with COPD within 6 months.

Conclusion: The number of AAT determinations in the PC is low in relation to the prevalence of COPD but increased slightly along the study period. The indication to perform the test is not always clear, and patients detected with deficiency are not always referred to a specialist.

Keywords: alpha-1 antitrypsin deficiency, population based, diagnosis, screening, COPD

Introduction

Alpha-1 antitrypsin deficiency (AATD) is a congenital autosomical codominant condition characterized by low plasma levels of alpha-1 antitrypsin (AAT) in the blood and tissues. More than 120 genetic variants of the AAT gene have been identified and classified into three major categories: normal, with genotype M, characterized by AAT within normal ranges; deficient, characterized by reduced but detectable AAT plasma levels with genotypes Z, S, and M-like; and null, currently designated as Q0, with no detectable plasma levels.[1] AATD is one of the most common congenital disorders with an estimated prevalence between one in 2,857 and one in 5,097 in USA[1] and between one in 2,175 and one in 5,164 in Spain.[2] AATD predisposes the development of certain diseases, especially COPD in adults and liver disease, which is more frequent in children. Other less frequent conditions associated with AATD are panniculitis, vasculitis, and fibromyalgia.[1]

The World Health Organization recommends the testing of all COPD patients,[3] and the European Respiratory Society and American Thoracic Society guidelines recommend the testing of all symptomatic adults with persistent airway obstruction,

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Dovepress
http://dx.doi.org/10.2147/COPD.S108565

such as COPD, emphysema, and asthma with incompletely reversible airflow obstruction, individuals with unexplained liver disease, and adults with necrotizing panniculitis or multisystemic vasculitis.[1] Similarly, the Spanish Society of Pneumology and Thoracic Surgery (SEPAR) recommends that all COPD patients should be tested at least once in their lives.[4] Despite these recommendations, AATD is significantly underdiagnosed, and most of the patients are detected long after the onset of pulmonary or liver disease. Another implication of this late diagnosis is the delay in the detection of affected relatives, which hinders the implementation of measures, such as abstaining from tobacco exposure.[5,6]

Underdiagnosis of AATD is a challenge, particularly, for primary care (PC) physicians who attend most of the COPD patients, and this is usually the first point of contact of patients with health care providers. Computerized databases of medical records are increasingly used in clinical research to enhance the knowledge about the management and progression of this disease based on real-life data.[7] Database studies help to understand real clinical practice and to design public health strategies to improve the quality of care. The objective of this study was to describe the patterns of diagnosis of AATD in PC in Catalonia, Spain.

Methods

This was an epidemiological, population-based, observational study aimed to quantify and compare the number of AAT determinations performed in the PC in Catalonia during two 2-year periods (2007–2008 and 2010–2011) and to describe the characteristics of the individuals tested and the management of those with deficient values. Data for this study were obtained from the System for the Development of Research in Primary Care (SIDIAP) database, a computerized database containing anonymized patient records for the 5.8 million people registered in the 279 PC centers of the Catalan Health Institute (>80% of Catalonia's population). All general practitioners in the Catalan Health Institute use the same specific software called eCAP to record the clinical information of their patients. Health professionals gather this information using codes of International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, and structured forms designed for the collection of variables. SIDIAP combines information from the electronic medical records with data from other databases and registers, such as laboratory test results (from the laboratory databases), the pharmacy register, and the National Mortality Register.[8,9] For the purpose of the study, we checked the quality of the SIDIAP database. High-quality data were obtained from 2007 onward; however, data from 2012 were not available at the time of the initiation of the study. Therefore, to compare two periods of the same length, we used data from 2007 to 2008 and 2010 to 2011. The study was approved by IDIAP Jordi Gol Ethics Committee (Barcelona, Spain). This was a retrospective study with data from an anonymized database, so it was not necessary to request patient consent.

Population

All the individuals with an AAT determination during the study period were included. Based on the levels obtained in the determination, individuals were classified as follows: no deficiency: AAT >100 mg/dL; intermediate deficiency: AAT between 50 mg/dL and 100 mg/dL; and severe deficiency: AAT <50 mg/dL.[10] Since indications for AAT testing differ by age group, we classified individuals younger than 15 years as children and analyzed them separately. Demographic and clinical characteristics were recorded for all the study populations. For individuals with intermediate and severe deficiencies, we collected data on referrals to a specialist, complementary tests (spirometry and computerized tomography scans), pharmacologic treatment, and number of respiratory infections during the 6 months following the determination.

Statistical analysis

A descriptive analysis of each period (2007–2008 and 2010–2011) and of the totality of the sample was performed separately for children and adults. For qualitative variables, absolute frequencies and corresponding percentages were calculated. Quantitative variables following a normal distribution were described by mean and standard deviation, while those not following a normal distribution were described using the median and 25–75 percentiles. Differences between groups were performed using the chi-square test for categorical variables, while continuous variables were tested using the Student's *t*-test (or the Mann–Whitney *U*-test, if the variables were not normally distributed). All tests were two-tailed, and significance was set at 5%. All statistical analyses were performed using a statistical software package (SPSS Version 20.0; IBM Corporation, Armonk, NY, USA).

Results

Frequency of AAT determinations

In total, 12,409 determinations of serum AAT were performed during the 4 years of the study, of which 1,335 (10.7%) were children. The number of determinations was higher in the second period (5,559 determinations in 2007–2008 and 6,850 determinations in 2011–2011) due to the low number of individuals tested in 2007. Nonetheless, the rate of individuals tested per year did not increase

Table 1 Number of AAT determinations performed by year

Period	Children	Adults	Total	n/10,000 inhabitants
2007	331	1,998	2,329	4.33
2008	382	2,848	3,230	6.85
2007–2008	713	4,846	5,559	
2010	325	3,351	3,676	6.77
2011	297	3,676	3,174	5.82
2010–2011	622	6,228	6,850	

Abbreviation: AAT, alpha-1 antitrypsin.

significantly after 2008 (Table 1). Figure 1 shows the number of determinations performed by age groups.

Characteristics of the individuals tested

The mean age of the individuals tested was 52.6 (SD 16.3) years in adults and 4.6 (SD 4.1) years in children, with an equal distribution between sexes. Among adults, 37.1% were smokers or former smokers. The most frequent comorbidities in adults were dyslipidemia (27.6%), hypertension (27.4%), diabetes mellitus (11.7%), depression (10.1%), and ischemic heart disease (4%). Up to 41% of children and 18.5% of adults were receiving treatment for a respiratory disease at the time of the determination. The majority of the determinations were performed in urban areas. Demographic characteristics are shown in Tables 2 and 3.

Indications for AAT determinations, AAT concentrations, and follow-up

As a possible indication for AAT determination, 3,195 (28.9%) adults and 393 (29.4%) children had a previous diagnosis of a disease related to AATD. Up to 17.7% of children and 47.1% of adults had transaminase levels above normal (Tables 2 and 3). Nine percent of children were between the age 0 year and 1 year, suggesting neonatal jaundice as the most likely indication. During the previous year, 31.3% of individuals had had at least one respiratory infection and 1.3% had had pneumonia.

The mean AAT plasma level was 147.2 (36.7) mg/dL in adults and 154.1 (37.2) mg/dL in children. In total, 663 (5.3%) individuals (56 children) had an intermediate AAT deficiency, while 24 (0.2%) individuals (two children) had a severe deficiency, with a prevalence of 0.19 cases of severe deficiency per 100 determinations. Patients with severe deficiency were younger than individuals with normal AAT levels (42.5 years vs 52.9 years, $P=0.003$) and were more likely to have a previous diagnosis of COPD or emphysema (45.5% vs 10.8%, $P<0.05$) (Table 3).

During the 6-month follow-up, four of the patients with severe deficiency (18.1%) were newly diagnosed with COPD or emphysema, two (9.1%) following diagnostic spirometry and one (4.2%) after a computerized tomography scan. Only three patients (13.6%) were referred to a pneumologist and another patient was referred to internal medicine (Table 4).

Discussion

The results of this study show that the number of AAT determinations performed in the PC in Catalonia, Spain, is low and has not increased after 2008. In addition, in most cases, we could not identify the reason for requesting the test, and after detection of a severe deficiency, some individuals were not tested further or referred to a specialist.

AATD is one of the most common congenital disorders but remains significantly underdiagnosed despite the

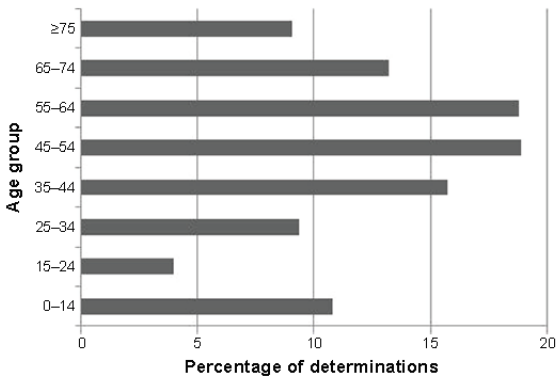

Figure 1 Distribution of percentage of AAT determinations performed by age group.
Abbreviation: AAT, alpha-1 antitrypsin.

Table 2 Demographic characteristics and diseases related to AATD of children tested for AAT during the study period

Variables	Children (n=1,335)
Mean age (SD)	4.61 (4.1)
Sex (males)	769 (57.6)
Urban setting	868 (65)
Smokers	12 (0.9)
Former smokers	2 (0.1)
Bronchiectasis	2 (0.1)
Asthma	298 (22.3)
Hepatitis	7 (0.5)
Cirrhosis	0
Hepatocarcinoma	0
High transaminase levels	236 (17.7)

Note: Data are shown as n (%) unless specified otherwise.
Abbreviations: AAT, alpha-1 antitrypsin; AATD, alpha-1 antitrypsin deficiency.

recommendations of national and international guidelines.[1,2] Moreover, there is still a large delay between the onset of symptoms and diagnosis,[11] with no significant improvement in this delay during the last decades.[12] In Spain, it is estimated that 12,026 patients have a severe deficiency,[13] with ~1,700 of these cases corresponding to Catalonia alone.[14] Nonetheless, only 511 cases from all over the country are diagnosed and included in the Spanish registry for AATD.[15]

Possible explanations for the underdiagnosis of AATD have been addressed in previous studies. Knowledge of AATD is generally poor even for trainees who declared a special interest in respiratory medicine.[16] Among nonpulmonologists, awareness of AATD is low in comparison with other respiratory diseases,[17] with the consequent low rate of testing for AATD.[11,12,18] A survey carried out in Spain and Portugal showed that the main reasons for not testing for AATD are the referral of patients to other specialists for testing or the erroneous perception of the high cost of the test.[19]

Despite the current recommendations of testing symptomatic adults with persistent airway obstruction and individuals with unexplained liver disease,[1,2] the rate of AAT determinations observed in our study along the years varied from 4.33 determinations per 10,000 inhabitants in 2007 to 6.85 determinations per 10,000 inhabitants in 2008, with intermediate values for 2010 and 2011. Data from a recent study performed with data from SIDIAP indicated that a mean of 6,932 new patients were diagnosed with COPD per year between 2007 and 2012, a figure well above the 375 mean number of COPD patients tested yearly for AATD during the 4 years of our study.[9] Although underdiagnosis of the deficiency has been reported in many countries, to our knowledge, this low rate of AAT determinations in the general population and in COPD patients has not been previously reported, thereby not allowing comparison of our findings with data from other countries or geographical areas.

Regarding the reasons for requesting AAT determination, we observed that only 13% of the adults tested had COPD,

Table 3 Comparison of the characteristics of adult patients tested for AAT during the study period according to AAT levels

Variable	Normal AAT levels (n=10,445)	Intermediate deficiency (n=607)	Severe deficiency (n=22)	Total (n=11,074)
Age, mean (SD)	52.9 (16.3)	48.0 (14.4)**	42.5 (15.7)**	52.6 (16.3)
Sex (males)	5,756 (55.1)	377 (62.1)**	14 (63.6)	6,147 (55.5)
Smoker	2,219 (21.2)	113 (18.6)	7 (31.8)	2,339 (21.1)
Former smoker	1,668 (16)	101 (16.6)	3 (13.6)	1,772 (16)
AAT (mg/dL), mean (SD)	150.9 (34.2)	87.6 (10.8)	27.6 (11.6)	147.2 (36.7)
Previous diseases related to AATD				
COPD	937 (9)	34 (5.6)*	6 (27.3)*	977 (8.8)
Emphysema	193 (1.8)	14 (2.3)	4 (18.2)**	211 (1.9)
Chronic bronchitis	293 (2.8)	14 (2.3)	0	307 (2.8)
Bronchiectasis	284 (2.7)	11 (1.8)	0	295 (2.7)
Asthma	794 (7.6)	45 (7.4)	3 (13.6)	842 (7.6)
Hepatitis	768 (7.4)	32 (5.3)	1 (4.5)	801 (7.2)
Cirrhosis	127 (1.2)	3 (0.5)	0	130 (1.2)
Hepatocarcinoma	4 (0)	0	0	4 (0)
High transaminase levels	5,430 (52)	313 (51.6)	8 (36.4)	5,751 (51.9)
Previous respiratory infections	3,486 (33.8)	162 (26.6)*	9 (40.9)	3,657 (33.02)
Previous pneumonia	136 (1.6)	5 (0.8)	1 (4.5)	142 (1.3)
Hypertension	2,908 (27.8)	126 (20.8)**	2 (9.1)*	3,036 (27.4)
Dyslipidemia	2,901 (27.8)	158 (26)	2 (9.1)*	3,061 (27.6)
DM	1,247 (11.9)	44 (7.2)**	1 (4.5)	1,292 (11.7)
Depression	1,070 (10.2)	51 (8.4)	2 (9.1)	1,123 (10.1)
Ischemic heart disease	428 (4.1)	13 (2.1)**	0	441 (4)

Notes: *$P<0.05$ and **$P<0.01$ compared to individuals with normal AAT levels. Data are expressed as n (%) unless specified otherwise.
Abbreviations: AAT, alpha-1 antitrypsin; AATD, alpha-1 antitrypsin deficiency; DM, diabetes mellitus.

Table 4 Six-month follow-up of adults tested for AATD according to AAT levels

Diagnosis after AAT determination	Normal AAT levels (n=10,445)	Intermediate deficiency (n=607)	Severe deficiency (n=22)
COPD	106 (1)	5 (0.8)	2 (9.1)*
Emphysema	36 (0.3)	1 (0.2)	2 (9.1)**
Chronic bronchitis	18 (0.2)	2 (0.3)	0
Respiratory infections	3,090 (29.5)	148 (24.4)**	10 (45.5)*
Pneumonia	58 (0.6)	3 (0.5)	0
Spirometry	407 (2.9)	24 (4)	2 (9.1)
Referrals			
Pneumology	229 (2.2)	22 (3.6)*	3 (13.6)*
Gastroenterology	489 (4.7)	42 (6.9)*	0
Internal medicine	73 (0.7)	2 (0.3)	1 (4.5)

Notes: *$P<0.05$ and **$P<0.01$ compared to individuals with normal levels of AAT. Data are expressed as n (%).
Abbreviations: AAT, alpha-1 antitrypsin; AATD, alpha-1 antitrypsin deficiency.

chronic bronchitis, or emphysema and half had high transaminase levels, which could justify the request for AAT determination. These results concur with the observation that >70% of PC physicians in Spain were aware of liver complications of AATD, but very few decided to test all COPD patients.[19] Similarly, only 0.5% of children had a codified liver disease at the time of AAT determination, and interestingly, the number of children tested for transaminitis and asthma was similar, although AATD is not a recognized cause of respiratory diseases in childhood.[20]

In an attempt to improve the rate of diagnosis of AATD in COPD, several screening initiatives or case findings have been developed,[21–25] some being carried out in the PC.[22,23] In the IDDEA project of case finding of AATD in COPD patients, volunteer PC physicians were provided with filter paper to collect dried blood spots, together with information about AATD and a Web tool. The ratio of recruitment only reached 6.6 patients per participant over the 9-month collection period, being somewhat low considering that the estimated prevalence of COPD in Spain is 10.2% of adults older than 40 years.[26] However, among the individuals tested, 4% were carriers of the severe deficient allele Z, and 0.34% were diagnosed with severe homozygous PiZZ deficiency.[23] Jain et al[24] implemented an electronic alert to encourage guideline-based testing for AATD. This alert was displayed for patients with obstructive spirometry results, and this tool was associated with an increase in the frequency of testing.

Other strategies, such as programs to educate respiratory physicians[27] and the combination of an awareness program with the offer of free diagnostic testing,[28] resulted in high rates of detection of individuals with severe AATD. Population screening programs in areas of high prevalence or protocols to measure and phenotype AAT in selected patients were found to be effective at detecting AATD patients.[29–31]

Our study has some limitations. First, the reason to request a complementary test is not recorded in the SIDIAP database, and we cannot be completely certain of the indication leading to the AAT determination. We can only assume the reason based on the codified diagnosis or the results of liver function tests. Second, databases are also subject to possible diagnostic and miscoding biases.[32] However, considering that our main objective was to quantify the number of AAT determinations performed, we believe that this possible bias had little impact, if any, on the main objective of the study. On the other hand, the SIDIAP database includes data from >80% of the population of our area, thereby ensuring the representativeness of the results for the whole population of Catalonia.

Conclusion

Our study shows that the rate of testing for AAT in PC is still low, and the reasons for requesting the determination often remain unclear. These results should help to design interventions to increase the awareness and the diagnosis of AAT in selected individuals or populations according to the current guidelines for the diagnosis and management of AATD.

Acknowledgment

This study was funded by unrestricted grants from Grifols, Fundació Catalana de Pneumologia, and the Spanish Society of Pneumology and Thoracic Surgery.

Disclosure

Marc Miravitlles has received speaker fees from Almirall, Boehringer Ingelheim, Pfizer, AstraZeneca, Chiesi, Esteve, GlaxoSmithKline, Menarini, Grifols, Nycomed, and Novartis and consulting fees from Almirall, Boehringer Ingelheim, Pfizer, GlaxoSmithKline, GebroPharma, CSL Behring,

MediImmune, Novartis, Grifols, and Nycomed. Carl Llor received a grant from the Fundació Jordi Gol I Gurina for research at the University of Cardiff in 2013. He has also received research grants from the European Commission (Sixth and Seventh Programme Frameworks), the Catalan Society of Family Medicine, and Instituto de Salud Carlos III. Pere Simonet has received speaker fees from Chiesi, Gebro Pharma, Menarini, and TEVA. Miriam Barrecheguren has received speaker fees from Menarini, GlaxoSmithKline, and GebroPharma and consulting fees from Novartis. The other authors report no conflicts of interest in this work.

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ANNEX II

ANNEX II. List of national and international presentations

- Barrecheguren M, Monteagudo M, Ferrer J, Borrell E, Llor C, Miravitlles M. "Treatment patterns in the newly diagnosed COPD patients in Catalonia between 2007-2012".

  - ERS Congress, Munich 6-10 September 2014.
  - ATS 2015 Denver, 15-20 May 2015

- Barrecheguren M, Monteagudo M, Llor C, Borrell E , Miravitlles M. " Patterns of initial treatment for COPD according to clinical phenotypes in Catalonia". REG Summit, London 28-29 June 2014

- Barrecheguren M, Monteagudo M, Esquinas C, Ferrer J, Borrell E, Llor C, Miravitlles M. "Prescription patterns in the newly diagnosed COPD patients according to severity" / "Pautas de tratamiento en la EPOC de nuevo diagnóstico según gravedad"

  - REG Summit, Rotterdam 23-24 January 2015
  - SEPAR 2015, Gran Canaria 5-8 June 2015
  - ERS Congres Amsterdam 26-30 September 2015

-Barrecheguren M, Monteagudo M, Rodríguez-Blanco T, Esquinas C, Ferrer J, Borrell E, Simonet P, Llor C, Miravitlles M. "Characteristics of newly diagnosed COPD patients without a maintenance treatment: a population-based study". / "Características de los pacientes diagnosticados de EPOC sin tratamiento de mantenimiento: studio poblacional".

  - REG Summit, Lyon 15-16 April 2016
  - SEPAR 2016, Granada 10-13 June 2016

-Barrecheguren M, Monteagudo M, Simonet P, Llor C, Esquinas C, Rodriguez E, Ferrer J, Miravitlles M. "Diagnosis of Alpha 1 antitrypsin deficiency in Primary

Care: a Database Study". / "Déficit de Alfa 1 antitripsina: identificación de carencias en el diagnóstico en Atención Primaria".

- XXIII Diada Pneumológica. Barcelona 17-18 April 2015.
- SEPAR 2015, Gran Canaria 5-8 June 2015
- ERS Congres Amsterdam 26-30 September 2015