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Asthma-COPD Overlap: Findings of the EPOC.AR Study

Superposición Asma-EPOC: los hallazgos en el estudio EPOC AR

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ABSTRACT

Background: Asthma and COPD are heterogeneous diseases, and some patients share clinical features of both conditions. There are uncertainties about the criteria to define asthma-COPD overlap (ACO), and its prevalence is 15-25% in the adult population with chronic airflow obstruction. The purpose of this study was to determine the prevalence of ACO in Argentina, which is unknown.

Objectives: Primary: to determine the prevalence of ACO in the EPOC.AR study. **Secondary:** to evaluate and analyze the clinical features of patients with ACO, the severity of the symptoms, and the frequency and severity of exacerbations. to describe and compare the treatment of ACO with that of pure COPD.

Database of the EPOC.AR study: spirometries, asthma, atopy or rhinitis, respiratory symptoms: CAT (COPD Assesment Test) and mMRC (Modified Medical Research Council) scale, frequency of exacerbations/previous year, comorbidities and treatments. 2017 GOLD Guides (Global Initiative for Chronic Obstructive Lung Disease) to determine airflow obstruction degrees and Groups A, B, C, and D.

ACO diagnostic criteria (expert committee from USA, East Europe and Asia that took place in Denver, 2015):

MAJOR CRITERIA: 1. Persistent obstruction (post-BD [bronchodilator] FEV_1/FVC (forced expiratory volume in the first second/forced vital capacity) < 70% or LLN [lower limit of normal]) in ≥ 40 years. 2. SM (smoking) ≥ 10 packs/year, air pollution or biomass. 3. Documented history of asthma before 40 years or post-BD response ≥ 400 ml in FEV_1.

MINOR CRITERIA: 1. Documented history of atopy or allergic rhinitis. 2. Post-BD response in FEV_1 > 200 ml. 3. Peripheral blood eosinophil count ≥ 300 cells-UI^{-1} (not performed in EPOC.AR).

Chi-Square Test, Pearson's Chi Square Test, likelihood ratio, linear-by-linear association.

Results: COPD (n 498), n 95 with ACO criteria, males (53.4%), mean age 63.6 years. 1% without asthma and BD response ≥ 400 ml; 32.7% asthmatics (3.6% with BD response ≥ 400 ml and 14.5% between 200-400 ml); n 23 with BD response ≥ 400 ml (4.6%). ACO prevalence: 19.08% (CI [Confidence Interval] 15.6-22.5) and 2.6% of the total population of EPOC.AR. In the comparison between the ACO and COPD populations, we detected the following: lower mean age and pre-BD FEV_1 ($p < 0.01$), higher frequency of BD response

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(p < 0.05), higher frequency of sibilance (p < 0.01; CI 2.75-7.64), higher frequency of previous asthma diagnosis (p < 0.01; CI 3.79-10.05); and 26.08% had family history of asthma. Greater use of ATBs (antibiotics) (p < 0.05) and ICS (inhaled corticosteroids)/ LABA (long-acting beta- adrenergic agonists) (p < 0.05; CI 1.1-5.3). Higher frequency of exacerbations (12.47%; CI 9.56-15.39) that motivated the indication of medication in 90.48% and 2.49 times more alterations in daily activities and absence from work. There weren't any significant differences between patients with ACO and pure COPD regarding frequency of groups A, B, C and D.

Conclusions: the prevalence of ACO was 19.08% in the COPD patients of the EPOC. AR study; they were significantly younger, with higher degree of obstruction, frequency of sibilance, use of antibiotics/previous year and inhaled corticosteroids (LABA/IC). We emphasize the importance of identifying this phenotype in order to use a suitable treatment, given its clinical implications and deterioration in quality of life.

Key word: Asthma; Pulmonary disease; chronic obstructive; Smoking

RESUMEN

Introducción: Asma y EPOC son enfermedades heterogéneas, algunos pacientes comparten características clínicas de ambas. Existen incertidumbres en los criterios para definir superposición asma-EPOC (ACO) y la prevalencia es entre el 15% y el 25% de la población adulta con obstrucción crónica del flujo aéreo. Motiva este estudio determinar la prevalencia de ACO en Argentina, que es desconocida.

Objetivos: Primario: Determinar prevalencia de ACO en el estudio EPOC-AR. **Secundarios:** Evaluar y analizar las características clínicas de los pacientes con ACO, la gravedad de los síntomas, la frecuencia y gravedad de exacerbaciones. Describir y comparar el tratamiento entre ACO vs. EPOC puros.

Base de datos del estudio EPOC.AR: Espirometrías, asma, atopía o rinitis, síntomas respiratorios: CAT (prueba de evaluación de EPOC) y mMRC (Medical Research Council modificado), frecuencia de exacerbaciones/año previo, comorbilidades y tratamientos. Guías GOLD 2017 para determinar grados de obstrucción espirométrica y Grupos A, B, C y D.

Criterios diagnósticos de ACO (comité expertos USA, Europa del Este y Asia-Denver 2015):

CRITERIOS MAYORES: **1.** Obstrucción persistente (FEV_1/FVC pos-BD <70% o LIN) en ≥ 40 años. **2.** TBQ ≥ 10 paquetes/año, contaminación ambiental o biomasa. **3.** Historia documentada de asma antes de los 40 años o respuesta pos-BD ≥ 400 mL en FEV_1.

CRITERIOS MENORES: **1.** Historia documentada de atopía o rinitis alérgica. **2**. Respuesta pos-BD en FEV_1 > 200 mL. **3.** Recuento de eosinófilos en sangre periférica ≥ 300 células-UI^{-1} (no realizado en EPOC.AR).

Prueba de Chi-cuadrado, Chi-cuadrado de Pearson, razón de verosimilitud, asociación lineal por lineal.

Resultados: EPOC (n498), n95 con criterios de ACO, masculino (53,4%) y edad promedio 63,6 años.

El 1%, sin asma y respuesta BD ≥ 400 mL; el 32,7%, asmáticos (3,6% respuesta BD ≥ 400 mL y el 14,5%, entre 200-400 mL); n23 respuesta BD ≥ 400 mL (4,6%). Prevalencia ACO: 19,08% (IC 15,6-22,5) y del 2,6% del total de la población de EPOC.AR. En población ACO vs. EPOC, se detectó: menor promedio de edad y de FEV_1 pre BD (p < 0,01), mayor respuesta BD (p < 0,05), mayor frecuencia de sibilancias (p < 0,01; IC 2,75-7,64), mayor frecuencia de diagnóstico previo de asma (p < 0,01; IC 3,79-10,05) y el 26,08% tenían antecedentes familiares de asma. Mayor uso de ATB (p < 0,05) e ICS/LABA (p < 0,05; IC 1,1-5,3). Mayor frecuencia de exacerbaciones (12,47%; IC

9,56-15,39) que motivaron indicación de medicación en un 90,48% y 2,49 veces más de alteraciones en actividades diarias y ausentismo laboral. No se registraron diferencias significativas entre pacientes con ACO frente a EPOC puros en frecuencia de grupos A, B, C y D.

Conclusiones: La prevalencia de ACO fue del 19,08% en pacientes EPOC del estudio EPOC.AR; tenían significativamente menor edad, mayor grado de obstrucción, frecuencia de sibilancias, uso de antibióticos/año previo y CI (LABA/CI). Destacamos la importancia de identificar este fenotipo para un tratamiento adecuado por sus implicancias clínicas, y deterioro en calidad de vida.

Palabras clave: Asma; Enfermedad pulmonar obstructiva crónica; Tabaquismo

INTRODUCTION

With the growing recognition of asthma and COPD as heterogeneous diseases that share clinical, functional and inflammatory similarities, attention has been drawn to patients with clinical features of both diseases, who were qualified as patients with asthma-COPD overlap (ACO)[1, 2]. In smokers, asthma is considered a risk factor for developing COPD, as shown in the Tucson epidemiologic study, with a 12 times higher risk in asthmatic smokers versus non-asthmatic smokers[3].

Another information that supports the coexistence of the asthma-COPD overlap is the fact that it has been proven that bronchial hyperresponsiveness is an independent predictor of COPD and mortality from respiratory causes in population-based studies[4], as well as a risk indicator of the accelerated decline in lung function in patients with mild COPD[5].

At present, there isn't any evidence supporting the therapeutic decisions in patients with ACO, since traditionally they have been systematically excluded from research protocols in order to maintain the homogeneity of the population among those who complied with the standard definitions of COPD or asthma[1].

Approximately one every four patients with COPD has asthmatic features; those were recently qualified as ACO by the Global Initiative for Asthma (GINA) and the Global Initiative for COPD (GOLD). Therefore, to identify them in real life poses a diagnostic and therapeutic challenge[1]; also the accurate definition of ACO is still controversial[6].

However, there is emerging agreement that some of the key features of ACO include persistent airflow limitation defined as a post-bronchodilator FEV_1/FVC ratio < 70%, in symptomatic individuals aged 40 years or older with well-documented history of asthma during childhood or early adulthood, and exposure to cigarette smoke (more than 10 p/y) or to biomass[1].

In patients with COPD, the ACO diagnosis is fundamental for including the prescription for an inhaled steroid (ICS). On the other hand, asthmatic patients diagnosed with ACO don't show significant therapeutic implications, because initial therapy with the combination of long-lasting beta agonists plus ICS is the same for pure asthmatics and patients with asthma-COPD overlap[2].

The impact of the correct diagnosis for and adequate treatment choice is crucial, because patients with ACO have a higher symptom burden, such as dyspnea and cough, an increased risk of rapid decline in FEV_1, of exacerbations, hospitalization and mortality due to COPD[1] when compared to patients with pure COPD or asthma.

The purpose of this study about the prevalence of the asthma-COPD overlap through the database of the EPOC.AR epidemiological study[7] was to know the reality of our country, since up to now there isn't any information regarding this topic.

Objectives

Primary: to determine the prevalence of ACO in the EPOC.AR epidemiological study regarding the prevalence of COPD in Argentina[7].

Secondary

1. To evaluate and analyze the clinical features of patients with ACO compared to patients with COPD.
2. To describe and compare treatments received by patients with ACO and COPD.

MATERIALS AND METHODS

This study is a sub-analysis of the EPOC.AR study which includes all the patients diagnosed with COPD and differen-

tiates (within that group) patients with diagnostic criteria of ACO from those with COPD. The EPOC. AR. study [7] is multicenter, cross-sectional, and population-based. The population of the study has been randomly selected using cluster sampling and was divided into 6 urban clusters of Argentina, with the purpose of establishing the prevalence of COPD and evaluate the clinical and sociodemographic characteristics of patients, the treatment, and the various risk factors. The study was conducted between August 2014 and May 2016.

The following urban clusters were selected: La Plata, Rosario, Autonomous City of Buenos Aires, Northern Region of Gran Buenos Aires, Córdoba and Mendoza. The sample was selected by means of probability, multistage cluster sampling based on map units and described in detail in supplementary material. Each selected person was invited to participate in the study. Subjects who accepted were requested to sign the informed consent[7].

Definition of terms

COPD was defined as a post-bronchodilator FEV_1/FVC ratio < 0.7, and the GOLD 2017 classification was used to define the degree of obstruction and multidimensional ABCD assessment[10].

GOLD 2017 classification[10] Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017. http://goldcopd.org

Definition of ACO

The diagnostic criteria for ACO were recommended by a panel discussion with experts from North America, East Europe and Asia that took place in Denver (CO, USA) on May 16th, 2015.

There are 3 major criteria and 3 minor criteria. The Committee recommends the presence of all 3 major criteria and at least 1 of the minor criteria.

Even though the Committee acknowledges that it is an arbitrary definition that needs validation, these are dynamic criteria, and with the addition of new data, modifications will be required[11].

MAJOR CRITERIA

1. Persistent obstruction of the airway (post-BD FEV_1/FVC < 70% or LLN) in individuals aged 40 or older.
2. Smoking (at least 10 packs/year) or exposure to indoor or outdoor air pollution (for example, biomass).
3. Documented history of asthma before 40 years or bronchodilator response > 400 ml for FEV_1.

MINOR CRITERIA

1. Documented history of atopy or allergic rhinitis.
2. Bronchodilator response for FEV_1 < 200 ml.
3. Peripheral blood eosinophil count ≥ 300 cells-Ul^{-1}.

NOTE: the presence of eosinophilia in peripheral blood will be excluded from minor criteria, since no blood extractions were performed in patients from the EPOC. AR study for any type of test.

EXACERBATIONS

Exacerbations were defined according to the 2017 GOLD Guides[10] as acute worsening of symptoms that require additional treatment.

Exacerbations are classified as:

1. MILD: treated with short-acting bronchodilators (SABDs).
2. MODERATE: treated with SABDs plus antibiotics and/or oral corticosteroids.
3. SEVERE: the patient requires hospitalization or visits to the emergency department. They may also be associated with acute respiratory failure.

The following variables were analyzed in patients diagnosed with COPD:

1. Medical record data:
   - Smoking history (packs/year).
   - History of asthma, atopy or allergic rhinitis.
   - Respiratory symptoms: CAT (COPD Assessment Test) questionnaires [8] and mMRC (Modified Medical Research Council) questionnaire. [9]
   - Frequency of exacerbations the previous year with/without hospitalization.
   - Systemic comorbidities.
   - Treatment received.
2. Pre- and post-BD spirometries.

Statistical analysis

Chi-Square Test, Pearson's Chi Square Test, likelihood ratio, linear-by-linear association. The statistical analysis shall be conducted with the InfoStad 2014e program. A p-value < 0.05 shall be considered significant.

RESULTS

The population with diagnostic criteria for COPD included 504 patients, but there weren't any available data in 6 of them, so the analyzed population was 498 patients (n = 498). The prevalence of COPD was 14.5% (CI: 13.4-15.7%). In this population we detected 95 patients with criteria for ACO, mostly males (53.4%) with a mean age of 63.6 years (SD ± 10.83) distributed in the following way: 28% of the population between 40-59 years, 52% between 60-75 years, and 20% more than 75 years.

The prevalence of ACO in the population with diagnostic criteria for COPD was 19.08% (95% CI: 15.6-22.5), which is 2.6% of the whole population of the EPOC.AR study. The prevalence of cases compatible with ACO, according to the diagnostic criteria that were used, are shown in **Figure 1,** with 1% of patients with no history of asthma and a BD response ≥ 400 ml, and 32.7% of patients with asthma but with different bronchodilator responses: 3.6% with a BD response ≥ 400 ml and 14.5% with a BD response of 200-400 ml **(Figure 2).**

4.6% of the whole population with diagnostic criteria for ACO, including asthmatic and non-asthmatic patients (n = 23) showed a BD response ≥ 400 ml.

Table 1 compares the populations of patients with COPD with those with diagnostic criteria for ACO; it was detected that the latter show a

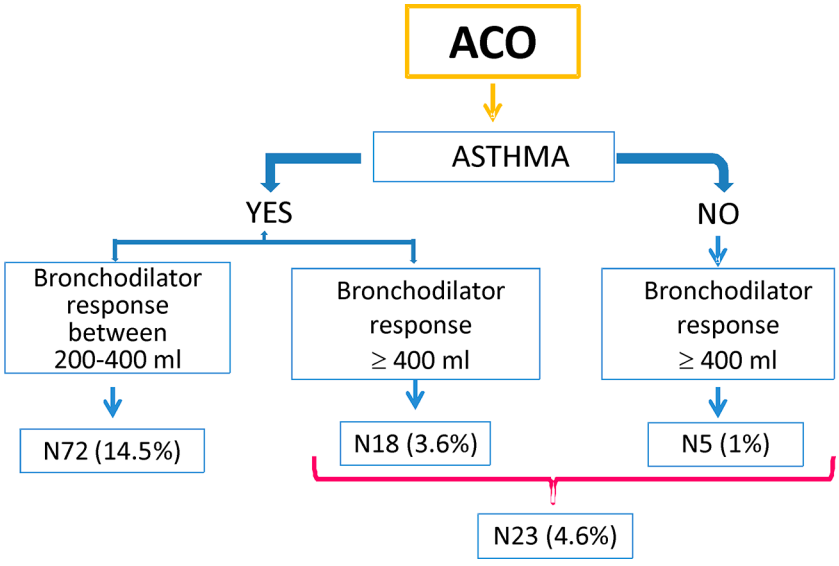

Figure 1. Frequency of criteria and prevalence of cases compatible with ACO.

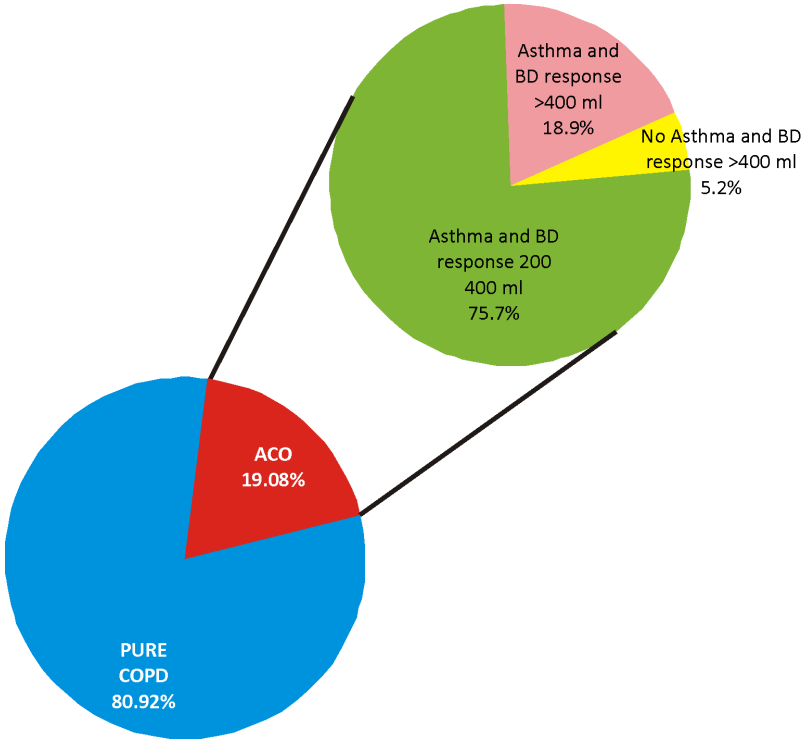

Figure 2. Frequency of criteria and prevalence of cases compatibles with ACO.

lower mean age and lower average pre-BD FEV_1, both with statistical significance ($p < 0.01$). There were also significant differences in post-BD spirometries, since a higher BD response was found ($p < 0.05$) in patients with ACO. Also a higher frequency of sibilance ($p < 0.01$; CI 2.75-7.64%), and larger increase in previous asthma and bronchitis diagnoses ($p < 0.01$; CI 3.79-10.05%) were detected, and in 26.08% (CI 22.16-29.99%) the patient was aware that some family member had an asthma diagnosis. If we consider the medication of patients with ACO,

TABLE 1. Frequency of variables selected between cases compatible with ACO versus COPD

Variables	ACO		COPD		p value
Mean age	63.6 (SD ± 10.83)		66 (SD ± 10.28)		p < 0.01
Sibilance the last 12 months	N:65	73%	N:150	37.1%	p < 0.01
Previous asthma diagnosis	N:272	54.6%	N:226	45.4%	< 0.05
Pre-BD FEV1: SD (standard deviation)	1.72 L	SD 0.62	SD 1.89	0.75 L	p < 0.01
BD response	0.330 L		0.050 L		p < 0.05
Use of ICS/LABA	N:13	34.2%	N: 52	55.9%	< 0.05
Use of antibiotics	N: 3	7.9%	N: 13	14%	< 0.05
Frequency of exacerbations/previous year Required ATB	N: 9	100	N: 29	65.9	< 0.05
Absence from work due to respiratory problems	N: 30	33.3%	N: 68	16.7%	< 0.05
Total	95	–	403	–	–
No information	6	–		–	–
Total	504	–		–	–

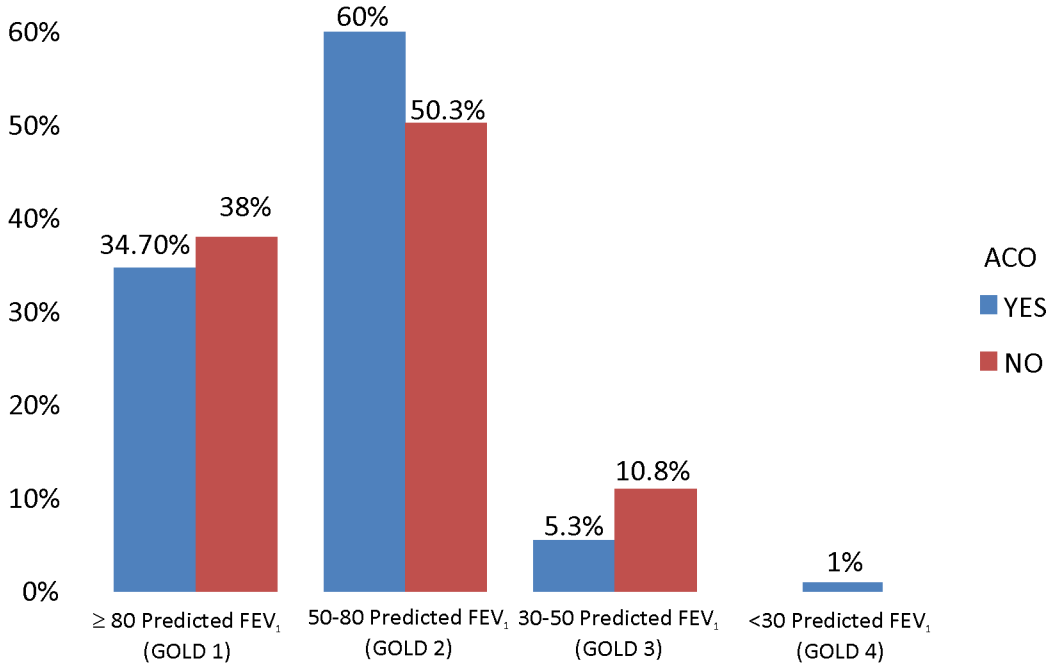

Figure 3. EPOC.AR: degrees of obstruction according to the GOLD Guides in ACO versus pure COPD groups.

they mostly used inhaled corticosteroids combined with long-acting B_2 agonist bronchodilators (ICS/LABA) $p < 0.05$; CI 1.1-5.3%. The frequency of exacerbations was higher in the group of patients with ACO (12.47%; CI 9.56-15.39%), with an increase in the use of ATBs ($p < 0.05$) indicated by health professionals in 90.48%. Patients with ACO showed 2.49 times (95% CI: 1.50-4.15) more probabilities of having respiratory problems that altered their daily activities or caused absence from work, in comparison with pure COPD patients ($p < 0.05$).

TABLE 2. Comorbidities in patients with ACO versus COPD

Comorbidities	ACO		COPD		p < 0.005
	N	%	N	%	
Heart diseases	90	22.2	13	14.6	0.11
Arterial diseases	51	12.7%	6	6.8%	0.11
Aht	192	47.6	38	42.7	0.39
Dbt	46	11.5	5	5.7	0.11
Dyslipidemia	103	26	21	24.7	0.80
Lung cancer	4	1	0	0	1.00
Vascular brain disease	6	1.5	1	1.1	1.00
Tuberculosis	10	2	0	0	0.22

DISCUSSION

There are wide variations in the prevalence of ACO that are related to the type of population under evaluation (database analysis or clinical trials), the different criteria used for the identification of ACO, and the definition of asthma and COPD[6], and also to the age group (all the adults or subjects older than 40 years).

The prevalence of ACO in the general population oscillates between 1.6 and 4.5%, in patients with COPD, between 12.1 and 55.2%, and in patients with asthma, between 13.3 and 61%[13].

In the UPLIFT (Understanding Potential Long-term Impacts on Function with Tiotropium) study, when considering the criterion of a significant response to bronchodilator, the prevalence in COPD patients was 52%[16].

In a recently published meta-analysis including 19 studies, the prevalence of ACO among patients with a COPD diagnosis was 27% in population-based studies, and 28% in studies carried out in hospitalized patients[6].

In Spain, results from the recent CHAIN study including 831 COPD patients from 36 university hospitals showed a prevalence of ACO of 15% (using the specific major and minor modified GesEPOC [Spanish COPD Guidelines] criteria). These results are similar to those of the COPDGene study, which were 13%[6].

In our study, the prevalence of ACO was 19.08% (CI 15.6-22.5) in the COPD population of the EPOC.AR study, representing 2.6% of the total population of this population-based study (N 3,469). These percentages coincide with the data reported in the literature. But ultimately, while the prevalence of ACO ranges widely according to the source that was taken into account and the criterion used to define it, we could say that it ranges between 1.6 and 4.5% of the adult general population and between 15 and 25% of the adult population with chronic obstruction of the airflow[6].

Llanos et al reported that patients with COPD had lower bronchodilator FEV_1 than patients with ACO[14], but in our study we observed that patients with ACO had significantly lower pre-bronchodilator FEV_1.

Several studies showed that individuals with ACO have higher frequency of respiratory symptoms in comparison with subjects with pure COPD. Maselli et al[15] found that this group of patients shows higher frequency of dyspnea and a great impact on their quality of life. The author says that at present there isn't any evidence of the worsening of symptoms, but this could be due to a "*double hit*", with disease both of the airway and the alveolus and increased susceptibility to exacerbations. Generally speaking, the group of patients with ACO show more symptoms, worse quality of life and higher risk of exacerbations than patients with COPD, but they have better survival[13]. These findings can be observed in our study, since patients with ACO had higher fre-

quency of sibilance and of previous diagnosis of asthma and bronchitis.

Both patients with asthma and those with COPD are characterized by acute worsening of respiratory symptoms, and these events have a significant impact on quality of life and healthcare costs[7]. Many cohorts compared only patients with asthma or COPD and observed that exacerbations were more frequent in the ACO group, but these observations are not consistent in mild degrees of the disease, and the mechanism explaining this assertion is unknown. In our studies we also observed a significantly higher frequency of exacerbations when comparing patients with ACO with the COPD group.

There is increasing interest in the factors affecting the disease, including comorbid conditions. Recent studies have shown a higher frequency of comorbid conditions in patients with ACO, but the mechanisms aren't clear[15]. In our group of patients, we didn't observe any increase in comorbidities within the ACO group when compared to the pure COPD group.

There are limitations to our study, some of them correspond to those of the EPOC-AR study. In the population evaluated within the group of patients with ACO there was majority of males, but the difference wasn't significant. This may be due to the fact that most surveyed women stayed at home, especially during daytime schedules, and to their better willingness to carry out the procedures of the study. One specific limitation of this work regarding the Prevalence of the Asthma-COPD Overlap in the EPOC. AR[7]study is the fact that we didn't get the peripheral blood eosinophil concentrationbecause no blood extractions were performed in patients from the EPOC. AR study for any type of test.

CONCLUSIONS

The prevalence of ACO was 19.08% in patients diagnosed with COPD from the EPOC.AR study. Patients who met the diagnostic criteria for ACO where significantly younger, had higher degrees of obstruction, greater use of inhaled corticosteroids, higher frequency of sibilance and exacerbations that required the use of antibiotics. We emphasize the importance of identifying this phenotype that has different and more severe clinical and prognostic implications, for the purpose of optimizing its management.

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