Defining the Asthma-COPD Overlap Syndrome in a COPD Cohort

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BACKGROUND: Asthma-COPD overlap syndrome (ACOS) has been recently described by international guidelines. A stepwise approach to diagnosis using usual features of both diseases is recommended although its clinical application is difficult.

METHODS: To identify patients with ACOS, a cohort of well-characterized patients with COPD and up to 1 year of follow-up was analyzed. We evaluated the presence of specific characteristics associated with asthma in this COPD cohort, divided into major criteria (bronchodilator test > 400 mL and 15% and past medical history of asthma) and minor criteria (blood eosinophils > 5%, IgE > 100 IU/mL, or two separate bronchodilator tests > 200 mL and 12%). We defined ACOS by the presence of one major criterion or two minor criteria. Baseline characteristics, health status (COPD Assessment Test [CAT]), BMI, airflow obstruction, dyspnea, and exercise capacity (BODE) index, rate of exacerbations, and mortality up to 1 year of follow-up were compared between patients with and without criteria for ACOS.

RESULTS: Of 831 patients with COPD included, 125 (15%) fulfilled the criteria for ACOS, and 98.4% of them sustained these criteria after 1 year. Patients with ACOS were predominantly male (81.6%), with symptomatic mild to moderate disease (67%), who were receiving inhaled corticosteroids (63.2%). There were no significant differences in baseline characteristics, and only survival was worse in patients with non-ACOS COPD after 1 year of follow-up ($P < .05$).

CONCLUSIONS: The proposed ACOS criteria are present in 15% of a cohort of patients with COPD and these patients show better 1-year prognosis than clinically similar patients with COPD with no ACOS criteria.

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ABBREVIATIONS: 6MWD = 6-min walking distance; ACOS = asthma-COPD overlap syndrome; BODE = BMI, airflow obstruction, dyspnea, and exercise; CAT = COPD Assessment Test; CHAIN = COPD History Assessment in Spain; DLCO = diffusion capacity for carbon monoxide; GINA = Global Initiative for Asthma; GOLD = Global Initiative for Chronic Obstructive Lung Disease; LAMA = long-acting antimuscarinic agent; mMRC = modified Medical Research Council

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Features of both asthma and COPD are common in a significant proportion of adult and elderly patients who present with symptoms of a chronic airways disease. The precise proportion of patients with features of both diseases is highly variable, and prevalence rates between 15% and 55% have been reported depending on the diagnostic criteria applied.\textsuperscript{1,3} Notably, concurrent doctor-diagnosed asthma and COPD has been reported in between 15% and 20% of patients.\textsuperscript{5,5}

The COPDGene study found a prevalence of 13% with the overlap asthma and COPD phenotype.\textsuperscript{6} These patients are considered to have a different clinical evolution, with more frequent and severe exacerbations, and consume a disproportionate amount of health-care resources.\textsuperscript{7} There is also a different treatment response which has led to the recommendation of early introduction of inhaled corticosteroids in these patients.\textsuperscript{7} However, convincing evidence of its clinical relevance is scanty, being necessary to assess its existence, determine its prevalence, and validate its different evolution and prognosis in a longitudinal study.

Recently, a joint project of GINA (Global Initiative for Asthma) and GOLD (Global Initiative for Chronic Obstructive Lung Disease) has coined the term asthma-COPD overlap syndrome (ACOS), defined as persistent airflow limitation with several features usually associated with asthma and several usually associated with COPD; the project recommends a stepwise approach to diagnosis.\textsuperscript{8} It provides a list of common features of asthma and COPD, and one of the two diseases is suggested if three or more features are found in a single patient. A diagnosis of ACOS is suggested if there are similar number of features for both asthma and COPD. This approach can be imprecise in a clinical setting although it describes a series of usual features of ACOS which includes age older than 40 years, previous or current history of doctor-diagnosed asthma and allergies, marked airflow reversibility (> 400 mL), or eosinophils and/or neutrophils in sputum. Moreover, this novel approach has never been validated in a clinical setting.

Previously, an attempt to define ACOS using clinical and functional criteria chosen by expert consensus had been proposed.\textsuperscript{7} These criteria, however, have not yet been validated. This study aims to explore the feasibility of some clinical criteria to detect ACOS and to compare these patients with ACOS to patients with COPD not fulfilling those criteria by analyzing data from a Spanish multicenter prospective cohort study with a multidimensional evaluation of patients with COPD.\textsuperscript{10}

**Materials and Methods**

**Patients**

Patients with COPD participating in the COPD History Assessment in Spain (CHAIN) cohort were included. CHAIN is a multicenter study of 36 Spanish prospective cohorts carried out at university hospitals. Methodology and recruitment strategy have been reported elsewhere.\textsuperscript{10}

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Briefly, this is an active ongoing prospective cohort study of patients with COPD being followed since 2010. COPD was defined by smoking history $\approx$ 10 pack-years and a postbronchodilator FEV\textsubscript{1}/FVC $< 0.7$ after 400 µg of inhaled salbutamol. The main goal of the CHAIN study is to perform a multidimensional evaluation of the evolution of patients with COPD to better define its natural history and potential clinical phenotypes (NCT01122758). The recruitment period was between January 15, 2010, and March 31, 2012. Patients are currently in the follow-up period, but data analyzed in the present study come from the baseline and 1-year assessments.

Demographic and clinical data, evaluated at baseline and at the first annual visit, included anthropometric data (age, sex, and BMI), previous history of doctor-diagnosed asthma and atopy, comorbidities (Charlson index), smoking history, dyspnea (modified Medical Research Council [mMRC] scale), exacerbations in the previous year, health status by the validated Spanish version of the COPD Assessment Test (CAT) and Clinical COPD Questionnaire, anxiety and depression (hospital anxiety and depression [HAD] scale), pharmacologic treatments, respiratory function (arterial blood gases, spirometry, lung volume and diffusion capacity), exercise capacity (6-min walking distance [6MWD]), and BMI, airflow obstruction, dyspnea, and exercise capacity (BODE) index.\textsuperscript{10}

Patient data were anonymized in a database with a hierarchical access control to guarantee secure information access. All patients signed an informed, written consent form, which was previously approved by each one of the ethics committee of each participating center (Comité de Etica de la Investigación, Hospital Universitario la Candelaria, Tenerife, institutional review board No.: 258/2009).
Clinical and Physiologic Measurements

Trained staff in a personal interview obtained the following information at the time of recruitment and at yearly appointments: age, sex, and BMI, calculated as the weight in kilograms divided by height in meters. A specific questionnaire was used to determine smoking status (current or former) and smoking history (pack-years).

Pulmonary function tests were performed following American Thoracic Society guidelines. The diffusion capacity for carbon monoxide (DLCO) was determined by the single-breath technique following the European Respiratory Society/American Thoracic Society guidelines. The 6MWD test was measured as the better of two walks separated by at least 30 min. Dyspnea was evaluated by the mMRC scale. Chronic bronchitis was defined as cough with phlegm during at least 3 consecutive months in 2 consecutive years.

The percentage of FEV1, BMI, 6MWD, and mMRC values were integrated into the BODE index as previously described. Emphysema was defined by a radiologist diagnosis on CT scan or DLCO < 80% without other alternative explanation. Exacerbations were defined by use of antibiotics, steroids, or both captured from a diary of exacerbations (handled between the patient, the primary care physician, and the chest physician) or admission to hospital related to worsening of respiratory symptoms with no evidence of alternative diagnosis. A blood sample was obtained to determine the number and percentage of blood eosinophils and quantification of IgE.

Feasibility of ACOS Criteria

The ACOS was defined using some of the usual features stated by the GINA/GOLD joint project stratified by major and minor criteria to increase the sensitivity and specificity to detect the overlap between COPD and asthma in this cohort. Since patients are included in this cohort with a diagnosis of COPD, it is assumed that all the patients fulfill three or more of the usual features of COPD, as suggested by the GINA/GOLD joint project, namely: age > 40 years, postbronchodilator FEV1/FVC < 0.7, and exposure to cigarette smoke. Among those patients with COPD, we identified several features of asthma such as a previous history of asthma, a bronchodilator response to albuterol higher than 15% and 400 mL, IgE > 100 IU, history of atopy, a percentage of blood eosinophils > 5%, or two separated bronchodilator responses to albuterol higher than 12% and 200 mL, requiring at least one major or two minor criteria to set the diagnosis of ACOS (Table 1). ACOS criteria were reassessed after 1 year.

Longitudinal Assessment

CAT, mMRC score, BODE index, and health resources use measured by the rate of moderate to severe exacerbations at baseline and during the 1-year follow-up were evaluated. Life status was assessed up to 1 year of follow-up, and cause of death was coded by the local investigator as respiratory failure, acute exacerbation of COPD, lung cancer, other cancer, pneumonia, cardiovascular, other causes, or unknown. It is worth noting that all patients were treated according to current guidelines in use upon recruitment.

Statistical Analysis

Data are summarized as relative frequencies for categorical variables, mean ± SD for normally distributed scale variables, and frequency and percentage for ordinal or nonnormal scale variables. Comparisons were performed using Pearson χ² for categorical variables and analysis of variance for continuous variables, according to the variables type and distribution. Standard Kaplan-Meier statistics were applied, including a Cox model to determine the significance of survival probabilities by covariates (age, sex, and GOLD severity) of patients with COPD with or without ACOS. The significance level was established as a two-tailed P value < .05.

Results

Patient Characteristics

Eight-hundred thirty-one patients included in the CHAIN cohort were analyzed and 125 patients (15%) met the criteria for ACOS (Fig 1). Demographic and clinical characteristics of these patients as compared with patients with COPD not fulfilling the criteria for ACOS are shown in Table 2. As expected from a population with COPD, patients were predominantly male, with predominantly mild to moderate disease assessed by lung function or BODE and with high prevalence of respiratory symptoms. Out of all comparisons, no statistically significant differences between patients with ACOS and those without ACOS were found, although there was a trend for higher disease severity in patients without ACOS (proportion of patients with BODE index ≥5 was 6.7% vs 19.5%). Similarly, no differences in comorbidities were found between both groups, other than past diagnosis of asthma.

The treatments that these patients were receiving by the time of recruitment were similar for inhaled therapies in both groups, except for long-acting antimuscarinic agents (LAMAs) that were less frequently used in the ACOS group (Table 2). Seventy-nine patients (63.2%) in the ACOS group were receiving inhaled corticosteroids. Oral theophylline was also prescribed significantly less frequently in the ACOS group (P < .05). In a sensitivity analysis, the significant differences observed when comparing ACOS to patients without ACOS in use of LAMA and theophylline were rendered nonsignificant when stratifying by GOLD severity spirometry.

<table>
<thead>
<tr>
<th>Major Criteria</th>
<th>Minor Criteria</th>
</tr>
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<tbody>
<tr>
<td>Previous history of asthma</td>
<td>IgE &gt; 100 IU, or</td>
</tr>
<tr>
<td>Bronchodilator response to salbutamol &gt; 15%</td>
<td>History of atopy,</td>
</tr>
<tr>
<td>and 400 mL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 separated bronchodilator responses</td>
</tr>
<tr>
<td></td>
<td>to salbutamol &gt; 12% and 200 mL</td>
</tr>
<tr>
<td></td>
<td>Blood eosinophils &gt; 5%</td>
</tr>
</tbody>
</table>

ACOS = asthma-COPD overlap syndrome.
thresholds mild and moderate (I and II) vs severe and very severe (III and IV), with P values for LAMA .081 and .188, while .115 and .249 for theophylline.

Distribution of ACOS Criteria

Following the proposed ACOS criteria, 66 patients would be diagnosed with ACOS by fulfilling one major criterion (28 patients with previous diagnosis of asthma and 39 with a bronchodilator response to albuterol higher than 15% or 400 mL) and 59 patients with two minor criteria. A Venn diagram with squares proportional to the weight of the major criteria in this population (Fig 2A) and with circles showing the overlap between minor criteria (Fig 2B) was built.

Of the 125 identified patients with ACOS at baseline, only two (1.6%) did not sustain the ACOS criteria 1 year after follow-up; on the contrary, there were 48 (9.8%) new (incident) ACOS participants at 1 year among those not initially identified at baseline (Fig 3).

Differential Characteristics of Patients With ACOS

According to the diagnostic criteria applied, patients with ACOS show specific characteristics at baseline different to those without ACOS criteria (Table 3). Patients with ACOS defined by one major criterion or two minor criteria were not different by age (P = .170) or sex (P = .076) but there were significant differences by blood eosinophils (P < .01) and IgE (P < .05).

Clinical Outcomes Associated With ACOS at Follow-up

Up to 1 year of follow-up, patients with ACOS did not show statistically significant differences in the BODE index, changing from 1.92 ± 1.7 to 1.71 ± 1.8, similarly to what was found in the non-ACOS group that changed from 2.03 ± 1.9 to 1.78 ± 1.7 (P = .846).

CAT changed from a baseline score of 12.02 ± 7.5 to 10.73 ± 6.1 after 1 year in the ACOS group (P = .140). Patients without criteria for ACOS did not show statistically significant differences, changing from 12.94 ± 7.1 to 11.54 ± 6.43.

Moderate or severe exacerbations in the previous year were present in 22 of the 125 patients with criteria for ACOS (17.6%), which were reduced to 12 patients (9.6%) after 1 year of follow-up. In the non-ACOS group, the number of patients with previous exacerbations was 146 (20.6%), which were found in 65 patients (9.2%) during follow-up (P = .155). No differences between groups were found (P = .15).
Up to 1 year of follow-up, 67 deaths were observed in the whole population, 60 in those without ACOS and seven in those with ACOS, with a Kaplan-Meier cumulative survival of 87.3% and 94.7%, respectively ($P < .05$) (Fig 4). These differential survival differences by ACOS were sustained when adjusting by baseline covariates like age, sex, and GOLD severity (data not shown). Finally, the distribution of causes of death was not significantly different between those with or without ACOS ($P = .924$).

**Discussion**

We have applied prospectively, for the first time, precise diagnostic criteria to identify patients with the asthma and COPD overlap syndrome in a large cohort of well-characterized patients with COPD followed for up to 1 year. We found that, by using usual features of asthma in a well-characterized COPD population but stratified by major and minor criteria, we can identify this particular phenotype in 15% of a hospital-based COPD outpatient cohort, and these criteria were sustained after 1 year. However, the ACOS phenotype was not clinically different at baseline (other than the specific criteria used to define it) from patients with no criteria for ACOS. Interestingly, survival after 1 year of follow-up was significantly better in patients with ACOS.

**Previous Studies**

There is increased awareness of the importance of recognizing ACOS using simple biochemical or genetic...
biomarkers. Soler-Cataluña et al9 made the first approach to use major and minor clinical criteria to define the ACOS phenotype, and those criteria were included in the Spanish guideline for the management of COPD. Previously, different studies had tried to identify the ACOS phenotype using different criteria, mainly retrospectively, and found different figures that vary from 11.6% to 52%.1,16 The former corresponds to Proyecto Latinoamericano de Investigación en Obstrucción Pulmonar (PLATINO), a population-based study which used functional (postbronchodilator FEV1/FVC < 70%) and clinical criteria (wheezing and bronchodilator reversibility > 12% and 200 mL), and the latter is an analysis of large databases demonstrating airway obstruction in patients with concomitant asthma, emphysema, and chronic bronchitis. Our finding of 15% of patients with COPD fulfilling the ACOS phenotype is in keeping with the results of similar well-characterized cohorts of patients with COPD such as the COPDGene study, reporting 13% overlap between COPD and asthma.6 In contrast, there is increasing awareness of the role of eosinophils in some types of patients with COPD, and blood eosinophilia has been identified as a surrogate marker of response to steroids in patients with COPD.17

Interestingly, previous studies have found that patients with ACOS have the worst clinical outcomes when compared to patients with non-ACOS COPD (mainly rate of severe exacerbations6,16), whereas, in our population, patients with ACOS did not show this difference; on the contrary, patients with ACOS showed a reduced 1-year mortality compared with patients who do not have ACOS COPD.

**Interpretation of Novel Findings**

The clinical characteristics of patients with ACOS are described and compared with patients without criteria for ACOS. Probably because this is a real-life study in which patients are receiving treatment for COPD in an outpatient hospital setting, clinical differences at baseline between patients with ACOS and those who did not have ACOS were not found, which differs from all previous reported analyses. A possible explanation is that previous reports included populations with a past medical history of asthma as the main inclusion criteria to define ACOS, which could determine different outcomes when compared with our population of patients with COPD in which only 22% had a clinical history of asthma. Another possible explanation is that the CHAIN population includes 22% of patients with mild disease and 55% with moderate disease, which differs from previous publications with more severe COPD. Of note, 63% of patients with ACOS were receiving inhaled corticosteroids despite being predominantly of mild to moderate severity, which likely contributed to amelioration of the clinical differences with the non-ACOS group. Also, LAMA and long-acting β-agonist use at baseline was similar in both groups regardless of the degree of severity, probably reflecting that this is a more symptomatic hospital-selected
population that is not different once they are under treatment.

**Clinical Implications**

The search for this particular COPD phenotype has one clear aim, which is to address the best therapeutic options for these patients. With the modified criteria to define ACOS, a diagnosis can be made without the need of more complicated tests, such as sputum eosinophil count, and should it be required, a treatment with antiinflammatory therapy can be initiated. This is clearly stated in the GINA/GOLD joint project, where early initiation of inhaled corticosteroids is recommended in patients with coexisting asthma and COPD. Also, a recent review brings attention to the need of identifying and treating disease components by multidimensional assessment, which is in keeping with our approach.

**Limitations**

Our study has several limitations. First, there is no gold standard for the diagnosis of asthma in the COPD population. However, this is the reason for searching and validating diagnostic criteria, although we were limited by the lack of additional measurements such as sputum cellular profiles, airway hyperresponsiveness, and fractional exhaled nitric oxide. Second, our patients were recruited from public hospitals with universal health care and receiving treatment for COPD according to best clinical practice, and this can affect the results of the clinical outcomes, as has been discussed previously. Results are not directly generalized to patients coming from asthma clinics. Third, patients were recruited and followed-up in an outpatient hospital setting, which could not be reflecting what is happening in a different setting such as primary care. And fourth, 1 year of follow-up might be too short a period of time to identify changes in some outcomes like COPD exacerbations, BODE, or CAT, together with a reduced sample size for some subanalyses.

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**TABLE 3 | Differential Characteristics of Patients With COPD Fulfilling the Criteria for ACOS**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>ACOS (n = 125)</th>
<th>No ACOS (n = 706)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchodilator reversibility</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>46 (36.8)</td>
<td>633 (89.7)</td>
<td>.000</td>
</tr>
<tr>
<td>Minor (&gt; 200 mL and &gt; 12%)</td>
<td>40 (32)</td>
<td>73 (10.3)</td>
<td></td>
</tr>
<tr>
<td>Major (&gt; 400 mL and &gt; 15%)</td>
<td>39 (31.2)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Diagnosis of asthma</td>
<td>28 (22.4)</td>
<td>0 (0)</td>
<td>.000</td>
</tr>
<tr>
<td>IgE serum &gt; 100</td>
<td>70 (65.4)</td>
<td>88 (19.8)</td>
<td>.000</td>
</tr>
<tr>
<td>IgE serum</td>
<td>206.6 ± 232</td>
<td>115.7 ± 273</td>
<td>.002</td>
</tr>
<tr>
<td>Eosinophils blood &gt; 5%</td>
<td>39 (32.5)</td>
<td>34 (5.2)</td>
<td>.000</td>
</tr>
<tr>
<td>Eosinophils blood &gt; 3%</td>
<td>61 (50.8)</td>
<td>174 (26.7)</td>
<td>.000</td>
</tr>
<tr>
<td>Eosinophils blood</td>
<td>3.56 ± 2.2</td>
<td>2.40 ± 1.38</td>
<td>.000</td>
</tr>
<tr>
<td>Chronic bronchitis</td>
<td>75 (60)</td>
<td>414 (58.6)</td>
<td>.428</td>
</tr>
<tr>
<td>Dlco &lt; 80%</td>
<td>50 (40)</td>
<td>314 (44.5)</td>
<td>.203</td>
</tr>
<tr>
<td>Dlco %</td>
<td>78 ± 22</td>
<td>73.8 ± 24.1</td>
<td>.128</td>
</tr>
<tr>
<td>Emphysema on CT scan, n/N (%)</td>
<td>19/35 (54.3)</td>
<td>167/252 (66.3)</td>
<td>.116</td>
</tr>
</tbody>
</table>

Data are given as mean ± SD or No. (%) unless otherwise indicated. Dlco = diffusion capacity for carbon monoxide. See Table 1 legend for expansion of other abbreviations.

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Figure 4 – One-year Kaplan-Meier cumulative survival, by ACOS. See Figure 1 legend for expansion of abbreviations.
Conclusions

We propose a set of easily applicable clinical criteria (Table 1) that can be useful to define the ACOS. In a well-characterized cohort of patients with COPD, 15% of patients fulfilled these criteria, sustained them after 1 year, and, although this phenotype was not associated with baseline clinical differences, were associated to different survival.

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