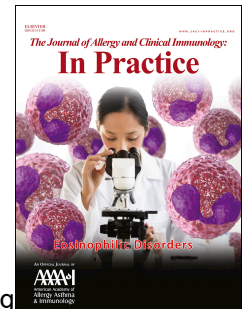


Journal Pre-proof

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PII: S2213-2198(20)30042-8

DOI: <https://doi.org/10.1016/j.jaip.2020.01.004>

Reference: JAIP 2632

To appear in: *The Journal of Allergy and Clinical Immunology: In Practice*

Received Date: 8 July 2019

Revised Date: 19 November 2019

Accepted Date: 2 January 2020

Please cite this article as: Jo YS, Hwang YI, Yoo KH, Kim TH, Lee MG, Lee SH, Shin KC, In KH, Yoon HK, Rhee CK, on behalf of the Korean Asthma Research Group & KOCOSS cohort, Effect of inhaled corticosteroids on exacerbation of asthma–COPD overlap according to different diagnostic criteria, *The Journal of Allergy and Clinical Immunology: In Practice* (2020), doi: <https://doi.org/10.1016/j.jaip.2020.01.004>.

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Original article

Effect of inhaled corticosteroids on exacerbation of asthma–COPD overlap according to different diagnostic criteria

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Abstract

Background: Few reports have investigated the efficacy of using inhaled corticosteroid (ICS)-containing inhalers to treat patients with asthma–chronic obstructive pulmonary disease (COPD) overlap (ACO).

Objective: To investigate the effect of ICS treatment on patients with ACO using five sets of diagnostic criteria.

Methods: Patients with stable COPD enrolled in the Korean COPD subgroup study (KOCOSS) cohort were assessed for asthma overlap. Patients who were prospectively followed-up for 1 year were included in an exacerbation analysis.

Results: Among 1,067 COPD patients, 138 (12.9%), 32 (3.0%), 171 (16%), 221 (20.7%), and 264 (24.7%) were classified as having ACO by the Global Initiative for Asthma (GINA)/Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria, the American Thoracic Society (ATS) roundtable criteria, the modified Spanish criteria, the updated Spanish criteria, and specialists' diagnoses, respectively. According to the specialists' diagnoses, the ACO exacerbation rate was higher than that for COPD alone (incidence rate ratio [IRR] = 1.65; $p < 0.01$), even after adjustment for covariates. Patients with ACO who used ICSs experienced less exacerbation, according to the specialists' diagnoses and the GINA/GOLD criteria (IRR = 0.55, $p = 0.026$; IRR = 0.69, $p = 0.046$; respectively). The only factor associated with a decrease in ACO exacerbation following ICS use was a blood eosinophil count of ≥ 300 cells/ μ L (IRR = 0.52, $p = 0.03$) irrespective of the diagnosis of ACO by any set of criteria.

Conclusions: This study suggests that ICS treatment can decrease the risk of exacerbation in patients with ACO, and that a blood eosinophil count of ≥ 300 cells/ μ L can predict the

response to ICS treatment.

Clinical Trial Number: NCT02800499

● **What is already known about this topic?**

There have been no clinical trials investigating the effectiveness of ICS (inhaled corticosteroids) treatment on exacerbation risk in ACO patients.

● **What does this article add to our knowledge?**

ICS treatment significantly decreased ACO exacerbation according to the specialists' diagnoses and the GINA/GOLD criteria, and the only factor associated with decreased exacerbation following ICS treatment was a blood eosinophil count of ≥ 300 cells/ μ L.

● **How does this study impact current management guidelines??**

The present study highlights that a comprehensive specialist-led approach is more effective than individual criteria for identifying ACO and ICS treatment reduced exacerbation. For uncertain cases, a high blood eosinophil count may be a good indication for ICS treatment.

Keywords: Asthma-COPD overlap, exacerbation, inhaled corticosteroid, blood eosinophil

Conflicts of interest: The authors declare that they have no competing interests.

Abbreviations: ACO, asthma-COPD overlap; ATS, American Thoracic Society; BDR, bronchodilator response; CAT, Chronic Obstructive Pulmonary Disease Assessment Test; COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; GINA, Global Initiative for Asthma; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroid; IgE, immunoglobulin E; LABA, long acting beta2 receptor agonist; LAMA, long acting muscarinic receptor agonist; mMRC, modified Medical Research Council; SGRQ, St. George's Respiratory Disease Questionnaire; 6MWD, 6-min walk distance

Introduction

Asthma and chronic obstructive pulmonary disease (COPD) are airway diseases with similar clinical manifestations, despite their different pathophysiologies. Asthma–COPD overlap (ACO) is a condition that is characterized by overlapping clinical features from both diseases. Childhood asthma is regarded as an independent risk factor for COPD, especially when accompanied by smoking¹, with substantial proportion of COPD patients showing significant improvements in their forced expiratory volume in 1 s (FEV₁) following the use of a bronchodilator (BD)². In addition, as many as 30% to 40% of COPD patients show signs of eosinophilic inflammation in either their blood or sputum³. Christenson *et al.*⁴ collected transcriptomic data using bronchial brushes and reported an “asthma genetic signature”, which involves the T-helper 2 inflammatory pathway, was more obvious in the airways of patients with COPD compared to healthy control subjects and smokers who did not have COPD.

Although it has recently been recognized as a disease, it remains debatable whether ACO is a single disease entity distinct from asthma and COPD. This is due to the exclusion of patients with characteristics of both asthma and COPD from clinical studies on either disease, and to the lack of consensus on ACO diagnosis and treatment.

The ACO diagnostic criteria proposed by the Global Initiative for Asthma (GINA) and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) are difficult to apply in clinical practice because they are based on questionnaires rather than laboratory results. Therefore, several studies have suggested alternative diagnostic criteria, such that the

prevalence of ACO can vary widely (from 10–50%) depending on the criteria used^{5,6}. In addition, there is a lack of evidence-based guidelines for treatment, although GINA/GOLD recommends inhaled corticosteroids (ICSs) when ACO is suspected.

In this study, involving a multicenter cohort of South Korean COPD patients, we used different diagnostic criteria to investigate the exacerbation risk, and effect of ICS treatment on the exacerbation risk, in patients with ACO who were followed-up prospectively for 1 year. We also sought factors predicting whether ICS treatment would have a positive effect.

Materials

Study population and data collection

All subjects were registered with the Korean COPD subgroup study (KOCOSS) cohort, which is a prospective cohort for investigating the COPD phenotype of patients drawn from 48 tertiary referral hospitals in the Republic of Korea. The KOCOSS has been running since December 2011 and the study details have been published previously⁷. The inclusion criteria for the cohort were aged ≥ 40 years with post-bronchodilator FEV₁/forced vital capacity [FVC] < 0.70 .

At enrolment, data including age, sex, smoking history and pack-years, comorbidities, spirometry results, exercise capacity (i.e., 6-min walking distance), symptoms (based on questionnaires including the Modified Medical Research Council Dyspnea Scale), and self-reported quality of life (based on the COPD assessment test and the St. George's Respiratory Questionnaire) were recorded by physicians or trained nurses using electronic case-report forms. Spirometric data were collected using standard equipment and lung volume was measured in accordance with the American Thoracic Society (ATS)/European Respiratory Society guidelines^{8,9}. Blood samples, including for measurement of eosinophils and total serum IgE, were collected from patients for baseline laboratory evaluations during a stable period.

We used an observational study design, and patients were treated by their pulmonologists. Patients were followed-up at least every 6 months and exacerbation data were recorded at every visit. Exacerbation was defined as a positive response to the question "Have you had an aggravation of your respiratory symptoms that led to a visit to the outpatient clinic sooner than planned, or hospitalization, or a visit to the emergency department during the past 6

months?” Moderate exacerbation was defined as an exacerbation that led a visit to an outpatient clinic earlier than scheduled with a prescription of systemic steroids and/or antibiotics, whereas severe exacerbation was defined as an exacerbation that led to a visit to the emergency department or hospitalization.

The ACO study was initiated by the Korean Asthma Research Group since July 2016. Korean Asthma Research Group asked KOCOSS members to perform ACO study prospectively. Thus, previously enrolled participants before ACO study and those in hospitals not participating in the ACO study were not included. Questionnaires were issued to determine the presence of ACO and collect data regarding previously diagnoses of asthma or allergic diseases, such as allergic rhinitis and atopy, in both patients and their families, age at asthma diagnosis, variation in symptoms over time and seasons, trigger factors, the course of symptoms, and any relieving factors. All 1,067 patients who were enrolled were included in the analyses, and exacerbation data from the baseline visit until the 1-year follow-up were available for 604 patients. All of the hospitals involved in the study obtained approval from the Institutional Review Board Committee and informed consent from their patients. The study protocol was approved by the Institutional Review Board of KONKUK university medical center (IRB No. KHH1010338).

Criteria for ACO

We selected four sets of diagnostic criteria for ACO, including the GINA/GOLD criteria, the ATS roundtable criteria, the modified Spanish criteria and the updated Spanish criteria. Details of each criteria are described in Table I. In addition to these four sets of criteria, pulmonology specialists at each of the hospitals who qualified by respiratory medicine

through national certification examination were asked the following question: “Is this patient likely to be classified with ACO?”. This questionnaire was conducted independently of whether individual other four diagnostic criteria were met. Thus, ACO patients were also identified according to specialists’ clinical judgement.

Statistical analysis

We compared the prevalence of ACO using the different sets of criteria. Then, we compared clinical features between patients with and without a diagnosis of ACO. Pearson’s chi-square tests and *t*-tests were used to analyze categorical and continuous data, respectively.

Diagnostic consistency among the sets of diagnostic criteria was assessed using the GINA/GOLD criteria, as the gold standard, and represented using receiver operating characteristic (ROC) curves.

All the comparisons presented in our results included all 1067 patients and were between patients with ACO and those with COPD only according to each of the diagnostic criteria.

The risk of exacerbation during the 1-year follow-up period was analyzed using a negative binomial regression model. Covariates including age, sex, smoking pack-years, FEV₁ at baseline, history of exacerbation during the year preceding enrolment, and the use of ICS treatment were included in the multivariate analysis.

All tests were two-sided and a *p*-value < 0.05 was considered statistically significant. All analyses were performed using STATA software (ver. 14.2; StataCorp, College Station, TX, USA).

Results

Prevalence of ACO and patient characteristics according to diagnostic criteria

Among 2,757 patients with COPD, 1,067 were classified as patients with or without ACO using the five sets of diagnostic criteria. Among these, 264 (24.7%), 32 (3%), 138 (12.9%), 171 (16%), and 221 (20.7%) patients with ACO were identified using the specialists' diagnoses, ATS roundtable criteria, GINA/GOLD criteria, modified Spanish criteria, and updated Spanish criteria, respectively (Figure 1, Table I and see Figure E1 in the Online Repository).

Various clinical characteristics were compared between patients with and without ACO using the five sets of diagnostic criteria, and the results are shown in Table E1 in the Online Repository. There was a higher proportion of men among the patients who did not have ACO according to the specialists' diagnoses and GINA/GOLD criteria. Patients with ACO had more pack-years of smoking according to the ATS roundtable and updated Spanish criteria. Patients with ACO were less likely to have dyspnea according to the specialists' diagnoses, but were more likely to have a poor quality of life according to the GINA/GOLD criteria, and to have a history of exacerbation before enrolment according to the modified Spanish criteria. Inhalers containing ICS only, ICS/long-acting β_2 -agonist (LABA), and ICS/LABA/long-acting muscarinic antagonist combinations were prescribed more frequently for patients with ACO according to the specialists' diagnoses, the GINA/GOLD criteria, and the modified Spanish criteria.

Patients with ACO had superior FEV₁ and FVC results, according to the specialists' diagnoses, ATS roundtable criteria, and GINA/GOLD criteria, as well as less severe airflow

obstruction, compared to patients who did not have ACO according to the specialists' diagnoses (see Table E2 in the Online Repository).

Diagnostic consistency across criteria

The GINA/GOLD criteria were used as the gold standard, and the specialists' diagnoses showed the greatest diagnostic consistency (area under the ROC curve [AUROC], 0.871), followed by the updated Spanish and modified Spanish criteria (AUROC, 0.723 and 0.697, respectively). The ATS roundtable criteria showed the least agreement with the GINA/GOLD criteria (AUROC, 0.56; see Figure E2 in the Online Repository).

Asthmatic features

The medical history data from patients and their families, together with respiratory symptoms suggesting an asthmatic component, are presented in Table E3 in the Online Repository. Patients with ACO were significantly more likely to have a history of asthma, according to all sets of criteria except the updated Spanish criteria. Patients with ACO were also more likely to have a history of allergic disease, including atopy and allergic rhinitis, according to all sets of criteria. Regarding symptom variations, patients with ACO were more likely to show seasonal symptom variations according to all sets of criteria. Patients with ACO were also more likely to show diurnal symptom variations according to all sets of criteria, except the ATS roundtable criteria.

Risk of exacerbation and the effect of ICS treatment on exacerbation risk in ACO patients

A total of 604 patients followed-up prospectively for 1 year were included in the exacerbation analysis (Table II). According to the specialists' diagnoses, the incidence rate of exacerbation and frequency of moderate to severe exacerbation were higher in patients with ACO, even after adjustment for covariates. However, according to the modified Spanish criteria, the frequency and incidence of exacerbation in patients with ACO were significantly lower than in patients who did not have ACO.

ICS therapy was carried out in all 604 patients in the longitudinal sub-cohort, irrespective of whether or not they fulfilled criteria for ACO according to any of the five diagnostic criteria used. Patients with and without ACO were separated into two groups according to whether they had ICS treatment, and the incidence rates of exacerbation were compared using the five sets of diagnostic criteria during the 1-year follow-up period (Table III). Among the patients with ACO, those who had ICS treatment had a significantly lower risk of exacerbation than those who did not have ICS treatment, according to the specialists' diagnoses and GINA/GOLD criteria. According to the updated Spanish criteria, patients with ACO who had ICS treatment also had a lower risk of exacerbation than those who did not have ICS treatment; however, the risk of exacerbation was not lower after adjustment for covariates. For patients who did not have ACO, all five sets of criteria showed no change in the risk of exacerbation, regardless of whether the patients had ICS treatment.

We also compared various clinical parameters and proportion of ACO depending on adopted diagnostic criteria according to inclusion or not in one year exacerbation analysis (see Table E4 and Figure E3 in the Online Repository).

Factors predicting a response to ICS treatment

To identify factors that may predict a positive response to ICS treatment, seven clinical criteria were evaluated in 604 patients who followed-up for a year irrespective of whether or not they satisfied with any of five criteria for ACO. These were all components of the five sets of ACO diagnostic criteria and included a history of asthma in patients under 40 years of age, a history of atopy or allergic rhinitis, a BDR > 15% and 400 mL, a BDR $\geq$ 12% and 200 mL, a blood eosinophil count $\geq$ 300 cells/ μ L, blood eosinophils > 5%, and IgE > 100 IU (Figure 2). Only a blood eosinophil count $\geq$ 300 cells/ μ L distinguished patients who showed a significant decrease in exacerbation risk in response to ICS treatment from those who did not (incidence rate ratio, 0.52; $p = 0.03$).

Discussion

We applied five sets of diagnostic criteria derived from a large cohort study, expert consensus, and specialists' diagnoses to investigate a group of patients with both asthmatic and COPD characteristics. In this study, there is a broad spread when using 5 different definitions. It is mainly because each component of each criterion differs. Among features of asthma, each criterion requires different components. Moreover, the number of components required in major and minor criteria also differ. Our study is valuable because we have validated the usefulness of five different criteria. We followed-up patients with ACO drawn from a large, well-characterized cohort of patients with COPD. We confirmed that both the prevalence of ACO and the risk of exacerbation in relation to the presence of ACO versus COPD only were variable, and depended on the diagnostic criteria used to define ACO. ICS treatment significantly decreased the risk of ACO exacerbation according to the specialists' diagnoses and GINA/GOLD criteria. Specialists' diagnosis of ACO and updated Spanish ACO showed good consistency with the GINA/GOLD criteria. Our results can be helpful for clinicians to select and utilize one among many ACO definitions in practice, and we also showed that a high blood eosinophil count was the only useful index for distinguishing responders from non-responders to ICS treatment, irrespective of the diagnosis of ACO by any set of criteria.

Patients with ACO have more severe respiratory symptoms, poorer quality of life and lung function, a higher risk of exacerbation, and higher mortality rates than patients with COPD alone^{6, 10-13}. However, the ACO diagnostic criteria have varied among studies. Therefore, identifying consistent ACO traits has proven difficult, and studies have produced conflicting results. We compared various clinical features, and the diagnostic consistency, among four

widely used sets of ACO diagnostic criteria, together with specialist judgement in our previous study¹⁴. Overall, the differences in clinical features between patients with and without ACO showed similar patterns across the sets of diagnostic criteria. We found that the patients with ACO included a lower proportion of men, and lower proportion of light or non-smokers, than did the patients who did not have ACO. Patients with ACO also had a lower quality of life and less severe airflow limitation than patients who did not have ACO. These findings are consistent with previously reported characteristics of patients with ACO^{4, 12, 15, 16}. We performed this study to investigate the risk of ACO exacerbation and the beneficial effects of ICS treatment on reducing exacerbations.

Whether ACO is a unique disease entity, i.e., distinct from asthma and COPD, is controversial. However, it is generally recommended that it is important to identify patients with ACO so that ICS treatment can be initiated as soon as possible. Although several studies reported that ICS treatment was not shown to have a favorable impact on outcome in ACO patients¹⁷⁻¹⁹, there have been no large scale studies on ICS treatment of ACO patients that focused on exacerbation. In this study, we found that ICS treatment decreased the risk of exacerbation in patients with ACO according to the specialists' diagnoses, GINA/GOLD criteria, and updated Spanish criteria. We also showed that a peripheral blood eosinophil count ≥ 300 cells/ μ L may be a good predictor of a favorable response to ICS treatment irrespective of the diagnosis of ACO. These observations were derived from a large cohort of patients with COPD who had asthma or COPD features, according to the GINA/GOLD recommendations. None of the asthmatic features, including a previously diagnosis of asthma, allergic diseases such as atopy and/or allergic rhinitis, elevated total IgE levels, or positive BDR were capable of identifying ICS responders. Only a blood eosinophil count ≥ 300

cells/ μ L was useful for identifying patients who showed a significant response to ICS treatment designed to decrease exacerbations. It is noteworthy that this study showed a positive effect of ICS treatment on exacerbation risk reduction in patients with ACO, and identified a predictor of a favorable response to ICS treatment.

Currently, the GOLD report recommends ICS treatment for patients with a blood eosinophil count ≥ 300 cells/ μ L, history of asthma, or elevated risk of exacerbation in response to initial therapy²⁰. However, our results did not show that a history of asthma was a predictor of the ICS treatment response. Thus, providing ICS treatment to patients who only have a history of asthma may not be beneficial. Further studies are needed to resolve this issue. Since ICS therapy was carried out irrespective of whether or not they fulfilled criteria for ACO, our findings that a blood eosinophil count ≥ 300 cells/ μ L predicted a favorable response to ICS with respect to exacerbations could apply equally well to patients with or without ACO.

Studies on patients with ACO have generally reported poorer clinical outcomes than those on patients with COPD alone^{13, 21-23}. In this study, we observed inconsistent results with respect to moderate to severe exacerbation at the 1-year follow-up. We found that the risk of exacerbation was greater in patients diagnosed with ACO by specialists, but the opposite finding was observed in those diagnosed using the modified Spanish criteria. The possible reason for this is that the specialists' judgment regarding the presence of ACO has probably better identified patients who are at higher risk of exacerbation than the modified Spanish criteria. As such, specialists'-diagnosed ACO patients had a significant difference in exacerbations depending on ICS use, but this was not observed in modified Spanish criteria-defined ACO patients. In contrast to our results, a previous study¹⁶ reported an

increase in the risk of exacerbation in patients with ACO, according to the modified Spanish and GINA/GOLD criteria. Although we included more patients than the previous study and applied the same diagnostic criteria, the result is quite opposite. We do not know the reason of discrepancy. Furthermore, the risk of exacerbation in patients with ACO was low according to the ATS roundtable criteria; it was higher according to the updated Spanish criteria, although the difference was not clinically significant. Several well-established ACO diagnostic criteria have been developed based on cohort studies, but no consensus has been achieved. We applied ACO diagnostic criteria to patients with COPD to identify those most likely to benefit from ICS treatment. We found that ICS treatment for patients with ACO decreased the risk of exacerbation, according to the specialists' diagnoses and GINA/GOLD criteria. This implies that because COPD is a heterogeneous disease, a multidimensional approach to asthmatic symptoms and clinical laboratory results, reflecting T-helper 2 inflammation, is more important for ACO diagnoses and early ICS treatment than satisfying a list of diagnostic criteria²⁴.

This is the first study to prospectively evaluate the effect of ICS treatment on patients with ACO via several widely used sets of diagnostic criteria. We confirmed that a blood eosinophil count ≥ 300 cells/ μ L is a significant predictor of decreased the risk of exacerbation in response to ICS treatment. Our study does have several limitations. First, because our patients were recruited from outpatient clinics at tertiary referral hospitals, and not from primary care, our results may not be representative of the entire patient population. However, due to the high accessibility of medical care in the Republic of Korea, this cohort may well reflect the prevalence and clinical features of ACO patients in clinical practice. Second, additional parameters for evaluating asthmatic components, such as sputum cellular profile,

bronchial provocation test results, and fractional exhaled nitric oxide were not available. Third, in Republic of Korea, the approved dose of fluticasone propionate for COPD is 250mcg. The results of our study needs to be interpreted with caution since the approved dose in Europe is 500 mcg. It is unclear whether the decrease of exacerbations by ICS in COPD is affected by the dose. Further validation studies of our results in other parts of the world such as Europe are needed. Finally, because this was an observational cohort study, the ICS prescriptions depended on physician judgment, and some patients were not followed up and were not included in the one year exacerbation analysis.

Conclusions

Several sets of ACO diagnostic criteria were compared to improve our understanding of ACO and promote appropriate treatment. Compared to other diagnostic criteria, the judgement of specialists was most consistent with the GINA/GOLD diagnostic criteria and was capable of characterizing both the high risk of ACO exacerbation and the beneficial effects of ICS treatment. However, it is more difficult for non-specialists to diagnose ACO. In such cases, a high blood eosinophil count serves as a good indication for ICS treatment, irrespective of whether the patient fulfills any of the diagnostic criteria of ACO or not. In conclusion, ACO diagnoses made by a specialist, or according to the GINA/GOLD criteria, and a high blood eosinophil count predicted the response to ICS treatment. Our results require validation in future prospective clinical trials.

Acknowledgement

Author contributions: The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors. YS Jo and CK Rhee take responsibility for the data and analysis. YI H, KH Yoo, TH Kim, MG Lee, SH Lee, KC Shin, KH In, HK Yoon contributed initiation of ACO project and acquisition of data. YS Jo and CK Rhee designed the study and YS Jo did statistical analysis of data and wrote the initial manuscript. All authors provided critical review and approved of the version to be published.

Funding information: This research was supported by a fund (2016ER670102 & 2018ER670100) by Research of Korea Centers for Disease Control and Prevention.

Conflicts of interest: CK Rhee received consulting/lecture fees from MSD, AstraZeneca, GSK, Novartis, Takeda, Mundipharma, Boehringer-Ingelheim, Teva, and Bayer, but the sponsor had no role in the design of the study, the collection and analysis of the data, or writing a manuscript. But, CK Rhee has no competing interest to declare and the other authors declare that they have no competing interests.

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Table I. The prevalence of asthma–chronic obstructive pulmonary disease overlap based on five diagnostic criteria

Criteria	Number of patients, n (%)	
	meet the criteria	do not meet the criteria
specialists' diagnosis ACO	264 (24.7)	720 (67.5)
ATS roundtable criteria ²⁵		
Major		
Post-BD FEV ₁ /FVC < 0.7 and Age ≥40	1067 (100)	-
Smoking ≥ 10 pack-year or exposure to air pollution ≥ 10year	898 (89.4)	5.3 (5.3)
History of Asthma before 40years or BDR > 400mL in FEV ₁	75 (7.0)	911 (85.4)
Minor		
History of atopy or allergic rhinitis	77 (7.2)	893 (83.7)
separate BDR ≥ 12% and 200mL	45 (4.2)	1022 (95.8)
Blood eosinophil count ≥ 300cell/μL	234 (21.9)	739 (69.3)
ACO (all 3 major and at least 1 minor)	32 (3.0)	841 (78.8)
GINA/GOLD document [*]		
Component of asthmatic feature ≥3	152 (14.2)	915 (85.8)
Component of COPD feature ≥3	1026 (96.2)	41 (3.8)
ACO (≥3 asthma and ≥3 COPD features)	138 (12.9)	929 (87.1)
modified Spanish COPD Guidelines ²⁶		
Major criteria		
Previous history of asthma	330 (30.9)	722 (67.7)
BDR >15% and 400 mL	13 (1.2)	1054 (98.8)
Minor criteria		
IgE >100 IU, or history of atopy	396 (37.1)	305 (28.6)
BDR >12% and 200 mL	45 (4.2)	1022 (95.8)
Blood eosinophil >5%	180 (16.9)	832 (78.0)
ACO (At least 1 major or 2 minor)	171 (16.0)	821 (76.9)
updated Spanish COPD Guidelines ²⁷		
1. Age ≥35, smoker ≥10 pack year and Post-BD FEV ₁ /FVC < 0.7	898 (84.2)	56 (5.3)
2. Current diagnosis of asthma [†]	10 (0.9)	1057 (99.1)
3. BDR ≥15% and 400 mL, and/or eosinophilia in blood ≥300 cell/μL	243 (22.8)	731 (68.5)
ACO (1 and 2 or 1 and 3)	221 (20.7)	509 (47.7)

^{*}GOLD/GINA criteria based ACO was defined if the patients met at least 3 items in both the asthma and COPD categories ^{20, 28}. [†] Current diagnosis of asthma must include (a) and (b): (a) respiratory symptoms of variable course with history and/or symptoms causing clinical suspicion; family asthma history or personal history of asthma in childhood, or personal history of atopy, or inflammation of the upper airway (e.g. rhinosinusitis), (b) post BD FEV₁ ≥ 12% and 200 mL, or diurnal variability of PEF ≥20%, or FENO ≥ 50 ppb

ACO, asthma-COPD overlap; BDR, bronchodilator response; ATS, American Thoracic Society; BMI, body mass index; COPD, chronic obstructive pulmonary disease; ATS, American Thoracic Society; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; GINA, Global Initiative for Asthma; GOLD, Global

520 Initiative for Chronic Obstructive Lung Disease; FENO, fractional exhaled nitric oxide; IgE, immunoglobulin E;
521 PEF, peak expiratory flow

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522 **Table II. The risk of exacerbations within a year among patients with ACO and those with non-ACO (N=604)**

	specialists' diagnosis		P	ATS roundtable		P	GINA/GOLD		P	modified Spanish		p	updated Spanish		P
	ACO (N=264)	non-ACO (N=720)		ACO (N= 32)	non-ACO (N= 841)		ACO (N= 138)	non-ACO (N= 929)		ACO (N= 171)	non-ACO (N= 821)		ACO (N= 221)	non-ACO (N= 509)	
Frequency of moderate to severe AE	4.3±5.5	2.6±2.0	0.02	3.3±3.8	1.5±0.7	0.52	3.1±2.5	3.2±3.7	0.94	2.3±1.0	3.5±4.0	0.12	4.1±6.0	2.9±2.3	0.21
Unadjusted IRR	1.65 (1.24-2.19)		0.00	0.46 (0.11-1.83)		0.27	0.99 (0.74-1.31)		0.92	0.65 (0.46-0.92)		0.02	1.38 (0.97-1.95)		0.07
Adjusted IRR [*]	1.70 (1.26-2.29)		0.00	0.46 (0.12-1.82)		0.27	1.01 (0.86-1.35)		0.95	0.66 (0.46-0.94)		0.02	1.43 (1.01-2.03)		0.05
Adjusted IRR [†]	1.71 (1.27-2.32)		0.00	0.47 (0.12-1.85)		0.28	1.01 (0.76-1.35)		0.95	0.66 (0.46-0.94)		0.02	1.42 (1.00-2.01)		0.05
Adjusted IRR [‡]	1.81 (1.31-2.50)		0.00	0.49 (0.13-1.92)		0.31	1.04 (0.76-1.43)		0.79	0.65 (0.43-0.97)		0.03	1.36 (0.96-1.93)		0.08
Adjusted IRR [§]	1.82 (1.31-2.54)		0.00	0.49 (0.13-1.92)		0.31	1.05 (0.76-1.44)		0.78	0.65 (0.43-0.97)		0.03	1.37 (0.97-1.95)		0.08

523 AE, acute exacerbation; HR, hazard ratio; IRR, incident rate ratio; See the expansion of abbreviation in Table 1

524 ^{*} Adjusted by age, sex, post-bronchodilator FEV₁(%)

525 [†] Adjusted by age, sex, post-bronchodilator FEV₁(%), use of ICS containing inhaler

526 [‡] Adjusted by age, sex, post-bronchodilator FEV₁(%), use of ICS containing inhaler, smoking pack-year

527 [§] Adjusted by age, sex, post-bronchodilator FEV₁(%), use of ICS containing inhaler, smoking pack-year, previous history of exacerbation

Table III. Analysis of exacerbation according to the use of ICS in patients with ACO and non-ACO by diagnostic criteria**A) Specialist diagnosis**

	specialists' diagnosis ACO (n=264)		P value	specialists' diagnosis non-ACO (n=720)		P value
	With ICS (n=152)	Without ICS (n=112)		With ICS (n=174)	Without ICS (n=546)	
Frequency of moderate to severe AE	3.24±1.61	5.87±8.25	0.17	2.70±2.25	2.58±1.7	0.80
Unadjusted IRR	0.55 (0.33-0.93)		0.026	1.05 (0.77-1.42)		0.78
Adjusted IRR [*]	0.52 (0.31-0.89)		0.017	0.98 (0.72-1.34)		0.90
Adjusted IRR [†]	0.35 (0.18-0.68)		0.002	1.02 (0.75-1.41)		0.89
Adjusted IRR [‡]	0.34 (0.17-0.69)		0.003	1.09 (0.78-1.52)		0.62

B) ATS roundtable criteria

	ATS roundtable ACO (n=32)		P value	ATS roundtable non-ACO (n=841)		P value
	With ICS (n=21)	Without ICS (n=11)		With ICS (n=268)	Without ICS (n=573)	
Frequency of moderate to severe AE	-	5.87±8.25	-	2.95±2.12	3.57±4.87	0.44
Unadjusted IRR	N/A		-	0.83 (0.60-1.14)		0.25
Adjusted IRR [*]	N/A		-	0.87 (0.62-1.21)		0.39
Adjusted IRR [†]	N/A		-	0.86 (0.62-1.20)		0.38
Adjusted IRR [‡]	N/A		-	0.85 (0.61-1.18)		0.34

C) GINA/GOLD

	GINA ACO (n=138)		P value	GINA non-ACO (n=929)		P value
	With ICS (n=81)	Without ICS (n=57)		With ICS (n=268)	Without ICS (n=472)	
Frequency of moderate to	2.58±1.26	3.76±2.65	0.05	3.0±2.08	3.33±4.57	0.64

severe AE				
Unadjusted IRR	0.69 (0.47-0.99)	0.046	0.90 (0.67-1.22)	0.49
Adjusted IRR [†]	0.68 (0.46-0.99)	0.046	0.90 (0.66-1.23)	0.51
Adjusted IRR [†]	0.57 (0.37-0.88)	0.011	0.92 (0.67-1.28)	0.64
Adjusted IRR [‡]	0.61 (0.39-0.95)	0.031	0.96 (0.68-1.35)	0.81

D) modified Spanish criteria

	modified Spanish ACO (n=171)		P value	modified Spanish non-ACO (n=821)		P value
	With ICS (n=74)	Without ICS (n=97)		With ICS (n=256)	Without ICS (n=565)	
Frequency of moderate to severe AE	2.45±1.13	2.12±0.99	0.41	3.08±2.20	3.82±5.13	0.40
Unadjusted IRR	1.16 (0.70-1.91)		0.56	0.80 (0.57-1.13)		0.21
Adjusted IRR [*]	1.18 (0.70-1.97)		0.54	0.84 (0.59-1.20)		0.34
Adjusted IRR [†]	1.14 (0.59-2.20)		0.70	0.93 (0.64-1.34)		0.69
Adjusted IRR [‡]	1.30 (0.65-2.62)		0.46	0.92 (0.63-1.34)		0.67

E) updated Spanish criteria

	updated Spanish ACO (n=221)		P value	updated Spanish non-ACO (n=509)		P value
	With ICS (n=93)	Without ICS (n=128)		With ICS (n=141)	Without ICS (n=368)	
Frequency of moderate to severe AE	2.38±1.19	5.38±7.68	0.19	3.07±2.45	2.83±2.23	0.70
Unadjusted IRR	0.45 (0.24-0.87)		0.02	1.08 (0.75-1.56)		0.66
Adjusted IRR [*]	0.57 (0.28-1.15)		0.12	1.01 (0.70-1.44)		0.98
Adjusted IRR [†]	0.57 (0.29-1.15)		0.12	0.99 (0.72-1.35)		0.95
Adjusted IRR [‡]	0.58 (0.28-1.18)		0.13	0.99 (0.71-1.39)		0.98

547 ^{*} Adjusted by age, sex, post-bronchodilator FEV₁(%)

548 [†] Adjusted by age, sex, post-bronchodilator FEV₁(%), smoking pack-year

549 [‡] Adjusted by age, sex, post-bronchodilator FEV₁(%), smoking pack-year, previous history of exacerbation

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Figure legends

Figure 1. Study flow

Figure 2. Comparing the risk of exacerbation depending on the use of ICS for seven clinical criteria

2757 patients with COPD

Survey for specialists' diagnosis of ACO
Survey for GINA/GOLD questionnaire
Survey for history of allergic disease and age of asthma diagnosis
Measurement of blood eosinophil and total IgE
Spirometry with bronchodilator response

Identified ACO according to five diagnostic criteria (N=1067)

Specialists'
diagnosed ACO
(n=264)

ATS roundtable
criteria defined
ACO (n=32)

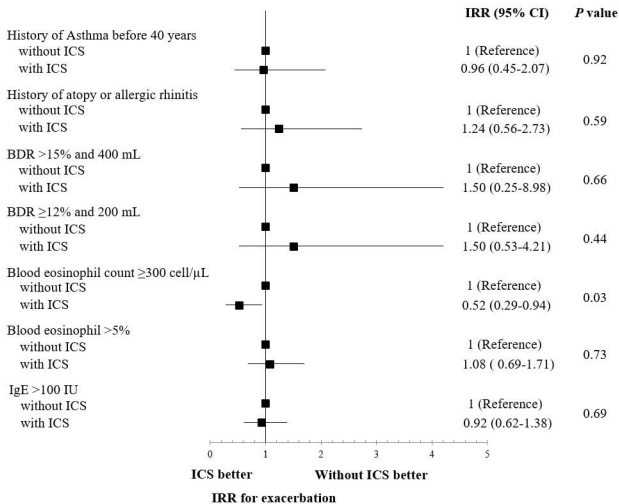
GINA/GOLD
document defined
ACO (n=138)

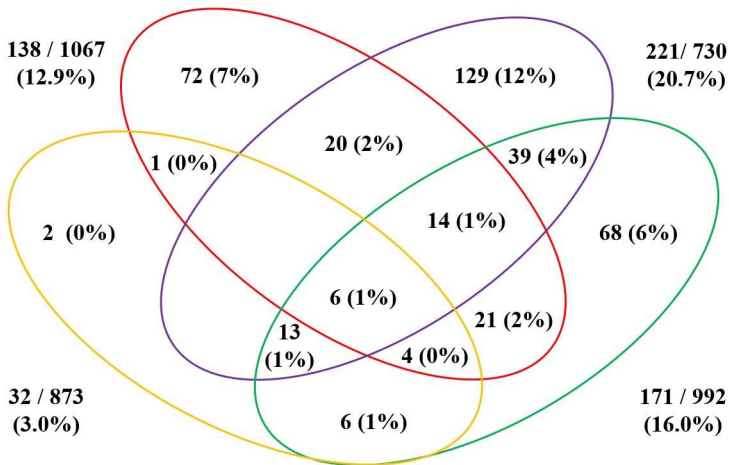
modified Spanish
criteria defined
ACO (n=171)

updated Spanish
criteria defined
ACO (n=138)

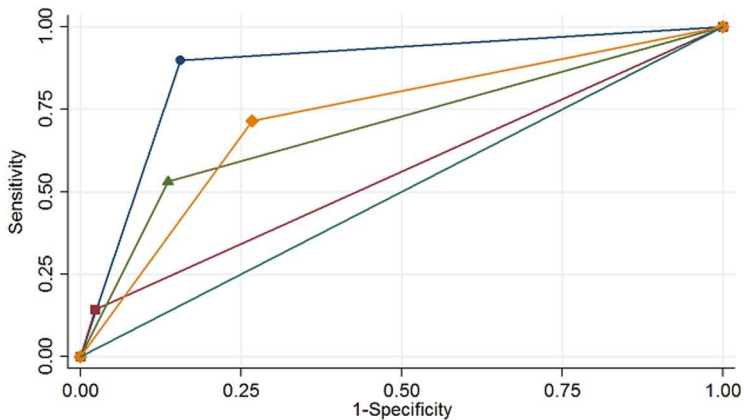
Prospectively followed up for a year

604 patients were included in exacerbation analysis





— GINA/GOLD — Updated Spanish
— ATS roundtable — modified Spanish



specialists' diagnosis: 0.871 ATS roundtable criteria: 0.560
modified Spanish criteria: 0.697 updated Spanish criteria: 0.723
Reference

