

Asthma-COPD Overlap—A Discordance Between Patient Populations Defined by Different Diagnostic Criteria



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What is already known about this topic? A number of definitions have been proposed for asthma-chronic obstructive pulmonary disease overlap (ACO), however, these definitions differ in terms of diagnostic criteria.

What does this article add to our knowledge? Our study showed that the concordance between the current ACO definitions is poor. These definitions identify distinct patient populations that differ in terms of age, symptom level, and the degree of pulmonary function impairment.

How does this study impact current management guidelines? Lack of a widely used uniform ACO definition impacts the estimation of the true burden of this condition and does not allow to establish appropriate management strategies for individual patients.

BACKGROUND: The concordance between asthma-chronic obstructive pulmonary disease overlap (ACO) defined according to Global Initiative for Asthma (GINA)/Global Initiative for Chronic Obstructive Lung Disease (GOLD) and other diagnostic criteria is unknown.

OBJECTIVE: To assess the concordance between different ACO definitions and to estimate the definition-based ACO prevalence and characteristics.

METHODS: A prospective, real-life study based on a 32-item data set was performed in a mixed population of patients with asthma and chronic obstructive pulmonary disease (COPD). Five different definitions of ACO, including the GINA/GOLD criteria, were analyzed.

RESULTS: A total of 1609 patients were included in the final analysis. Application of Venn diagram for ACO populations resulted in 31 ACO subpopulations, which were further reduced to 6 separate populations by introducing a rank order for the analyzed definitions to classify patients from intersecting groups. Overall, the level of agreement between different ACO definitions was poor. Cohen kappa coefficient for the agreement between ACO GINA/GOLD definition and other ACO definitions varied from 0.06 to 0.21. Only 2 patients (0.12%) met all the ACO definitions. Definition-based ACO prevalence ranged between 3.8% (Spanish criteria) and 18.4% (clinician's diagnosis). A total of 573 (33.4%) patients met the criteria from at least 1 ACO definition. Patients who could not be classified as

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Abbreviations used

ACO- Asthma-chronic obstructive pulmonary disease overlap
CHAIN- Chronic Obstructive Pulmonary Disease (COPD)
History Assessment In Spain
COPD- Chronic obstructive pulmonary disease
GesEPOC- Guía española de la enfermedad pulmonar obstructiva
crónica
GINA- Global Initiative for Asthma
GOLD- Global Initiative for Chronic Obstructive Lung Disease

suffering from “pure” asthma, “pure” COPD, or ACO accounted for as much as 27.5% of the whole investigated group. The most severe symptoms were observed in patients with ACO defined as COPD and asthma diagnosed at age less than 40 years.

CONCLUSIONS: The current ACO definitions identify distinct populations that share only a small number of common features and present with different disease phenotypes. ACO prevalence is highly variable, depending on the definition applied. © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:2326-36)

Key words: Asthma-COPD overlap; GINA/GOLD; Venn diagrams

INTRODUCTION

The term “asthma-chronic obstructive pulmonary disease (COPD) overlap syndrome” was introduced in 2009 by Gibson and Simpson¹ to characterize patients presenting features of both asthma and COPD. Five years later, this term was approved by the joint report of Global Initiative for Asthma (GINA) and Global Initiative for Chronic Obstructive Lung Disease (GOLD).² In 2017, the term “asthma-COPD overlap” (ACO) replaced the term “asthma-COPD overlap syndrome” to avoid the general tendency to construe asthma-COPD overlap syndrome as a distinct entity.³ In accordance with this statement, the term ACO will be further uniformly used in this article.

Apart from Gibson and Simpson’s early definition of ACO and the GINA/GOLD criteria, a number of other diagnostic criteria for ACO have been proposed. One of the most sophisticated examples are the classic Spanish ACO criteria, their modified version used in the Chronic Obstructive Pulmonary Disease (COPD) History Assessment In Spain (CHAIN) study,⁴ and the newest Spanish Guía española de la enfermedad pulmonar obstructiva crónica (GesEPOC) 2017 ACO criteria.⁵ Another frequently used criterion for ACO is a current COPD diagnosis in a patient who had been previously diagnosed with asthma before the age of 40 years.^{6,7} Finally, clinicians may classify some of their patients as suffering from ACO, on the basis of their own beliefs and experience.

The abundant number of different ACO definitions resulted in a wide range of the reported ACO prevalence. Estimates were as low as 1.8% and as high as 61%, depending on the type of population studied and, particularly, the diagnostic criteria applied.⁸⁻¹⁷ Of note, most studies published to date applied only one definition of ACO to identify patients with overlapping diseases. In addition, the investigators usually evaluated the

proportion of patients with ACO among patients with COPD, less often among patients with asthma, but only rarely in the population of patients with asthma and COPD together. Recently, new data were published in mixed, real-life populations of patients with asthma and COPD.^{18,19} Nevertheless, such data are still scarce, and, to our knowledge, no study published to date compared multiple reported criteria of ACO including those incorporated in the GINA/GOLD report.

Therefore, this study was aimed to (1) assess the concordance of the GINA/GOLD ACO diagnostic criteria with other widely used ACO definitions, (2) estimate the prevalence of ACO in a large, mixed, and real-life population of patients with asthma and COPD treated by specialists in outpatient pulmonary care; (3) provide the characteristics of ACO subpopulations diagnosed with the use of different criteria and compare them to the characteristics of patients with “pure” asthma and “pure” COPD.

METHODS

Study design and study population

This multicenter prospective cross-sectional study was conducted between January and June 2015. The rationale and methodology of the study was designed by the Steering Committee in 2014. A 32-item data set on patient and disease characteristics, created solely for the purpose of the study (see this article’s Online Repository at www.jaci-inpractice.org), was obtained from pulmonary specialists from outpatient clinics of university teaching hospitals and pulmonary specialist offices. The target population comprised patients with chronic airway disease who attended their routine follow-up visit. The specific inclusion criteria were as follows: diagnosis of asthma, COPD, chronic bronchitis or emphysema, age more than 35 years, and spirometry with bronchial reversibility testing performed within the last 12 months before study enrollment. The exclusion criterion was disease exacerbation in the last 4 weeks. Besides the features of airway disease, the data set comprised information on the symptom level evaluated with the COPD Assessment Test, the Asthma Control Test, and the modified Medical Research Council dyspnea scale. These scores were obtained from every study participant, regardless of the primary diagnosis.

Nine outpatient clinics of teaching hospitals expected to recruit 100 patients each and 176 pulmonary specialist offices, designated to recruit 10 patients each, participated in the study. To avoid selection bias, we adopted the strategy to recruit all the consecutive patients who agreed to participate.

Because of the observational nature of the study, an ethical approval was not required. This opinion was supported by an earlier decision of the Ethics Committee of the Medical University of Silesia on the similarly designed Phenotypes of COPD in Central and Eastern Europe (POPE) study.²⁰

Definition of study groups

The following definitions of ACO were applied: (1) GINA/GOLD criteria,² (2) the Spanish criteria proposed by Soler-Cataluna et al,²¹ (3) current diagnosis of COPD in a patient with asthma diagnosed before the age of 40 years (COPD + asthma < 40 years),^{6,7,22} (4) the definition proposed by Gibson and Simpson (Gibson’s criteria),¹ and finally, (5) physician’s diagnosis based on own experience and beliefs (clinician’s diagnosis). These definitions are presented in detail in Table 1.

The GINA/GOLD Consensus statement² presents 11 separate features of asthma and COPD and states that ACO should be considered in patients presenting with at least 3 features of each

TABLE I. Definitions of ACO used in the study

ACO definition	Diagnostic criteria	
GINA/GOLD consensus ²	More likely asthma if	More likely COPD if
	1. onset < age 20 y	1. onset > age 40 y
	2. variation in symptoms within short periods	2. persistence of symptoms
	3. worsening of symptoms at night/early morning	3. daily symptoms with and exertional dyspnea with good/bad days
	4. symptoms triggered by exercise, emotions/laughter, dust, or exposure to allergens	4. chronic cough and sputum preceded onset of dyspnea, unrelated to triggers
	5. documented airflow limitation variability (peak flow, spirometry)	5. documented persistent airflow limitation (postbronchodilator FEV ₁ /FVC < 70%)
	6. lung function normal between symptoms	6. lung function abnormal between symptoms
	7. previous doctor diagnosis of asthma	7. previous doctor diagnosis of COPD, chronic bronchitis, or emphysema
	8. family history of asthma or atopy/eczema	8. heavy exposure to a risk factor (tobacco smoke, biomass fuel)
	9. no worsening of symptoms over time. Symptoms vary either seasonally or from year to year	9. symptoms slowly worsening over time (progressive course over years)
	10. may improve spontaneously or have an immediate response to bronchodilators or to inhaled steroids over weeks	10. rapid-acting bronchodilator treatment provides only limited relief
Spanish criteria ²¹	11. chest X-ray normal	11. chest X-ray with features of severe hyperinflation
	If ≥3 items are present for either asthma or COPD, the patient is likely to have that disease. A similar* number of items for asthma and COPD is suggestive for ACO	
	Diagnosis of COPD and	
COPD + asthma < 40 y	≥2 of the following major criteria:	
	- Bronchodilator response ≥15% and 400 mL	
	- Sputum eosinophilia >3%	
	- Diagnosis of asthma <age 40 y	
	OR	
	1 major and ≥2 of the following minor criteria:	
	- High total IgE level	
	- Atopy	
	- At least 2 separated bronchodilator responses ≥12% and ≥200 mL	
	- Current diagnosis of COPD (history of smoking, postbronchodilator FEV ₁ /FVC < 70%)	
Gibson's criteria ¹	- Diagnosis of asthma before the age of 40 y	
	- Clinical symptoms of chronic airway disease—FEV ₁ /FVC < 70%	
	- FEV ₁ < 80%	
Physician's diagnosis	- BHR, PD ₁₅ < 12 mL	
	- Diagnosis of ACO based on physician's own knowledge and experience	
ACO definitions used for additional analyses		
New Spanish criteria (CHAIN study) ⁴	Age > 40 y, postbronchodilator FEV ₁ /FVC < 70%, exposure to cigarette smoke	
	AND	
	≥ 1 of the following major criteria:	
	- History of asthma	
	- Bronchodilator response to salbutamol >15% and 400 mL	
	OR	
	≥ 2 of the following minor criteria:	
	- IgE level > 100 IU or history of atopy	
	- 2 separated bronchodilator responses to salbutamol >12% and 200 mL	
	- Blood eosinophils > 5%	

(continued)

TABLE 1. (Continued)

ACO definition	Diagnostic criteria
Newest Spanish criteria (GesEPOC 2017) ⁵	Age > 35 y, postbronchodilator FEV ₁ /FVC < 70%, ≥10 pack years
	AND
	- Current diagnosis of asthma
	OR
	- No current diagnosis of asthma but a bronchodilator response to salbutamol ≥15% and 400 mL and/or blood eosinophils ≥ 300 cells/μL
“Pure asthma”	- Physician-diagnosed asthma
	- Never smoker
	- History of positive bronchial reversibility test
	- ≥3 of 11 features for asthma and <3 of 11 features for COPD in the GINA/GOLD ACO criteria
“Pure” COPD	- Physician-diagnosed COPD
	- ≥10 pack years of smoking history
	- Postbronchodilator FEV ₁ %/FVC < 70%
	- Presence of ≥3 of 11 features for COPD and <3 of 11 features for asthma in the GINA/GOLD ACO criteria
	- No asthma diagnosis before the age of 40 y
	- No history of sputum eosinophilia

BHR, Bronchial hyperresponsiveness; FVC, forced vital capacity; PD₁₅, provocation dose of hypertonic saline causing a 15% drop in FEV₁.

*For the purpose of the study, a threshold of <30% relative difference in the number of asthma and COPD features was applied for ACO diagnosis. For example, if a patient presented with 7 features of COPD and 5 features of asthma, the relative difference was calculated as follows: $[(7 - 5)/7] \times 100\% = 29\%$; the patient met the above 30% criterion for ACO diagnosis.

disease and the number of features for asthma and COPD is “similar.” However, the term “similar” was not defined. In this study, patients were qualified as ACO, if their relative difference in the number of asthma and COPD features was lower than 30% (ACO GINA/GOLD 30%) (for the principles of the calculation of the relative difference in asthma and COPD features and a description of the analyzed ACO definitions, see this article’s Online Repository at www.jaci-inpractice.org). For statistical purposes, a distinct ACO group was formed from all the patients who met the ACO GINA/GOLD 30% criteria with at least one of the other ACO definitions described above—with exception of clinician’s diagnosis, which was not considered because this definition was based on subjective judgment. This distinct group (GINA/GOLD 30% + at least 1 other ACO definition) is further referred to as the “violet group” to facilitate the understanding of our results presented in the graphs. This approach enabled a more comprehensive statistical analysis by a significant reduction of the number of subpopulations (resulting from diagnostic criteria overlap) to be analyzed. The “violet” group probably most reliably represents patients with ACO because this subpopulation includes patients meeting at least 2 ACO definitions including the “criterion standard”—the GINA/GOLD criteria.

Five different ACO definitions were labeled with 5 different colors: GINA/GOLD 30%, blue; Spanish criteria, red; COPD + asthma less than 40 years, orange; Gibson’s criteria, yellow; and clinician’s diagnosis, green. These colors were consequently applied in all the figures presenting the results.

Patients with “pure” asthma and patients with “pure” COPD were selected as comparators for the ACO groups described above. Patients with “pure” asthma were defined as follows: physician-diagnosed asthma; never smoker; history of positive bronchial reversibility test; and presence of at least 3 of 11 features for asthma and less than 3 of 11 features for COPD in the GINA/GOLD ACO criteria. Patients with “pure” COPD had to meet all the following criteria: physician-diagnosed COPD; at least 10 pack years of

smoking history; postbronchodilator FEV₁%/FVC less than 70%; presence of at least 3 of 11 features for COPD and less than 3 of 11 features for asthma in the GINA/GOLD ACO criteria; no asthma diagnosis before the age of 40 years; and no history of sputum eosinophilia.

A post hoc analysis was performed for 2 additional ACO definitions, which were further used as substitutes for the Spanish criteria: the criteria presented by Cosio et al⁴ for the population of patients with COPD from the Spanish CHAIN study (further referred to as “the new Spanish criteria—CHAIN study”) and the criteria incorporated in the Spanish 2017 guidelines for COPD (GesEPOC), labeled as “the newest Spanish criteria—GesEPOC 2017.”⁵ Although these 2 definitions were proposed after the completion of our data collection, all their criteria could be identified in our data set. The only exception was the criterion of blood eosinophilia level of greater than or equal to 300 cells/μL in the newest Spanish criteria. Because we did not have access to data on the precise blood eosinophil count, this criterion had to be substituted by information on “increased percentage of blood eosinophils,” which was originally included in our data set (Table I).

ACO populations defined on the basis of the new Spanish criteria and the newest Spanish criteria were analyzed separately from the Spanish criteria population and are presented in this article’s Online Repository figures at www.jaci-inpractice.org. Both were assigned with red, as in the figures they appeared as substitutes for the Spanish criteria population (originally presented in this color).

Statistical analysis

Statistical analyses were performed using R language and environment for statistical computing.²³ The normality of the distributions of continuous variables was assessed by Shapiro-Wilk test and using q-q plots.

Categorical variables were presented as frequency and percentage in groups, whereas continuous variables as mean and SD. Non-proportional Venn diagrams were used to present different

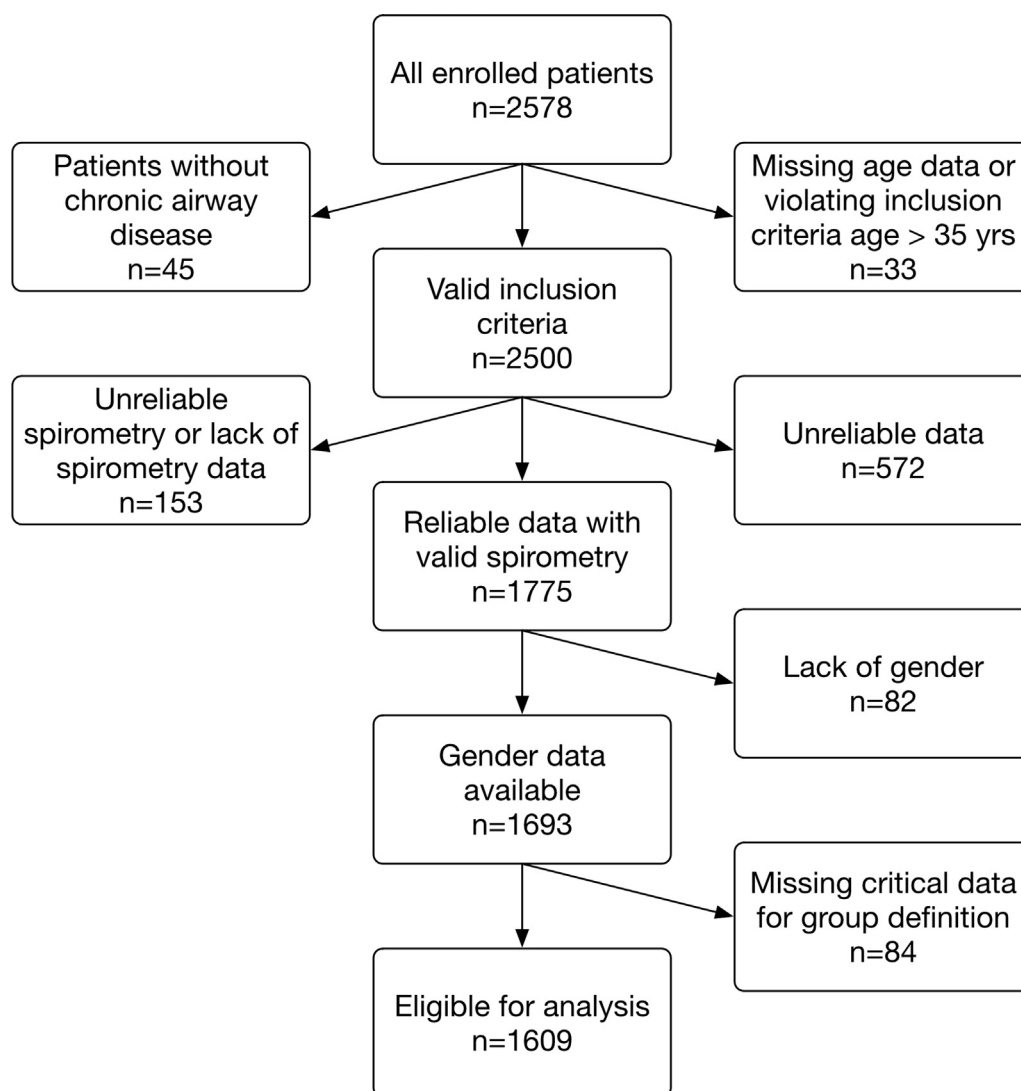


FIGURE 1. The reasons for noneligibility of patients for final analysis.

definition-based ACO subpopulations and their mutual intersections. Statistical significance of differences between categorical variables was analyzed using chi-square test, followed by Fisher exact test for comparisons of 2 groups. The differences among groups in terms of continuous variables were analyzed using Kruskal-Wallis rank sum test, followed by Mann-Whitney *U* test for multiple group comparisons.

The Cohen kappa statistical test was used to assess the degree of agreement between diagnosis of ACO with different criteria. The obtained kappa values were interpreted as proposed by Fleiss et al²⁴: greater than 0.75, excellent; 0.40 to 0.75, fair/good; and less than 0.40, poor. All *P* values were 2-tailed, and *P* values of less than .05 were considered statistically significant.

RESULTS

Study population

Overall, a total of 2578 consecutive patients were enrolled (854 patients recruited in university outpatient clinics and 1724 patients in pulmonary specialist offices). After thorough data

verification, only 1609 patients (62.4%) were eligible for final analysis (710 patients from university outpatient clinics and 899 from pulmonary specialist offices, respectively). The flow chart presenting the reasons for patient noneligibility for the final analysis is shown in [Figure 1](#).

Ultimately, the investigated group comprised 808 women and 801 men, with a mean age of 62.6 ± 11.6 years. The patient characteristics are presented in [Table II](#).

Prevalence of ACO

The prevalence of ACO defined according to different criteria is shown in [Figure 2](#). The highest ACO prevalence was noted for patients with clinician's diagnosis (18.4%), whereas the lowest was seen for patients with the Spanish criteria (3.8%). GINA/GOLD 30% definition and the newest Spanish criteria GesE-POC 2017 yielded a very similar result (10.8% vs 10.7%, respectively). As expected, for the GINA/GOLD definition, ACO prevalence rose gradually with increasing relative difference between the number of features of asthma and those of COPD,

TABLE II. Basic characteristics of the investigated group (n = 1609)

Variable	Value
Sex: female/male, n (%)	808 (50.2)/801 (49.8)
BMI (kg/m ²)	28.0 ± 5.5
Age at inclusion (y)	62.6 ± 11.6
Age at diagnosis of obstructive lung disease (y)	49.1 ± 17.5
FEV ₁ , % of predicted value	71.9 ± 24.6
FEV ₁ /FVC, %	64.1 ± 14.8
Smoking status, n (%)	
Never/current/ex-smokers	565 (35.1)/321 (20.0)/723 (44.9)
Pack years	18.7 ± 22.4
mMRC, points	1.50 ± 1.03
CAT, points	15.9 ± 8.0
ACT, points	17.6 ± 4.7

ACT, Asthma Control Test; BMI, Body mass index; CAT, COPD Assessment Test; FEV₁, forced expiratory volume at 1st second; FVC, forced vital capacity; mMRC, modified Medical Research Council dyspnea scale. Values are mean ± SD unless indicated otherwise.

the studied groups (see the [Methods](#) section). It creates an additional subpopulation (“violet” group, 57 patients) formed from the intersection of ACO GINA/GOLD 30% and at least 1 other validated ACO criterion. Therefore, this figure shows 6 distinct subpopulations (diagnosis based on 5 different ACO definitions and the “violet” group), all marked in different colors. These subpopulations were included in the final analysis (see the [Methods](#) section). The reduction from 31 to 6 populations was achieved by introducing a rank order of the analyzed definitions to classify patients from intersecting subpopulations. The following strategy was applied: first (1), the “violet field” corresponding with patients meeting the GINA/GOLD 30% and at least 1 other ACO definition was created, followed by (2) the “blue field” corresponding with patients who met the GINA/GOLD 30% criteria only but not included in the “violet field,” then (3) the “red field” corresponding with patients who met the Spanish criteria but not the GINA/GOLD 30% definition (therefore not contributing to the “violet field” and the “blue field”), (4) the “orange field,” representing patients with ACO defined by COPD + asthma at age less than 40 years but not

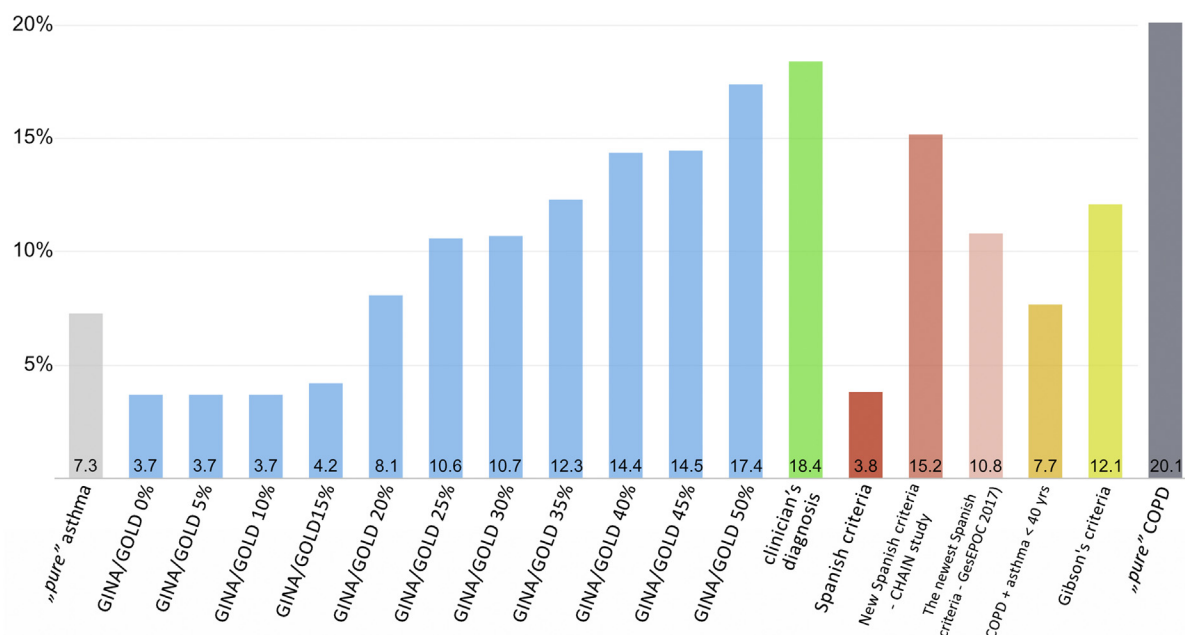


FIGURE 2. The prevalence of ACO defined according to different diagnostic criteria. In addition, the prevalence of “pure” asthma and “pure” COPD in the study population is presented.

ranging from 3.7% for the relative difference of 0% to 17.4% for the relative difference of 50% ([Figure 2](#)).

Venn diagrams

[Figure 3](#) shows a Venn diagram for ACO populations diagnosed on the basis of different criteria. Patients who met the criteria from different definitions were placed in the intersections, forming the number of 31 ACO subpopulations. Only 2 (0.12%) patients from the whole investigated group met criteria for all the ACO definitions.

[Figure 4](#) depicts a simplified version of the diagram, introduced to enable comprehensive statistical comparisons among

GINA/GOLD 30% and Spanish criteria (hence not included in the “violet field,” the “blue field,” and the “red field”) followed by (5) the “yellow field” for patients with ACO defined by Gibson’s criteria and not the COPD + asthma at age less than 40 years, GINA/GOLD 30% definition, and the Spanish criteria (created by patients not contributing to the “violet,” “blue,” “red” fields nor the “orange field”), and finally, (6) the “green field,” representing patients with ACO clinician’s diagnosis but not meeting any other ACO diagnostic criteria and therefore not contributing to any of the 5 above-mentioned groups.

Analogous diagrams were prepared with the use of the new and the newest Spanish criteria^{4,5} instead of Spanish criteria²¹

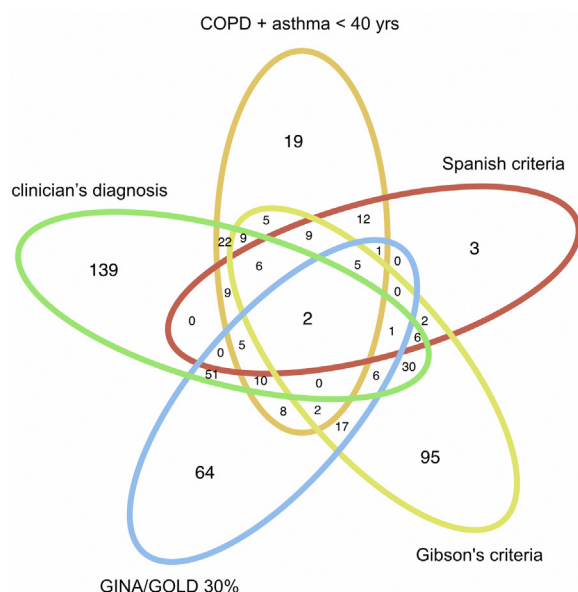


FIGURE 3. Venn diagram of the prevalence of ACO (absolute numbers) as defined by different diagnostic criteria.

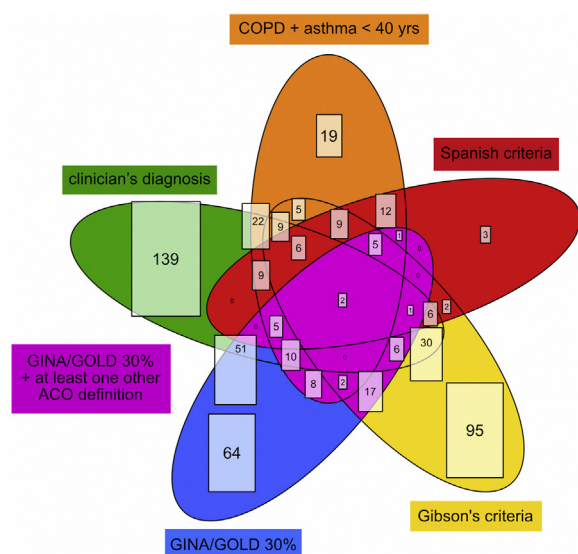


FIGURE 4. Venn diagram of the prevalence of ACO (absolute numbers) as defined by different diagnostic criteria. The area of the rectangles is proportionate to the number of patients in the respective ACO populations.

(see Figures E1 and E2 in this article's Online Repository at www.jaci-inpractice.org). This small change resulted in an almost 4-fold and 2.8-fold increase in ACO prevalence, respectively.

Figure 5 shows the prevalence of ACO estimated with the use of the approach applied in the Venn diagram from Figure 4. Patients who met all the criteria from at least 1 ACO definition comprised 33.4% of the investigated group, whereas patients with "pure" asthma and "pure" COPD accounted for 7.3% and

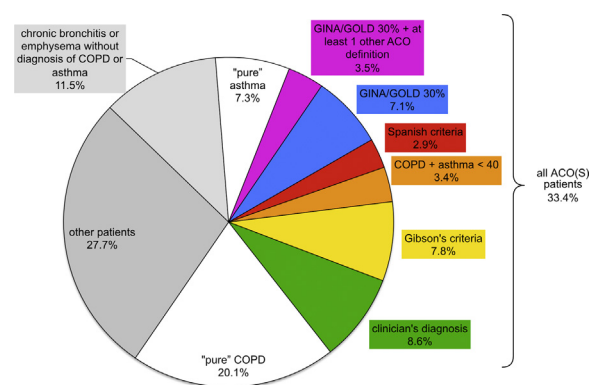


FIGURE 5. The prevalence of ACO in our cohort.

20.1% of the group, respectively. In 27.7% of cases, the disease could not be identified as ACO, "pure" asthma, "pure" COPD, chronic bronchitis, or emphysema.

Differences between distinct ACO populations

The differences between clinical parameters in the groups defined by various criteria are summarized in Table III. This analysis showed significant differences in terms of age, post-bronchodilator FEV₁, COPD Assessment Test and modified Medical Research Council dyspnea scale score, smoking history, and the number of exacerbations (see Figures E3-E12 in this article's Online Repository at www.jaci-inpractice.org). The highest symptom level was found in patients with ACO defined as COPD and the diagnosis of asthma before the age of 40 years. Patients with "pure" asthma reported a significantly lower number of exacerbations in 12 months preceding the study enrollment than that reported by patients with "pure" COPD and ACO.

Agreement between different ACO definitions

The results of Cohen kappa statistical test for the degree of agreement between ACO diagnosis with different criteria are presented in Table IV. Overall, the level of agreement between different ACO definitions was poor. The highest agreement (κ , 0.5) was noted between ACO defined by COPD + asthma at age less than 40 years and Spanish criteria.

DISCUSSION

To our knowledge, our study is the first to analyze the prevalence of ACO diagnosed with several most widely used criteria (including those proposed by GINA/GOLD) in a large population of mixed, real-life patients with asthma and COPD and to evaluate the concordance among different ACO definitions. We showed that each criteria define different ACO populations, which share only a small number of common features. The concordance between the ACO definitions was poor and ACO prevalence strongly depended on the diagnostic criteria applied to define affected patients. Finally, we showed that disease severity varies among the definition-based ACO subpopulations, which indicates that the diagnostic criteria applied may impact treatment approach.

Our study demonstrated that the currently used different ACO diagnostic criteria identify almost distinct subgroups of patients. This observation was possible because we applied

TABLE III. Comparison of clinical parameters in the definition-based ACO subgroups, patients with “pure” asthma, and patients with “pure” COPD

Variable		“Pure” asthma (n = 117)	ACO definitions						“Pure” COPD (n = 324)	P value (Kruskal-Wallis test)
			GINA/GOLD 30% criteria (n = 115)	Spanish criteria (n = 47)	COPD + asthma < 40 y (n = 55)	Gibson’s criteria (n = 125)	Clinician’s diagnosis (n = 139)	“Violet” group* (n = 57)		
Group code		A	B	C	D	E	F	G	H	
Female/male	n	65/52	67/55	18/29	21/34	43/82	69/70	29/28	114/210	<.001
	Significance for comparison with groups†	DEH	CDEH	B	AB	ABFG	EH	EH	ABFG	
Age at inclusion to the study (y)		53.7 ± 14.0	63.5 ± 10.3	56.6 ± 11.1	62.2 ± 13.0	65.9 ± 9.0	65.6 ± 10.1	63.5 ± 8.5	67.0 ± 8.2	<.001
	Significance for comparisons with groups†	BDEFGH	ACH	BDEFGH	ACH	AC	AC	ACH	ABCDG	
Age at diagnosis of obstructive lung disease (y)		37.1 ± 19.2	47.1 ± 16.6	32.5 ± 16.4	34.3 ± 17.7	57.5 ± 9.1	49 ± 16.5	40.0 ± 19.1	60.2 ± 9.4	<.001
	Significance for comparisons with groups †	BEFH	ACDEGH	BEFGH	BEFH	ABCDFGH	ACDEGH	BCEFH	ABCDEFG	
BMI (kg/m ²)		27.0 ± 4.9	28.1 ± 5.2	27.2 ± 4.5	26.5 ± 5.5	27.6 ± 5.2	27.7 ± 5.4	28.2 ± 6.1	27.3 ± 5.3	NS
	Significance for comparisons with groups†	—	—	—	—	—	—	—	—	
FEV ₁ , % of predicted value		90.1 ± 20.6	73.7 ± 22.2	71.1 ± 18.3	60.4 ± 19.4	65.8 ± 17.4	65.0 ± 21.2	66.7 ± 16.1	53.1 ± 17.9	<.001
	Significance for comparisons with groups†	BCDEFGH	ADEFH	ADEH	ABCH	ABCH	ABH	AH	ABCDEFG	
FEV ₁ /FVC, %		74.6 ± 10.0	66.5 ± 13.3	58.1 ± 8.7	54.7 ± 10.2	56.6 ± 9.7	63.8 ± 14.1	58.1 ± 9.1	51.1 ± 10.9	<.001
	Significance for multiple comparisons with groups†	BCDEFGH	ACDEGH	ABFH	ABFH	ABFH	ACDEGH	ABFH	ABCDEFG	
Smoking status		117/0/0	45/56/14	0/35/12	0/39/16	0/90/35	56/51/32	0/37/20	0/221/10	<.001
	Significance for comparisons with groups	BCDEFGH/ BCDEFGH/ BCDEFGH	ACDEGH/ACDEH/ ADEFH	ABF/ABF/A	ABF/ABF/AB	ABF/ABF/AB	ACDEGH/ ACDEGH/AB	ABF/AF/AB	ABF/ABF/AB	
Pack years (n)		0.0 ± 0.0	13.3 ± 17.7	19.5 ± 17.9	23.9 ± 18.2	34.4 ± 19.4	16.1 ± 19.6	31.0 ± 27.6	39.7 ± 20.9	<.001
	Significance for comparisons with groups†	BCDEFGH	ACDEGH	ABEFGH	ABEFH	ABCDFGH	ACDEGH	ABCDEH	ABCDEFG	
mMRC (points)		0.85 ± 0.8	1.38 ± 0.9	1.21 ± 1.0	1.87 ± 1.1	1.54 ± 0.9	1.77 ± 0.9	1.58 ± 0.9	2.06 ± 1.0	<.001

(continued)

TABLE III. (Continued)

Variable		"Pure" asthma (n = 117)	ACO definitions						P value (Kruskal-Wallis test)	
			GINA/GOLD 30% criteria (n = 115)	Spanish criteria (n = 47)	COPD + asthma < 40 y (n = 55)	Gibson's criteria (n = 125)	Clinician's diagnosis (n = 139)	"Violet" group* (n = 57)		"Pure" COPD (n = 324)
Group code		A	B	C	D	E	F	G	H	
	Significance for comparisons with groups†	BCDEFGH	ADFH	ADEFGH	ABCG	ACDH	ABCH	ACH	ABCEFG	
CAT (points)		11.7 ± 7.5	16.5 ± 7.5	14.5 ± 8.2	19.7 ± 8.1	16.1 ± 7.2	19.0 ± 7.2	16.8 ± 6.9	18.3 ± 7.7	<.001
	Significance for comparisons with groups†	BCDEFGH	ADFH	ADFH	ABCEG	ADFH	ABDEG	ADF	ABCG	
ACT (points)		19.6 ± 4.1	17.5 ± 4.6	17.6 ± 5.2	14.8 ± 4.9	18.0 ± 4.5	16.6 ± 4.2	16.6 ± 4.4	16.2 ± 4.7	<.001
	Significance for comparisons with groups†	BCDEFGH	ADH	AD	ABCEFGH	ADFH	ADE	AD	ABDE	
Disease exacerbations (N/Y)		0.94 ± 1.11	1.93 ± 2.47	1.49 ± 1.44	2.00 ± 1.98	1.59 ± 2.44	1.94 ± 2.05	2.17 ± 2.33	1.54 ± 1.65	<.001
	Significance for comparisons with groups†	BCDEFGH	A	A	A	AFG	AE	AE	A	

ACT, Asthma Control Test; BMI, body mass index; CAT, COPD Assessment Test; FEV₁, forced expiratory volume at 1st second; FVC, forced vital capacity; mMRC, modified Medical Research Council dyspnea scale; NS, not significant. Values are mean ± SD unless indicated otherwise.

*The violet group comprised patients who met the GINA/GOLD 30% criteria and at least 1 other ACO definition.

†P < .05.

TABLE IV. Cohen kappa coefficient for the agreement between the diagnosis of ACO according to different diagnostic criteria

ACO Definition	GINA/GOLD 30%	Spanish criteria	New Spanish criteria (CHAIN study)	Newest Spanish criteria (GesEPOC 2017)	COPD + asthma < 40 y	Gibson's 's criteria	Clinician's diagnosis
GINA/GOLD 30%	x	0.07	0.06	0.19	0.15	0.07	0.21
Spanish criteria	0.07	x	0.25	0.25	0.50	0.20	0.11
New Spanish criteria (CHAIN study)	0.06	0.25	x	0.04	0.14	NS	0.05
Newest Spanish criteria (GesEPOC 2017)	0.19	0.25	0.04	x	0.35	0.33	0.37
COPD + asthma < 40 y	0.15	0.50	0.14	0.35	x	0.16	0.21
Gibson's criteria	0.07	0.20	0.50	0.33	0.16	x	0.12
Clinician's diagnosis	0.21	0.11	NS	0.37	0.21	0.12	x

NS, Not significant.

almost all known ACO definitions and also because our investigated population comprised not only patients with COPD but also patients with asthma. Our results show that the population of patients with obstructive airway disease (asthma and COPD) is very heterogeneous, and besides patients with “pure” asthma and “pure” COPD, there are many small subpopulations identified by different ACO criteria in between. Interestingly, our subgroup analysis identified a population of patients that, to our knowledge, had not emerged in earlier studies. This refers to patients who had been diagnosed with chronic airway disease but could not be classified as suffering from ACO, “pure” asthma, “pure” COPD, chronic bronchitis, or emphysema. Of note, this subgroup was almost as numerous (27.7%) as all the ACO subgroups taken together. The presence of such a relatively large subpopulation further confirms the diversity and heterogeneity of the population of patients with chronic airway disease.

One of the major objectives of our study was to compare the GINA/GOLD ACO diagnostic criteria with other widely used ACO definitions. The estimation of the population of patients who met the GINA/GOLD criteria required an arbitrary decision on the precise description of the term “similar” referring to the comparison of the number of features typical for asthma and typical for COPD. A consensus on the “similarity” threshold value was reached after a long debate among the members of the study's Steering Committee. It seems that further precision of the GINA/GOLD ACO diagnostic criteria should be advocated to reduce possible doubts and misinterpretation. Our study may be helpful in this matter.

The prevalence of ACO reported in different studies varied substantially and ranged from 1.8% to 61%, depending on the investigated population and applied ACO definition.^{9-11,13,15-17} In our study, the definition-dependent prevalence estimated in our cohort varied from 3.8% (Spanish criteria) to 18.4% (clinician's diagnosis). Moreover, replacement of the Spanish criteria proposed by Soler-Cataluna et al²¹ by the new Spanish criteria⁴ resulted in an almost 4-fold increase in ACO prevalence. Approximately one-third of the patients in our cohort met the criteria from at least 1 ACO definition. However, this group includes patients with clinician-diagnosed ACO based on personal experience and not on objective criteria. When clinician's diagnosis is excluded, the proportion of patients meeting at least 1 of the other ACO definitions decreases to 24.8%. This is a similar value to the value found by Wurst et al²⁵ (21.3%) who analyzed ACO prevalence in the context of *International Classification of Diseases, Ninth Revision* coding-based ACO definitions.

The formation of 6 distinct subpopulations of patients with ACO on the basis of the Venn diagram enabled a comparative

analysis between the subgroups, as well as a comparison between patients with ACO and “pure” asthma and “pure” COPD. The highest symptom level was found in patients with ACO defined as COPD and asthma diagnosis before the age of 40 years. Patients with ACO defined according to these criteria had previously been identified as more severely ill than patients with asthma or COPD alone,^{6,7} although this had not been confirmed in some studies.^{17,26,27} In our study, the number of exacerbations in patients with ACO was significantly higher when compared with patients with “pure” asthma; however, no significant differences in exacerbation rate were found between patients with ACO and patients with “pure” COPD.

Our study has some limitations, which need to be recognized. First, the study was observational and based on a data set acquired from respiratory physicians. However, a large body of epidemiological studies acquired data from dedicated questionnaires or data sets, some of them relying on simple clinical indices.^{28,29} Nevertheless, we were not able to avoid a notable patient dropout rate, attributed mainly to missing data on both simple (sex, age) and key issues (no or low-quality spirometry, insufficient data for group definition). This dropout rate also resulted from our attempt to present highest quality data. Of note, the dropout rate was higher among patients recruited in pulmonary specialist offices than among those from outpatient clinics of university teaching hospitals (47.9% vs 16.9%, respectively). This difference probably results from a higher motivation and a wider experience in research in the latter. Second, although we applied the most frequently used ACO diagnostic criteria, for methodological reasons, we introduced some modifications to the definitions of the disease, for example, to the newest Spanish criteria (GesEPOC 2017).⁵ In this case, the modification was a result of the publication of these criteria after data completion in our study.

To conclude, our study confirmed that ACO prevalence is highly variable, depending on the definition applied. The current ACO definitions identify different populations that share only a small number of common features. This shows that patients with ACO are a heterogeneous group, in which different phenotypes may require a different therapeutic approach. The diversity and complexity of the existing ACO definitions may impact the estimation of the disease burden.

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ONLINE REPOSITORY

METHODS

Study design and study population

A 32-item data set on patient and disease characteristics, created solely for the purpose of the study, was obtained from pulmonary specialists from outpatient clinics of university teaching hospitals and pulmonary specialist offices. The data included demographic parameters, smoking history, occupational exposure, family history of respiratory/atopic diseases, current diagnosis of respiratory disease, disease duration, time of first diagnosis of chronic airway disease, history of atopy/allergy, results of spirometry with reversibility testing and provocation challenge test (if available), results of blood/sputum/bronchoalveolar lavage eosinophil count if ever investigated, number of respiratory disease exacerbations in the past year, COPD Assessment Test, Asthma Control Test score (in all patients), perception of dyspnea based on the modified Medical Research Council dyspnea scale, current treatment of airway disease, and concomitant diseases. In addition, the data set comprised information on specific parameters required to categorize patients according to different ACO criteria and an 11-point table with the GINA/GOLD criteria for differentiation between asthma and COPD.^{E1}

Definition of study groups

The GINA/GOLD Consensus statement^{E1} presents 11 separate features of asthma and COPD and states that ACO should be considered in patients presenting with at least 3 features of each disease and the number of features for asthma and COPD is “similar.” However, no explanation for the term “similar” was provided. We therefore used our own consensus definition, based on the calculation of the relative difference between the number of specific features. The threshold of 30%

was arbitrarily chosen for discriminating ACO from asthma or COPD; that is, patients were qualified as ACO, if their relative difference in the number of asthma and COPD features was lower than 30% (ACO GINA/GOLD 30%). For example, if a patient presented with 7 features of COPD and 5 features of asthma, the relative difference was calculated as follows: $[(7 - 5)/7] \times 100\% = 29\%$ and the patient met the above 30% criterion. To evaluate the impact of the relative difference on ACO prevalence, separate analyses for the thresholds ranging from 0% to 50% were performed.

The Spanish ACO definition proposed by Soler-Cataluna et al^{E2} (“Spanish criteria”) refers only to the population with COPD and not chronic airway disease in general. We therefore used 2 additional criteria, history of smoking and post-bronchodilator FEV₁/forced vital capacity (FVC) less than 70%, as mandatory for COPD diagnosis.

ACO defined as current COPD diagnosis in a patient with asthma recognized before the age of 40 years (COPD + asthma < 40 years) is one of the classic ACO definitions^{E3-E5} that can be used only for patients with COPD. Thus, we added an additional criterion for COPD diagnosis (positive smoking history and postbronchodilator FEV₁/FVC < 70%), as previously applied for the Spanish criteria.

ACO defined by Gibson and Simpson^{E6} as “symptoms of increased variability of airflow and incompletely reversible airflow obstruction” (Gibson’s criteria) was recognized when a patient had a history of smoking, postbronchodilator FEV₁/FVC less than 70%, and a history of at least 1 positive result of bronchial reversibility test.

Physician’s ACO diagnosis (clinician’s diagnosis) was acknowledged when in the opinion of the attending respiratory specialist, the proper diagnosis in his or her patient was asthma and COPD.

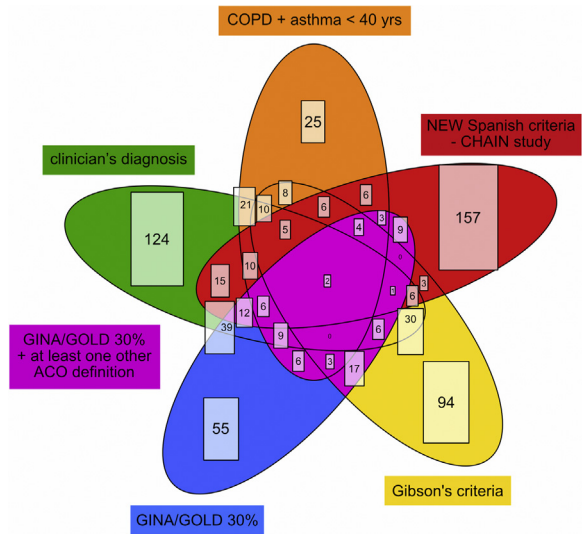


FIGURE E1. Venn diagram of the prevalence of ACO (absolute numbers) as defined by different diagnostic criteria, with the Spanish criteria replaced by the new Spanish criteria (applied for the CHAIN study population). The area of the rectangles is proportionate to the number of patients in the respective ACO populations. The area marked with violet represents the subpopulation of patients with ACO who met the criteria from the GINA/GOLD 30% definition and at least 1 other definition with the exclusion of clinician's diagnosis ("violet group").

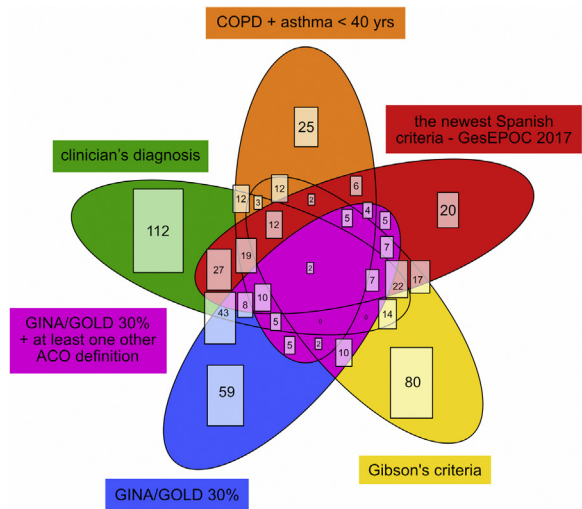


FIGURE E2. Venn diagram of the prevalence of ACO (absolute numbers) as defined by different diagnostic criteria, with the new Spanish criteria (applied for the CHAIN study population) replaced by the newest Spanish criteria (GesEPOC 2017). The area of the rectangles is proportionate to the number of patients in the respective ACO populations. The area marked with violet represents the subpopulation of patients with ACO who met the criteria from the GINA/GOLD 30% definition and at least 1 other definition with the exclusion of clinician's diagnosis ("violet group").

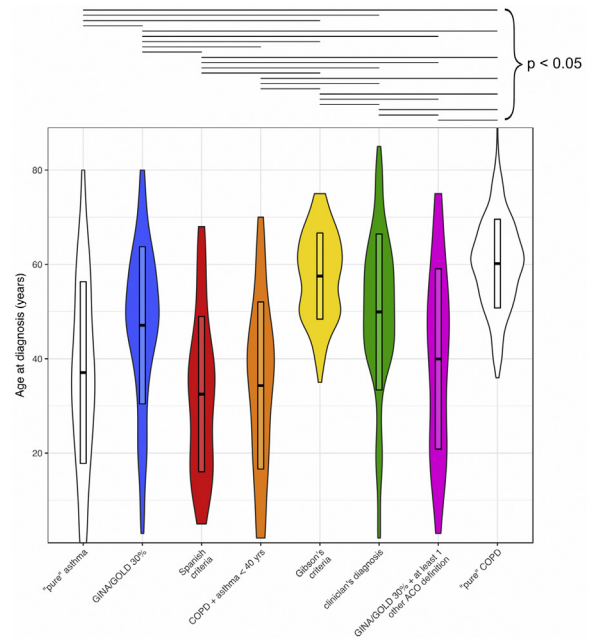


FIGURE E3. Differences in age at the time of diagnosis of airway obstructive disease among definition-based ACO subpopulations, patients with "pure" asthma, and patients with "pure" COPD.

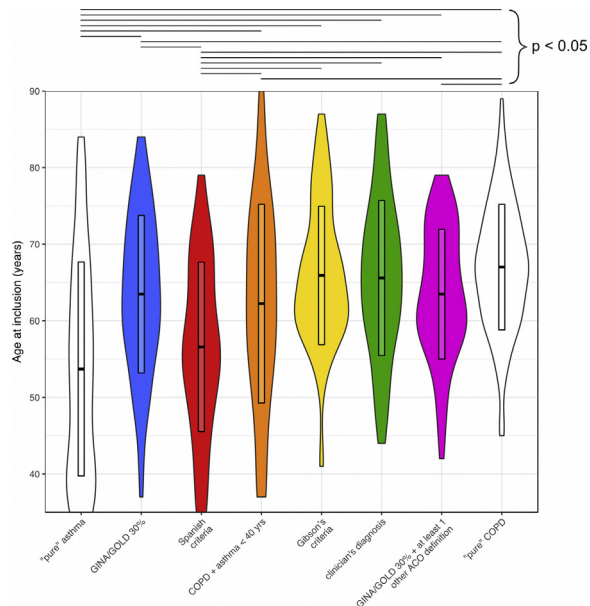


FIGURE E4. Differences in age at the time of inclusion to the study among definition-based ACO subpopulations, patients with "pure" asthma, and patients with "pure" COPD.

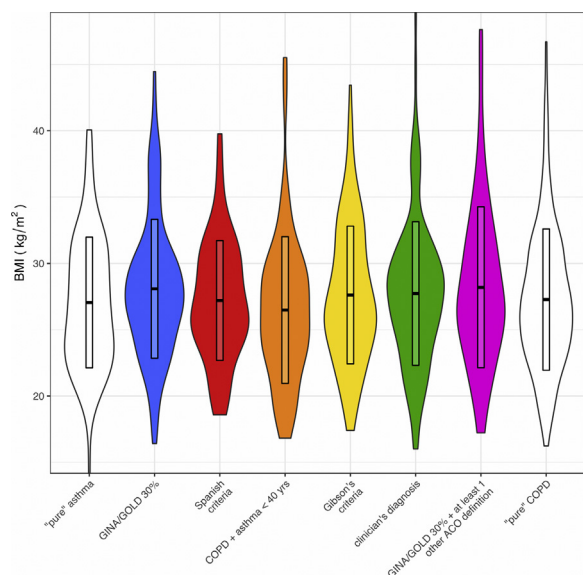


FIGURE E5. Differences in body mass index (BMI) among definition-based ACO subpopulations, patients with “pure” asthma, and patients with “pure” COPD.

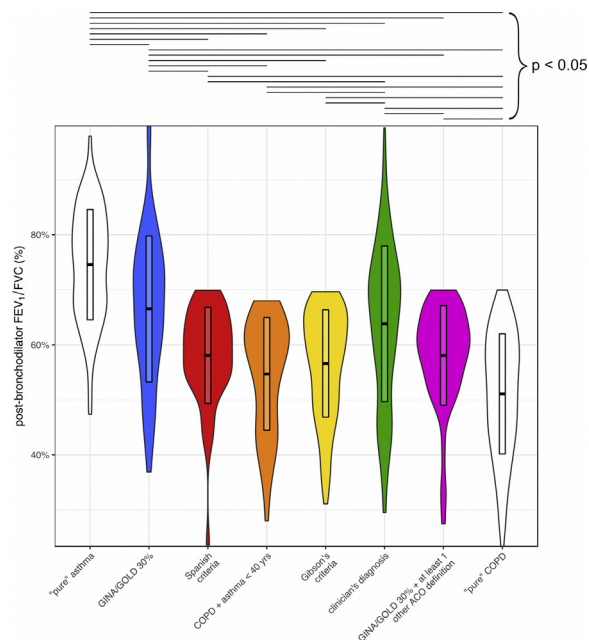


FIGURE E7. Differences in postbronchodilator FEV₁/FVC among definition-based ACO subpopulations, patients with “pure” asthma, and patients with “pure” COPD. FVC, Forced vital capacity.

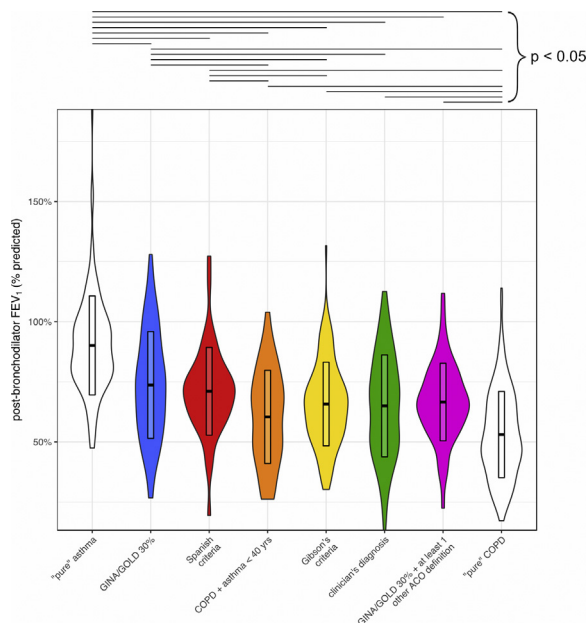


FIGURE E6. Differences in postbronchodilator FEV₁ (% of predicted value) among definition-based ACO subpopulations, patients with “pure” asthma, and patients with “pure” COPD.

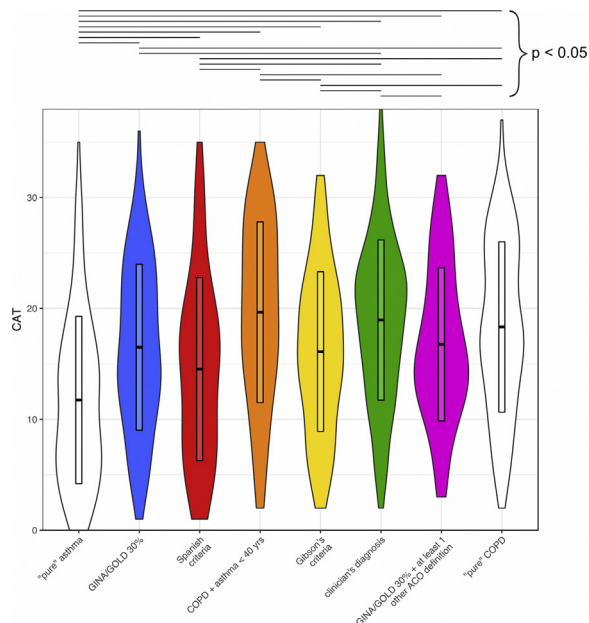


FIGURE E8. Differences in COPD Assessment Test (CAT) score among definition-based ACO subpopulations, patients with “pure” asthma, and patients with “pure” COPD.

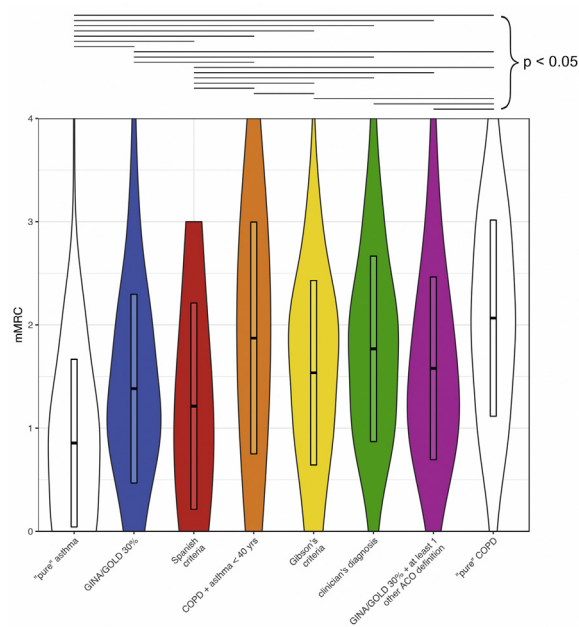


FIGURE E9. Differences in perception of dyspnea (modified Medical Research Council dyspnea scale [mMRC] score) among definition-based ACO subpopulations, patients with “pure” asthma, and patients with “pure” COPD.

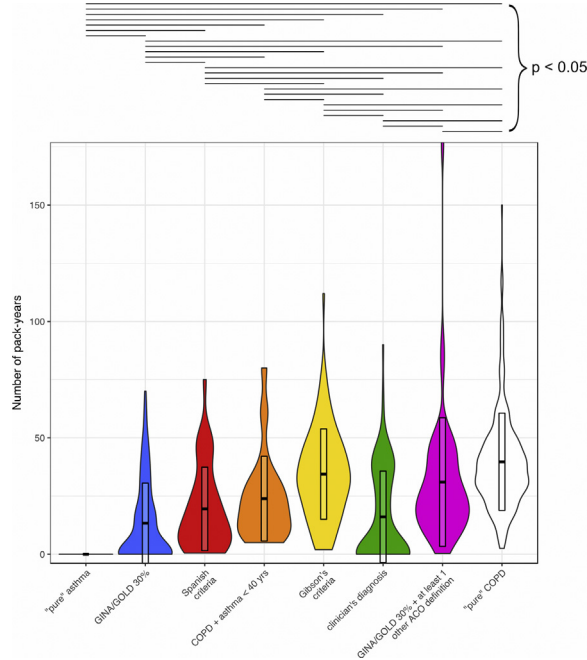


FIGURE E11. Differences in the number of pack years smoked among definition-based ACO subpopulations, patients with “pure” asthma, and patients with “pure” COPD.

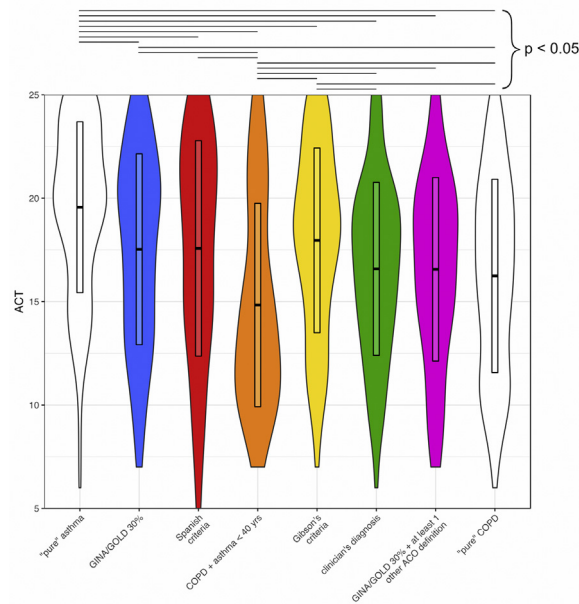


FIGURE E10. Differences in Asthma Control Test (ACT) score among definition-based ACO subpopulations, patients with “pure” asthma, and patients with “pure” COPD.

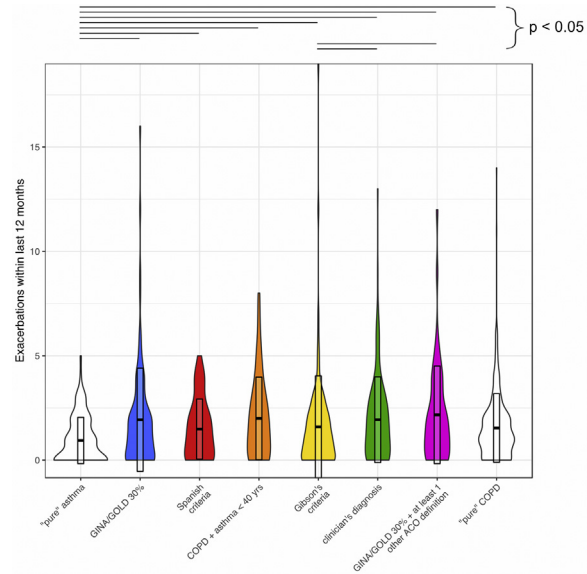


FIGURE E12. Differences in the number of exacerbations within the last 12 months preceding enrollment to the study among definition-based ACO subpopulations, patients with “pure” asthma, and patients with “pure” COPD.

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