Global Lung Initiative as Diagnostic Criteria in Asthma-COPD Overlap Syndrome: Prevalence and Disease Characterization in a Real-Life Asthma Cohort

Betancor D[1,*], Otal M[1,*], Olaguibel JM[2,3], Rodrigo-Muñoz JM[3,4], Alvarez Puebla MJ[2,3], Arismendi E[3,5], Barranco P[3,6], Barroso B[1,3], Bobolea I[3,5], Cárdaba B[3,4], Cruz MJ[3,7], Curto E[8], Del Pozo V[3,4], Domínguez-Ortega J[3,6], González-Barcala FJ[9], Luna-Porta JA[3,6], Martínez-Rivera C[3,10], Mullol J[3,11], Muñoz X[3,12], Picado C[5], Plaza V[8], Quirce S[3,6], Rial MJ[3,13], Roibás-Veiga I[14], Soto-Retes L[9], Valero A[3,5], Valverde-Monge M[1,3], Sastre J[1,3]

[1]Servicio de Alergología, Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain

[2]Servicio de Alergología, Hospital Universitario de Navarra, Pamplona, Spain

[3]CIBER de Enfermedades Respiratorias (CIBERES), Madrid, Spain

[4]Servicio de Inmunología, Instituto de Investigación Sanitaria del Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain

[5]Pulmonology and Allergy Department, Hospital Clínic Universitat de Barcelona, Spain

[6]Servicio de Alergia, Hospital Universitario La Paz, Madrid, Spain

[7]Departamento de Biología Celular, Fisiología e Inmunología, Universitat Autónoma de Barcelona, Barcelona, Spain

[8]Servicio de Neumología y Alergia, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

[9]Department of Respiratory Medicine, University Hospital of Santiago de Compostela, Santiago de Compostela, Spain.

[10]Servicio de Neumología, Hospital Germans Trias i Pujol, Badalona, Spain

[11]Rhinology Unit & Smell Clinic, ENT Department Universitat de Barcelona, Barcelona, Spain

[12]Servicio de Neumología, Hospital Vall d'Hebron, Barcelona, Spain

[13]Servicio de Alergología, Complexo Hospitalario Universitario A Coruña, A Coruña, Spain

[14]Servicio de Alergia, Hospital Clínico Universitario de Santiago de Compostela, Santiago de Compostela, Spain

**Both authors contributed equally.*

J Investig Allergol Clin Immunol 2024; Vol. 34(3): 192-195
doi: 10.18176/jiaci.0966

Key words: Asthma-COPD overlap syndrome. Asthma severity. Exacerbations. Medication use.

Palabras clave: Síndrome de solapamiento asma-EPOC. Gravedad del asma. Exacerbaciones. Uso de medicación.

Asthma and chronic obstructive pulmonary disease (COPD) are both prevalent obstructive disorders of the airways that present with different phenotypes and endotypes [1]. They share many features, including demographic and clinical characteristics, treatments, and diagnostic tests. Asthma/COPD

overlap (ACO) syndrome has features of both diseases and is characterized by a greater disease burden, with increased medication use [2,3], symptoms [4], risk of exacerbation [4,5], direct/indirect costs [2], emergency department (ED) visits [6,7], hospitalization rates [7], deterioration in quality of life [8], and mortality [5,9]. The biomarkers and underlying mechanisms of ACO remain to be discovered, and there has yet to be a uniform consensus on the definition of this entity [10]. An accurate diagnosis of ACO is needed to guide clinical treatment and evaluate prognosis.

Table. Demographic, Clinical, Functional, and Inflammatory Characteristics of the Study Population

	ACO	No ACO	*P* Value
No. of patients (%)	32 (14.7)	186 (85.3)	
Clinical characteristics	32 (14.7)	186 (85.3)	
Treatment, No. (%)			
ICS/LABA	26 (81.25)	141 (75.81)	NS
Long-term OCS	5 (15.63)	8 (4.30)	.02
Biologics	4 (12.50)	36 (19.35)	NS
Asthma severity, No. (%)			
Intermittent	0 (0)	13 (6.99)	.02
Mild-persistent	4 (12.50)	35 (18.82)	NS
Moderate-persistent	11 (34.38)	69 (37.10)	NS
Severe-persistent	17 (53.13)	63 (33.87)	.04
Pulmonary function tests and biomarkers			
Mean (SD) total IgE, IU/mL	636.6 (1039)	294.1 (395.1)	NS
Mean (SD) peripheral eosinophilia, cells/µL	338.5 (292.3)	333.4 (225.2)	NS
Mean (SD) FeNO, ppb	50.04 (35.89)	41.82 (40.15)	NS
Mean (SD) methacholine challenge, PC_{20}	2.84 (4.39)	3.33 (6.08)	NS
Sputum analysis			
Mean (SD) sputum eosinophilia	14.75 (24.30)	10.99 (18.46)	NS
Patients with sputum eosinophils >3%, No. (%)	2 (50.0%)	32 (52.46%)	NS
Mean (SD) plethysmography			
TLC, L	6.04 (2.19)	5.66 (1.62)	NS
RV, L	2.85 (1.50)	2.2 (0.95)	.02
Mean (SD) plethysmography with GLI			
TLC, z-score	1.52 (5.12)	–0.02 (1.46)	.01
RV, z-score	1.53 (1.81)	0.57 (1.11)	.004
TLC, LLN	4.14 (1.07)	4.43 (0.84)	NS
RV, LLN	0.91 (0.21)	0.85 (0.18)	.02

Abbreviations: ACO, asthma-COPD overlap syndrome; FeNO, fractional exhaled nitric oxide; GLI, Global Lung Initiative; ICS, inhaled corticosteroid; IgE, immunoglobulin E; LABA, long-acting; β2-receptor agonist; LLN, lower limit of normal; NS, nonsignificant; OCS, oral corticosteroids; PC_{20}, provocative concentration of methacholine causing a 20% fall in FEV_1; RV, residual volume; TLC, total lung capacity.

This study aimed to evaluate agreement on the diagnosis of ACO between the GesEPOC-GEMA consensus [11] and our criteria, which took into account the Global Lung Initiative (GLI) reference z-scores [12]. As secondary objectives, we applied our criteria to analyze the prevalence of ACO syndrome and demographic, clinical, and inflammatory characteristics in a large real-life cohort of asthma patients.

This cross-sectional observational study reviewed the electronic database of the MEGA cohort, a real-life cohort of patients with asthma of various severities [13]. ACO syndrome was diagnosed based on spirometry-confirmed obstruction according to a GLI reference FEV_1/FVC z-score of <–1.64 [12] and the GesEPOC-GEMA consensus [11]. Patients also had to be aged >35 years with a postbronchodilator FEV_1/FVC <0.7, and a former or current smoker (≥10 packs/year). The methods are summarized in the supplementary material.

The MEGA cohort electronic database contains 512 patients. The study sample comprised 218 patients (42.6%) with complete demographic and spirometry data. Of the 218 patients, 41 (18.8%) were diagnosed with ACO according to the GEMA-GesEPOC consensus [11], and 32 (14.7%) met the diagnostic criteria for ACO when the GLI criteria were added. The percentage of agreement between both diagnostic criteria was 78%.

Patients with ACO had significantly more exacerbations (3.2 vs 2.6), poorer disease control (90.62% vs 73.1% had an ACT score ≤19), and a greater need for treatment with oral corticosteroids than asthma patients (15.6% vs 4.3%, all P<.05). However, these exacerbations were not more severe and did not require more ED visits or intensive care unit admissions. According to the GINA guidelines, the percentage of patients with severe asthma was significantly higher in the ACO group (53.1% vs 33.9%, P<.05). Regarding the pulmonary function tests, the methacholine challenge showed no significant differences. As for plethysmography, both total lung capacity (1.5 vs 0.02) and residual volume (1.5 vs 0.6) were higher in the ACO group (P<.05). No statistically significant differences were observed for inflammatory profile (IgE, fractional exhaled nitric oxide [FeNO], peripheral and sputum eosinophilia). This information is summarized in the Table, S1, and S2.

The prevalence of ACO varies widely between studies owing to differences in diagnostic criteria, population characteristics, methods, and study designs [4]. The overall prevalence of ACO in the general population ranges from 0.96% to 4.5% [6,11]. The prevalence of ACO among patients with asthma and patients with COPD also varied widely, from 13.3% to 45.8% and from 5% to 55.1%, respectively [2,4,8]. Based on the GEMA-GesEPOC diagnostic criteria [11], prevalence also varies in asthma patients, ranging from 17.2% in our results to the 34.2% reported by Soler-Cataluña et al [4], as well as in COPD patients, where it has been reported to range from 15% to 45.5% [4,11].

Heterogeneity in the pathogenesis of ACO and changes in phenotype [14] have been demonstrated and proposed as confounding factors.

The inflammatory profile of ACO patients has not been well described. Peripheral blood eosinophilia has been related to more frequent symptoms [15] and a higher risk of exacerbation [4]. Plaza et al [11] and Cosio et al [14] proposed peripheral blood eosinophilia as a minor diagnostic criterion for ACO, although neither our study nor other articles [6,10,15] found an association between peripheral blood eosinophilia level and the presence of ACO or its severity. Moreover, it has been demonstrated that sputum eosinophilia and FeNO values are similar in ACO and asthma patients [6,16], consistent with our results but disagreeing with others [9]. High disease heterogeneity was proposed based on these varying findings.

ACO is associated with a high disease burden and poor outcomes. It is also characterized by more frequent exacerbations, uncontrolled and severe disease, and greater medication consumption [2,6,7] than asthma and COPD, consistent with our results but not with those reported elsewhere [10]. However, in contrast with other studies [6,7], we did not find increased ED visits or hospitalizations. Higher OCS consumption was related to ACO by Caillaud et al [3] and in the present study.

Smoking was an inclusion criterion in our study that is not considered elsewhere. Kauppi et al [8] and Caillaud et al [3] demonstrated that smoking was significantly less frequent in ACO than in asthma and COPD, respectively, in contrast with other authors [6], thus supporting the theory that different underlying pathogenic mechanisms could induce ACO. In our study, air trapping was more frequent in ACO patients, as demonstrated by plethysmography but not by spirometry. Air trapping has been related to asthma, above all severe asthma, although in particular to COPD, owing to the decreased airway caliber and loss of parenchymal elastic recoil in this disease [18]. A similar air trapping rate was demonstrated in ACO patients and COPD patients [3,5] but not in asthma patients [19], as also demonstrated in our results. This finding highlights the importance of performing plethysmography in addition to spirometry in ACO patients. Furthermore, using a z-score to define obstruction, we increased diagnostic specificity. Based on the standard GEMA-GesEPOC consensus, 22% more patients would be diagnosed with ACO. Overestimation of ACO could be adjusted using individual scales such as the GLI [12].

The limitations of our study are described in the supplementary material.

In conclusion, the various disease patterns suggest wide variety in pathogenesis. There are no specific demographic characteristics or inflammatory biomarkers defining ACO. Plethysmography is needed to evaluate air trapping in affected patients. Disease management and treatment should be improved to avoid the poor control and prognosis typical of the disease.

Funding

The authors declare that no funding was received for the present study.

Conflicts of Interest

Dr. Betancor was supported by a Rio Hortega Research Contract from Instituto Carlos III, Ministry of Science. Dr. Valverde has received fees for lectures from GSK and is a member of the advisory board for Organon. Dr. Rial reports personal fees from GSK, Allergy Therapeutics, and AstraZeneca outside the submitted work. Dr. González Barcala reports personal fees from ALK, AstraZeneca, Bial, Boehringer Ingelheim, Chiesi, Gebro Pharma, GlaxoSmithKline, Laboratorios Esteve, Menarini, Mundipharma, Novartis, Rovi, Roxall, Stallergenes-Greer, and Teva, as well as grants from Mundipharma outside the submitted work. Dr. Quirce reports personal fees from AstraZeneca, Novartis, Sanofi, Boehringer Ingelheim, Teva, ALK, Mundipharma, GSK, Chiesi, and Leti, outside the submitted work. Dr. Soto-Retes reports the following: nonfinancial support from CIBER de Enfermedades Respiratorias (CIBERES) during the conduct of the study; personal fees from Stallergenes-Greer, Menarini, and Novartis; personal fees from GSK, Hal Allergy, Allergy Therapeutics, and AstraZeneca; grants from Sociedad Española de Alergología e Inmunología Clínica (SEAIC), and Sociedad Española de Neumología y Cirugía Torácica (SEPAR), outside the submitted work. Dr. Martinez Rivera reports grants and personal fees from AstraZeneca, Teva, GSK, Novartis, and Mundipharma, outside the submitted work. Dr. Munoz reports personal fees from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Teva, Mundifarma, Chiesi, and Faes Farma, outside the submitted work. Dr. Sastre reports grants and personal fees from Sanofi, GSK, Novartis, AstraZeneca, Mundipharma, and Faes Farma, outside the submitted work. Dr. Olaguibel reports grants from Sanofi and/or personal fees from AstraZeneca and Mundipharma, outside the submitted work. Dr. Plaza reports grants and personal fees from AstraZeneca, Boehringer Ingelheim, Merck, Chiesi, Novartis, Menarini, and Sanofi, outside the submitted work. Dr. Mullol reports personal fees and other remuneration from Sanofi-Genzyme and Regeneron, Novartis, Viatris (Mylan pharma), Uriach Group, Mitsubishi-Tanabe, Menarini, UCB, AstraZeneca, GSK, and MSD, outside the submitted work. Dr. Del Pozo reports personal fees and other remuneration from Sanofi, AstraZeneca, and GSK, outside the submitted work. The remaining authors declare that they have no conflicts of interest.

References

1. Masoli M, Fabian D, Holt S, Beasley R; Global Initiative for Asthma (GINA) Program. The global burden of asthma: executive summary of the GINA Dissemination Committee report. Allergy. 2004;59(5):469-78.
2. Shaya FT, Dongyi D, Akazawa MO, Blanchette CM, Wang J, Mapel DW, et al. Burden of concomitant asthma and COPD in a Medicaid population. Chest. 2008;134(1):14-9.
3. Caillaud D, Chanez P, Escamilla R, Burgel PR, Court-Fortune I, Nesme-Meyer P, et al. Initiatives BPCO scientific committee and investigators. Asthma-COPD overlap syndrome (ACOS) vs 'pure' COPD a distinct phenotype. Allergy. 2017;72(1):137-45.
4. Soler-Cataluña JJ, Novella L, Soler C, Nieto ML, Esteban V, Sánchez-Toril F, et al. Clinical Characteristics and Risk of Exacerbations Associated With Different Diagnostic Criteria

of Asthma-COPD Overlap. Arch Bronconeumol (Engl Ed). 2020;56(5):282-90.
5. Hardin M, Silverman EK, Barr RG, Hansel NN, Schroeder JD, Make BJ, et al; COPDGene Investigators. The clinical features of the overlap between COPD and asthma. Respir Res. 2011;12(1):127.
6. Mendy A, Forno E, Niyonsenga T, Carnahan R, Gasana J. Prevalence and features of asthma-COPD overlap in the United States 2007-2012. Clin Respir J. 2018;12(8):2369-77.
7. Menezes AMB, Montes de Oca M, Pérez-Padilla R, Nadeau G, Wehrmeister FC, Lopez-Varela MV, et al; PLATINO Team. Increased risk of exacerbation and hospitalization in subjects with an overlap phenotype: COPD-asthma. Chest. 2014;145(2):297-304.
8. Kauppi P, Kupiainen H, Lindqvist A, Tammilehto L, Kilpeläinen M, Kinnula VL, et al. Overlap syndrome of asthma and COPD predicts low quality of life. J Asthma. 2011;48(3):279-85.
9. Huang S, Vasquez MM, Halonen M, Martinez FD, Guerra S. Asthma, airflow limitation and mortality risk in the general population. Eur Respir J. 2015;45(2):338-46.
10. Pérez de Llano L, Cosío BG, Miravitlles M, Plaza V; CHACOS study group. Accuracy of a New Algorithm to Identify Asthma-COPD Overlap (ACO) Patients in a Cohort of Patients with Chronic Obstructive Airway Disease. Arch Bronconeumol (Engl Ed). 2018;54(4):198-204.
11. Plaza V, Álvarez F, Calle M, Casanova C, Cosío BG, López-Viña A, et al. Consensus on the Asthma-COPD Overlap Syndrome (ACOS) Between the Spanish COPD Guidelines (GesEPOC) and the Spanish Guidelines on the Management of Asthma (GEMA). Arch Bronconeumol. 2017;53(8):443-9.
12. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al; ERS Global Lung Function Initiative. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J. 2012;40(6):1324-43.
13. Rial MJ, Álvarez-Puebla MJ, Arismendi E, Caballero ML, Cañas JA, Cruz MJ, et al. Clinical and inflammatory characteristics of patients with asthma in the Spanish MEGA project cohort. Clin Transl Allergy. 2021;11(1):e12001.
14. Cosio BG, Soriano JB, López-Campos JL, Calle-Rubio M, Soler-Cataluna JJ, de-Torres JP, et al; CHAIN Study. Defining the Asthma-COPD Overlap Syndrome in a COPDCohort. Chest. 2016;149(1):45-52.
15. Ma H, Yang L, Liu L, Zhou Y, Guo X, Wu S, et al. Using inflammatory index to distinguish asthma, asthma-COPD overlap and COPD: A retrospective observational study. Front Med (Lausanne). 2022;17;9:1045503.

Manuscript accepted for publication October 17, 2023; accepted for publication November 2, 2023.

Diana Betancor
Allergy Department
Hospital Universitario Fundación Jiménez Díaz
Av Reyes Católicos, 2
28040 Madrid, Spain
E-mail: diana13_b@hotmail.com