# Global Lung Initiative as diagnostic criteria in Asthma-COPD overlap syndrome. Prevalence and characterization of the syndrome in a real-life asthma cohort

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Asthma and chronic obstructive pulmonary disease (COPD) are two prevalent obstructive disorders of the airways that could be presented with different phenotypes and endotypes [1]. They share many common features, including demographic and clinical characteristics, treatments, and diagnostic tests. Asthma/COPD overlap (ACO) syndrome has features of both diseases. However, it implies an increased burden with increased medication use [2,3], symptoms [4], risk of exacerbation [4,5], direct/indirect costs [2], emergency room (ER) visits [6,7], hospitalization rates [7], deterioration in quality of life [8] and mortality [5,9]. The biomarkers and underlying mechanisms of ACO still need to be discovered. There has yet to be a uniform consensus on the definition of this entity [10]. An accurate ACO diagnosis is needed to guide clinical treatment and evaluate prognosis.

This study aimed to evaluate the agreement in ACO diagnosis between GesEPOC-GEMA consensus [11] with our criteria that also considered the Global Lung Initiative (GLI) reference values z-score [12]. As secondary objectives, we analyze the prevalence of ACO syndrome and the patient's demographic, clinical and inflammatory characteristics in a large real-life cohort of asthmatic patients with our criteria.

This cross-sectional observational study reviewed the MEGA cohort electronic database, a real-life cohort of asthmatic patients with various severities [13]. In our study, ACO syndrome was diagnosed based on spirometric obstruction according to GLI, FEV1/FVC z-score<-1.64 [12] and GesEPOC-GEMA consensus [11]: >35 years old, FEV1/FVC postBD<0.7 and ex-smoking or current smoking habit (≥10 packs/year). Methods are summarized in supplementary material.

The MEGA cohort electronic database contains 512 patients. A total of 218 (42.6%) were analyzed because they had complete demographic information and spirometry done. Of the 218 patients, 41 (18.8%) were diagnosed with ACO according to GEMA-



 
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GesEPOC consensus [11], and 32 (14.7%) met the diagnostic criteria for ACO, adding GLI criteria. The agreement percentage between both diagnosis criteria was 78%.

Patients with ACO had significantly more exacerbations (3.2 vs 2.6), worse control (90.62% vs 73.1% had an ACT scale ≤19) and a higher need for oral corticosteroid treatment (OCS) (15.6% vs. 4.3%), (all $p<0.05$) than asthmatic patients. However, these exacerbations were not more severe and did not require more ER 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%, $p<0.05$). Regarding the respiratory function tests, the methacholine challenge showed no significant differences. As for plethysmography, both total lung capacity (TLC) (1.5 vs.0.02) and residual volume (RV) (1.5 vs. 0.6) were higher in the ACO group ($p<0.05$). The inflammatory profile (IgE, FeNO, peripheral and sputum eosinophilia) showed no statistically significant differences. This information is summarized in Table I, S1 and S2.

The prevalence of ACO is highly variable between the studies due to the different diagnosis criteria, population characteristics, methods, and study designs [4]. The overall prevalence of ACO in the general population is around 0.96%-4.5% [6,11]. The prevalence of ACO among patients with asthma and COPD also varied widely from 13.3 to 45.8% and from 5 to 55.1%, respectively [2,4,8]. Using GEMA-GesEPOC diagnostic criteria [11], the prevalence is also variable in asthmatic patients, ranging from 17.2% in our results to the 34.2% obtained by Soler-Cataluña et al.[4], as well as in COPD patients, ranging from 15-45.5% [4,11].

Heterogeneity in ACO pathogenesis and phenotype change [14] has been demonstrated and has also been proposed as a co-founding factor.

The inflammatory profile of ACO patients has not been well described. PBE has been related to more symptoms [15] and a higher exacerbation risk [4]. Plaza et al.[11] and Cosio et al.[14] proposed PBE as one minor ACO diagnostic criteria. However, neither our study nor other articles [6,10,15] have found an association between PBE 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], which agrees with our results but disagrees with others[9]. High heterogeneity of the disease was proposed based on these differing findings.





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ACO is associated with a high disease burden and worse outcomes. Higher exacerbations, uncontrolled and severe disease, and greater medication consumption [2,6,7] compared with asthma and COPD, which aligns with our results but not with others [10]. However, we did not find increased ER visits or hospitalizations, which disagrees with other studies [6,7]. Higher OCS consumption has been related to ACO in Caillaud et al. [3] and our results.

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

Our study has some limitations described in supplementary material.

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

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**Table:** Demographic, clinical, functional, and inflammatory characteristics of studied population.

| | ACO | NO ACO | P value |
|---|---|---|---|
| **No. of subjects (%)** | 32 (14.7) | 186 (85.3) | |
| **Clinical characteristics** | | | |
| **Treatment, N (%)** | | | |
| ICS/LABA | 26 (81.25) | 141 (75.81) | NS |
| Long-term OCS | 5 (15.63) | 8 (4.30) | **0.02** |
| Biologicals | 4 (12.50) | 36 (19.35) | NS |
| **Asthma severity, N (%)** | | | |
| Intermittent | 0 (0) | 13 (6.99) | **0.02** |
| 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) | **0.04** |
| **Respiratory function tests and biomarkers** | | | |
| Total IgE, IU/mL, mean (SD) | 636.6 (1039) | 294.1 (395.1) | NS |
| Peripheral eosinophilia, cells/µL, mean (SD) | 338.5 (292.3) | 333.4 (225.2) | NS |
| FeNO, ppb, mean (SD) | 50.04 (35.89) | 41.82 (40.15) | NS |
| Methacholine challenge, PC20mean (SD) | 2.84 (4.39) | 3.33 (6.08) | NS |
| **Sputum analysis** | | | |
| Sputum eosinophilia, mean (SD) | 14.75 (24.30) | 10.99 (18.46) | NS |
| Patients with sputum eosinophils>3%, N (%) | 2 (50.0%) | 32 (52.46%) | NS |
| **Plethysmography, mean (SD)** | | | |
| TLC (L) | 6.04 (2.19) | 5.66 (1.62) | NS |
| RV (L) | 2.85 (1.50) | 2.2 (0.95) | **0.02** |
| **Plethysmography with GLI, mean (SD)** | | | |
| TLC (z-score) | 1.52 (5.12) | -0.02 (1.46) | **0.01** |
| RV (z-score) | 1.53 (1.81) | 0.57 (1.11) | **0.004** |
| TLC (LLN) | 4.14 (1.07) | 4.43 (0.84) | NS |
| RV (LLN) | 0.91 (0.21) | 0.85 (0.18) | **0.02** |

FeNO=fractional exhaled nitric oxide; IgE=immunoglobulin E; LABA=long- acting β2-receptor agonists; LLN=lower limit of normality; N=sample size; NS=non-significant; OCS=oral corticosteroids; $PC_{20}$=provocative concentration of methacholine causing a 20% fall in $FEV_1$; RV=residual volume; SD=standard deviation; TLC=total lung capacity.