



Asthma, COPD, and overlap in a national cohort: ACO on a gradient

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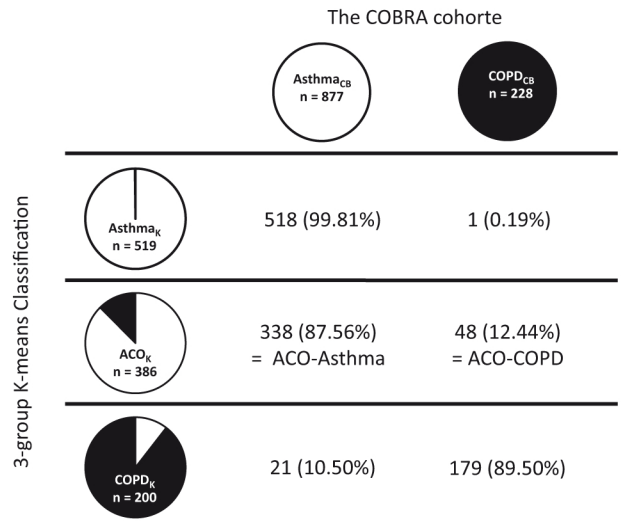


FIG 1. Patients originally diagnosed with asthma/COPD in the French national observational cohort of patients with asthma and COPD, termed “COBRA,” were reclassified via K-means clustering into (1) a new Asthma_K group, (2) an Asthma-COPD-Overlap group (ACO_K), and (3) a new COPD group (COPD_K). Designated by “CB,” the COBRA cohort prospectively enrolls patients with asthma and COPD from 15+ expert centers in France. Initial diagnoses were made by participating physicians. Asthma and COPD were defined according to GINA (symptom history and 200 mL/12% reversibility) and GOLD criteria, respectively. The presented ACO classification is solely the result of the clustering algorithm. The number (%) of COBRA patients falling into each K-means group are provided. The ACO_K group is further subdivided into “ACO-Asthma” and “ACO-COPD” groups. *GINA*, Global Initiative for Asthma; *GOLD*, Global Initiative for Chronic Obstructive Lung Disease.

heterogeneous, overlapping states. In older patients (typically older than 40 years), distinguishing between them becomes difficult because patients can increasingly share characteristics of either disease, resulting in “asthma-COPD overlap” (ACO).¹

Diagnosing ACO has been justified by reports of poorer outcomes for “intermediate” patients when compared with those who have clear diagnoses of asthma or COPD alone.^{1,2} Treatment options and responses may also differ, notably by the fact that patients with ACO have been found to better respond to inhaled corticosteroids as compared with patients with COPD.^{3,4} However, certain authors have expressed concern when blurring the lines between asthma and COPD, citing the potential for overmedication as a concern,⁵⁻⁷ as well as the lack of studies supporting specific treatments for intermediate groups.^{5,8} Nevertheless, the ability to easily identify an expected “poor-outcome” group via overlapping asthma and COPD clinical characteristics would be of great utility for clinicians.⁸ In addition, an important part of nosology is identifying diseases with similar outcomes: testing whether or not the requalification of patients with asthma and COPD into an ACO group more accurately identifies subgroups in terms of prognosis may represent one argument justifying this refined classification.

Given this context, we sought to verify the presence of disease severity in association with ACO using the French national Bronchial Obstruction and Asthma Cohort

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Asthma, COPD, and overlap in a national cohort: ACO on a gradient

To the Editor:

Asthma and chronic obstructive pulmonary disease (COPD) are characterized as distinct entities, though the clinical reality encountered by physicians includes a complex mixture of

TABLE I. Outcomes (at the end of follow-up) for the Asthma_K, ACO_K (divided into ACO-Asthma and ACO-COPD groups according to initial diagnosis), and COPD_K groups

Variable	Asthma _K (n = 519)	ACO _K (N = 386)		COPD _K (n = 200)	P value				
		ACO-asthma (n = 338)	ACO-COPD (n = 48)		Asthma _K vs COPD _K	ACO _K vs asthma _K	ACO _K vs COPD _K	ACO- asthma vs asthma _K	ACO- COPD vs COPD _K
FEV ₁ pre-β2 (L)	2.40 (1.63 to 3.06)	2.02 (1.54 to 2.59)		1.48 (0.95 to 2.09)	<.001	<.001	<.001	<.001	<.001
		2.06 (1.54 to 2.59)	1.98 (1.49 to 2.61)						
FEV ₁ pre-β2 (% predicted)	80 (64 to 94)	80 (64 to 97)		58 (38 to 77)	<.001	.660	<.001	.427	<.001
		81 (65 to 97)	71 (58 to 97)						
FVC pre-β2 (L)	3.36 (2.55 to 4.15)	2.93 (2.44 to 3.63)		2.89 (2.31 to 3.51)	<.001	<.001	.246	<.001	.179
		2.91 (2.41 to 3.62)	3.08 (2.52 to 3.77)						
FVC pre-β2 (% predicted)	96 (83 to 108)	95 (82 to 109)		84 (70 to 103)	<.001	.962	<.001	.570	.371
		96 (82 to 110)	90 (82 to 101)						
FEV ₁ /FVC (% predicted)	69 (60 to 78)	69 (59 to 79)		53 (40 to 62)	<.001	.549	<.001	.966	<.001
		69 (59 to 79)	64 (54 to 76)						
FEV ₁ post-β2 (L)	2.53 (1.77 to 3.22)	2.16 (1.67 to 2.69)		1.56 (1.01 to 2.20)	<.001	<.001	<.001	<.001	.002
		2.16 (1.69 to 2.69)	2.08 (1.61 to 2.61)						
FEV ₁ post-β2 (% predicted)	85 (68 to 98)	85 (67 to 100)		61 (40 to 80)	<.001	.500	<.001	.249	<.001
		86 (67 to 100)	74 (62 to 98)						
% Reversibility: $100 \times \frac{\text{FEV}_{1 \text{ post-}\beta 2(L)} - \text{FEV}_{1 \text{ pre-}\beta 2(L)}}{\text{FEV}_{1 \text{ pre-}\beta 2(L)}}$	6.74 (2.66 to 13.90)	6.67 (2.14 to 14.77)		4.65 (0.00 to 12.18)	.003	.959	.006	.522	.519
		7.00 (3.09 to 15.95)	5.40 (−0.31 to 7.21)						
Annualized change in FEV ₁ (% variation)	0.62 (−6.30 to 8.60)	1.70 (−6.40 to 9.86)		−1.16 (−3.86 to 1.48)	.203	.582	.067	.644	.174
		1.89 (−6.50 to 9.86)	1.51 (−2.29 to 40.79)						
No. of exacerbations during the last 12 mo of follow-up									
0	272 (54.73)	198 (55.00)		101 (53.16)	.263	.622	.414	.921	.388
		169 (53.82)	29 (63.04)						
1	100 (20.12)	69 (19.17)		45 (23.68)					
		62 (19.75)	7 (15.22)						
2	125 (25.15)	93 (25.83)		44 (23.16)					
		83 (26.43)	10 (21.74)						
No. of hospitalizations during the last 12 mo of follow-up	0 (0 to 1)	0 (0 to 0)		0 (0 to 0)	.010	.117	.147	.042	.418
		0 (0 to 0)	0 (0 to 0)						
Emergency department admission during the last 12 mo of follow-up	125 (25.77)	69 (19.88)		21 (11.23)	<.001	.282	.004	.212	.367
		66 (21.85)	3 (6.67)						
Intensive care unit admission during the last 12 mo of follow-up	25 (5.17)	8 (2.46)		6 (10.53)	.374	.019	1.00	.088	.171
		8 (2.66)	0 (0)						

Descriptive statistics are presented as medians (interquartile range) for quantitative variables and as numbers (percentage) for qualitative variables. *P* values indicate Mann-Whitney, χ^2 , or Fisher exact test results for the indicated comparisons. *FVC*, Forced vital capacity.

(“COBRA”), which is composed of prospective data (including satisfactory follow-up >2 years) for 877 patients with asthma (the Asthma_{CB} group) and 228 patients with COPD (the COPD_{CB} group; see Fig 1). COBRA was approved by the local Ethics Committee (*Comité de Protection des Personnes d’Ile de France*; reference no. 0811738) and written informed consent was gathered for all participants at inclusion. K-means clustering for 3 *a priori* groups on clinical characteristics (age at symptom onset, atopy, coughing, smoking, spirometry, family history of asthma, shortness of breath at rest) reclassified the Asthma_{CB} and COPD_{CB} group patients into 3 new groups (the “K” groups in Fig 1). The intermediate group, that is, the ACO_K group, was further subdivided into ACO-Asthma and ACO-COPD groups according to the patient’s original diagnosis (as demonstrated in Fig 1). Of note, K-means clustering well identified groups, underlining the validity of current classifications. Those patients who were reclassified were mainly originally from the Asthma_K group. Baseline parameters (age, skin prick tests, smoking parameters, hospitalizations before inclusion, airflow parameters, % reversibility, and baseline medications) were well in line with a disease gradient starting with the Asthma_K group, intermediate values for the ACO_K group, and ending with the COPD_K group.

As concerns outcomes at the end of follow-up (ranging from a median [interquartile range] of 1.90 [0.45-3.54] years for COPD_K group patients to 2.07 [0.48-3.99] years for Asthma_K group patients), most outcome variables (as presented in Table 1) were associated with significant group differences that were in line with the same gradient starting at the Asthma_K group going toward the COPD_K group, with ACO groups demonstrating intermediate values. These “gradient variables” included all measured airflow parameters (all FEV₁, forced vital capacity, FEV₁/forced vital capacity, and % reversibility variables) as well as the number of hospitalizations and emergency department admission frequencies during the last 12 months of follow-up. No significant differences (or trends) between groups that would support increased outcome severity in association with ACO groups were observed. There was a tendency for the ACO_K group to have higher annualized change in FEV₁ (% variation) values as compared with the COPD_K group. Intensive care unit admissions during the last 12 months of follow-up occurred among a significantly smaller percentage of ACO_K group patients as compared with COPD_K group patients. A similar tendency was found for ACO-Asthma group patients versus Asthma_K group patients. None of the ACO-Asthma versus Asthma_K or ACO-COPD versus COPD_K comparisons, which minimize potential confounding due to initial diagnostic group, provided evidence of particularly severe disease in association with ACO. At a glance, reclassifying asthma as ACO was not detrimental in terms of prognosis, whereas changing COPD to ACO more often identified a subgroup with better outcomes.

Like all cohort studies, the present work is limited by its observational nature and will need to be reproduced by other teams for confirmation. Nevertheless, the large size and broad population covered provide a new and valuable insight into the ACO debate. As stated in the Global Initiative for Asthma/

Global Initiative for Chronic Obstructive Lung Disease guidelines, ACO does not represent a single disease.¹ The intermediate position of patients with ACO on an asthma-to-COPD gradient supports and helps explain this plurality. Previous observations implying particularly severe disease in patients with ACO might be relevant only relative to patients with asthma, who are on the “less severe” side of the gradient. It also implies that the development of a treatment algorithm for patients with ACO is going to involve more than simply screening on clinical characteristics.

In conclusion, clustering patients according to the simultaneous presence of clinical signs for both asthma and COPD resulted in an “overlap” group whose outcomes and disease severity were generally intermediate on an asthma-to-COPD gradient, with poorer lung function and outcomes on the COPD side of the gradient. Overlap was not associated with particularly severe outcomes beyond this gradient, at least not in the relatively highly medicated, secondary-care COBRA cohort. We propose that although sharing overlap signs may not be sufficient to induce severe disease, perhaps the inverse is truer. It may be that patients with particularly severe obstructive lung disease are more likely to have complex phenotypes. In any case, using clinical characteristics to screen for patients with ACO may not have any utility in certain populations. Given the multifaceted nature of the spectrum, further effort should be focused on detailed patient profiling and personalized medicine.

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