SUPPLEMENTARY MATERIAL

Methods:

Asthma was diagnosed based on the GEMA guidelines and included a postBD FEV1>12% and 200ml on spirometry and/or methacholine PC20<16 mg/ml. Study data included demographic and clinical characteristics, asthma treatment, asthma severity (following GINA guidelines) [1] and control (assessed using the Asthma Control Test (ACT)) and the number and severity of exacerbations. Lung function tests (spirometry, methacholine, and plethysmography), sputum analysis, peripheral blood eosinophilia (PBE) and fractional exhaled nitric oxide (FeNO) were also collected. A full description of the MEGA cohort has been published previously [13]. The ethics committees of each participating hospital approved this study. All subjects provided signed informed consent.

Quantitative variables were described as mean and standard deviation, and qualitative variables by absolute and relative frequencies. Inter-group comparisons were performed using the chi-square test or Fisher's exact test for qualitative variables and the ANOVA or Kruskal-Wallis test for quantitative variables. The agreement percentage was used to calculate the agreement between both diagnosis criteria. Statistical analysis was carried out using GraphPadInstat6 (GraphPadSoftware Inc, San Diego, CA). P-values <0.05 were considered significant.

Limitations:

A large proportion of patients from the MEGA cohort, 57.4%, have not undergone post-bronchodilation spirometry, or there is no clinical data about them. As a result, they were excluded from the study. As the methacholine challenge was an inclusion criterion, postBD spirometry was not performed in all patients. Moreover, adequate sputum was obtained from a small sample of patients, just 12.5% from the ACO group and 32.8% from non-ACO. Therefore, the sputum inflammatory profile results could not represent all the studied patients.

References:

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Table S1. Demographic and clinical characteristics of studied patients.

	ACO	NO ACO	P value
No. of subjects (%)	32 (14.7)	186 (85.3)	
Demographic characteristics			
Individual characteristics			
Female sex, N (%)	22 (68.75)	130 (69.89)	NS
Age, years, mean (SD)	53.19 (8.935)	45.37 (12.01)	**0.0005**
Caucasian ethnicity, N (%)	32 (14.68)	176 (94.62)	NS
Body mass index (BMI), mean (SD)	28.25 (5.590)	27.66 (5.824)	NS
Obesity, N (%)	11 (34.38)	48 (25.81)	NS
Residency, urban area, N (%)	19 (59.38)	144 (77.42)	**0.04**
Comorbidities, N (%)			
Atopy	27 (84.38)	136 (73.12)	NS
Allergic rhinitis	17 (53.13)	96 (51.61)	NS
Bronchiectasis	5 (15.63)	16 (8.60)	NS
CRSwNP	14 (43.75)	53 (28.49)	NS (0.09)
CRSsNP	3 (9.38)	13 (6.99)	NS
Obstructive sleep apnoea syndrome (OSAS)	3 (9.38)	11 (5.91)	NS
Smoking habit, N (%)			
Never smoker	0 (0.0)	124 (66.67)	**<0.0001**
Current smoker	14 (43.75)	11 (5.91)	**<0.0001**
Ex-smoker	21 (65.63)	49 (26.34)	**<0.0001**
Education level, N (%)			
Higher education	24 (75)	136 (73.12)	NS
Primary education	5 (15.63)	43 (23.12)	NS
No studies	2 (6.25)	3 (1.61)	NS
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**
Exacerbations, N (%)			
Patients with asthma exacerbation during previous year	17 (53.13)	71 (38.17)	NS
Exacerbations over the previous year, mean (SD)	3.353 (1.869)	2.634 (2.674)	**0.02**
Severe asthma exacerbation during previous year	7 (21.88)	26 (13.98)	NS
Patient with emergency room (ER) visits	11 (34.38)	48 (25.81)	NS
≥5 ER visits	1 (3.13)	3 (1.61)	NS
Emergency room (ER) visits, mean (SD)	0.91 (1.42)	0.66 (1.56)	NS
ICU admission	3 (9.38)	14 (7.53)	NS
Asthma control in ACT N (%)			
Completely controlled (ACT ≥20)	3 (9.38)	50 (26.8)	**0.04**
Not-controlled (ACT ≤ 19)	29 (90.62)	136 (73.11)	**<0.05**

ACT=asthma control test; CRSwNP=chronic rhinosinusitis with nasal polyposis; CRSsNP=chronic rhinosinusitis without nasal polyposis; CI=confidence interval; ICU=intensive care unit.

Table S2. Functional and inflammatory characteristics of studied patients.

	ACO	NO ACO	P value
No. of subjects (%)	32 (14.7)	186 (85.3)	
Respiratory function tests and biomarkers			
Spirometry, mean (SD)			
FEV1 (L)	2.06 (0.81)	2.85 (0.83)	**<0.0001**
FVC (L)	2.28 (0.86)	3.01 (0.84)	**<0.0001**
FEV1/FVC (%)	61.12 (8.52)	85.27 (12.15)	**<0.0001**
Positive spirometry bronchodilator test, N (%)	16 (50)	34 (18.28)	**0.0004**
Spirometry with GLI, mean (SD)			
FEV1 (z-score)	-2.14 (1.2)	-0.56 (1.2)	**<0.0001**
FVC (z-score)	0.87 (6.36)	-0.30 (1.2)	NS
FEV1/FVC(z-score)	-2.79 (0.70)	-0.50 (1.01)	**<0.0001**
FEV1(LLN)	2.01 (0.64)	2.35 (0.61)	**0.04**
FVC (LLN)	2.59 (0.81)	2.91 (0.75)	**0.05**
FEV1/FVC (LLN)	0.68 (0.02)	0.69 (0.02)	**0.01**
Cellular sputum profile, N (%)	N=4	N=61	
Eosinophilic	2 (50.0%)	26 (42.6)	NS
Mixed	0 (0.0)	6 (9.8)	NS
Neutrophilic	1 (25)	7 (11.5)	NS
Paucigranulocytic	1 (25)	21 (34.4)	NS

FEV_1=forced expiratory volume in one second; FVC=forced vital capacity.