

Cluster Subanalysis of Patients With Severe Asthma Who Responded to Omalizumab

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Asthma is a heterogeneous disease that manifests with variations in signs and symptoms, age of onset, triggers, disease progression, pulmonary function, and airway inflammation [1].

Recently, significant efforts have been made to phenotype asthma, with the objective of identifying patients who are responsive to specific therapies [2]. The different methods used to phenotype asthma have generated bias [3]. In this sense, cluster approaches are one of the most frequently used unbiased techniques [4]. They are generally based on cohorts of patients analyzed using a cluster methodology, which gives rise to various phenotypes [5-7]. Here, we used an innovative contrasting approach, namely, a real-world study in which we selected patients with an excellent response to omalizumab (hyperresponders) and performed a cluster analysis to identify responder phenotypes.

FENOMA was a multicenter, retrospective observational real-world study of patients aged ≥18 years with severe asthma who achieved complete asthma control according to the Spanish Guideline on Asthma Management (GEMA) [8] after 1 year of

treatment with omalizumab. The design of this study has been published elsewhere [9]. Asthma control was considered to be complete if the patient had no diurnal asthma symptoms or asthma symptoms ≤2 d/wk, no nocturnal symptoms, no need for rescue medication ≤2 d/wk, normal pulmonary function, no activity limitation, and no severe asthma exacerbations during this period. These patients were considered hyperresponders. Patients had been retrospectively assigned by their physician to a pre-established phenotype [5,6,10] before receiving treatment with omalizumab. However, the definition of severe asthma phenotypes has evolved since the study was designed (2014), with current phenotypes being more concise and less numerous. The older definitions in the FENOMA study meant a large degree of overlap between phenotypes, thus making it difficult for physicians to select the phenotype (as required by the design of the study) [9]. Therefore, in order to obtain an unsupervised description of responders to omalizumab, we performed a post hoc cluster analysis to find phenotypes among patients who had achieved complete control of the disease during the first year of treatment with omalizumab and identify them in the real-world clinical setting. The variables used to determine clusters and Materials and Methods are described in the Table and Supplementary Information, respectively.

Four clusters were identified in 256 patients, namely, C1, C2, C3, and C4, which included 141 (55.1%), 96 (37.5%), 12 (4.7%), and 7 patients (2.7%), respectively. The cluster

Table. Variables Used to Determine Clusters

	Variables
Age	Forced expiratory volume in 1 second
Sex	Blood eosinophil count
Smoking history	Number of nonsevere asthma episodes
Comorbidities ^a	Number of visits to the emergency room due to asthma exacerbation
Time from asthma diagnosis to severe asthma diagnosis	Admissions to ICU due to asthma exacerbation
Duration of severe asthma until therapy	Dose of inhaled corticosteroids
BMI	Oral corticosteroids
Rescue medication (short-acting β ₂ agonist)	Total serum IgE
Asthma control (GEMA criteria)	Skin prick tests

Abbreviations: BMI, body mass index; GEMA, Spanish Guideline on the Management of Asthma; ICU, intensive care unit.
^aAllergic rhinitis, nasal polyps, chronic sinusitis, and atopic dermatitis.

analysis is described in Supplementary Table 1, and cluster demographics and clinical characteristics are presented in Supplementary Table 4. A correlation analysis was carried out to analyze the response to treatment among the main clusters and specific posttreatment parameters. The parameters included were severity, improvement in asthma control, decrease in exacerbations, use of health care resources, and background treatment (rescue medication and inhaled and oral corticosteroids [OCS]). Given the low number of patients, clusters C3 and C4 were not considered for further analysis. Supplementary Tables 5 and 6 show the comparison for C1 and C2 and summarize the results of the multivariate analysis.

We found 2 distinct and predominant severe asthma phenotypes in patients who responded fully to omalizumab, as clusters C1 and C2 accounted for 92% of the patients. C1 reflected a less allergic phenotype, namely, middle-aged patients (median, 55 years) who were overweight (median body mass index [BMI], 29) and mainly female (75.2%), with reduced lung function (forced expiratory volume in 1 second [FEV₁] ≤80%, 86.5%). Patients were highly symptomatic with more clinically significant exacerbations (median, 3.0), although they did not require hospital admission; 74.5% of patients required OCS. The C2 phenotype comprised younger patients (median age, 40.5 years) with a slight female predominance (56.3%), normal weight (median BMI, 23.6), and better pulmonary function (FEV₁ ≤80%, 42.7%). Patients were less symptomatic and experienced clinically significant exacerbations (median, 2.0), with a high percentage of atopy (46.9%) and high total IgE levels (median, 397.5 IU/mL). OCS were necessary in 45.8%.

As a whole, patients' characteristics for both phenotypes, including age, BMI, smoking status, sex, FEV₁, number of comorbidities, IgE levels, and the annual rate of severe asthma exacerbations, were very similar to those reported in previous studies, thus reinforcing the validity of the C1 and C2 clusters in the real-world clinical setting [5,7,11,12]. No differences were found between C1 and C2 for values of biomarkers such as eosinophils or fractional exhaled nitric oxide.

The study patients were selected because they were hyperresponders after treatment with omalizumab, ie, they achieved complete control of their asthma. Recently, there has been a focus on remission of asthma [13,14]. Menzies-Gow et al [14] defined remission as (1) sustained absence of significant asthma symptoms based on a validated instrument, (2) optimization and stabilization of lung function, and (3) no use of systemic corticosteroids to treat exacerbations or control long-term disease. The patients we report fulfilled these criteria after 1 year of treatment with omalizumab, although a longer-term follow-up is needed. Interestingly, the XPORT study population, in which no exacerbations were observed in 47.7% of patients 1 year after discontinuation of omalizumab, comprised mainly obese female asthmatics with poor lung function [15].

In conclusion, after unbiased cluster analyses, we found 2 specific types of responder. One was a middle-aged obese woman with poor lung function, who was highly symptomatic and dependent on corticosteroids. She was not necessarily allergic and had had many exacerbations. The other was an allergic nonobese asthmatic patient with many

exacerbations but better lung function and lower dependence on corticosteroids. Prospective studies should be performed to determine whether these phenotypes are particularly responsive to omalizumab.

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Conflicts of Interest

Dr Dávila reports nonfinancial support from Novartis during the conduct of the study, as well as personal fees from Novartis, Sanofi, GSK, AstraZeneca, LETI, ALK, Stallergènes, Diater, Chiesi, and ImmunoTek and grants and personal fees from Thermo Fisher outside the submitted work.

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SUPPLEMENTARY MATERIAL

Supplementary information

METHODS

Statistical Methods- Study variables

The variables included in the analysis were selected as per clinical criteria and statistical criteria (variables with many missing values were excluded). There was no control group. Therefore, it is a descriptive analysis in which no comparison between the different patient groups will be presented as per their treatment response but based on their pre-treatment baseline characteristics. Of the 345 evaluable patients from the FENOMA study, 89 were not included in the cluster analysis due to missing data. Thus, 256 patients (74%) served for cluster analysis.

Descriptive statistics were calculated for demographic and clinical characteristics. Continuous variables are presented as median and quartile 1 (Q1) and quartile 3 (Q3). Categorical variables are reported by using frequency and percentage.

For statistical comparisons, the following tests were used, as applicable: Kruskal-Wallis test, Chi-square test, Fisher's exact test, Wilcoxon signed-rank test, and t-test. A 2-tailed P value of less than 0.05 was used to denote statistically significant differences. All statistical analyses were performed with SAS® version 9.4 and SAS® Enterprise Guide V7.15 (SAS Institute, Cary, NC).

Variable correlation analysis

In the case of highly correlated variable groups, a representative of each group is selected, as the information that these variables would provide to the analysis would be redundant, and it may

hinder the clustering process. Of these primary variables, only those with at least 85% of available data were included (**Table 1**).

Search for the optimal number of clusters

Variance ratios that were explained for a wide range number of clusters were analyzed to find the optimal number of clusters in the calculation using the elbow method. **Supplementary Figure 1** shows the candidates found. Based on the explained variance progression, the optimal minimum number of clusters was 4 clusters.

Analysis of the result for the optimal number of clusters

Following the number of clusters found in the previous step, a clustering analysis was performed to obtain an identification cluster number that was assigned to each patient. **Supplementary Table 2** summarizes the number of patients that set each group and additional analysis data. Two main groups formed by 141 and 96 patients were created, while there were also two small groups with 12 and 7 patients. The latter groups were unrepresentative due to their small sizes.

To overcome the high number of variables analysis, canonical discriminant analysis and principal components analysis were performed. With the information on how those vectors were related to the original variables, the most representative variables (demographic, clinical, pulmonary function, biological markers) were extracted when classifying the patients in clusters to create a profile of the patients that formed each group. **Supplementary Table 3** shows the mean values of the canonical vectors for each of the clusters. The first canonical vector (Can1) significantly differentiated cluster 4 from the other clusters, the second vector (Can2) significantly differentiated

cluster 3 from the other clusters, and the third vector (Can3) had different values for clusters 1 and 2, which helped to differentiate these two groups. The three canonical vectors (Can1, Can2, and Can3) are represented in **Supplementary Figure 2** in pairs.

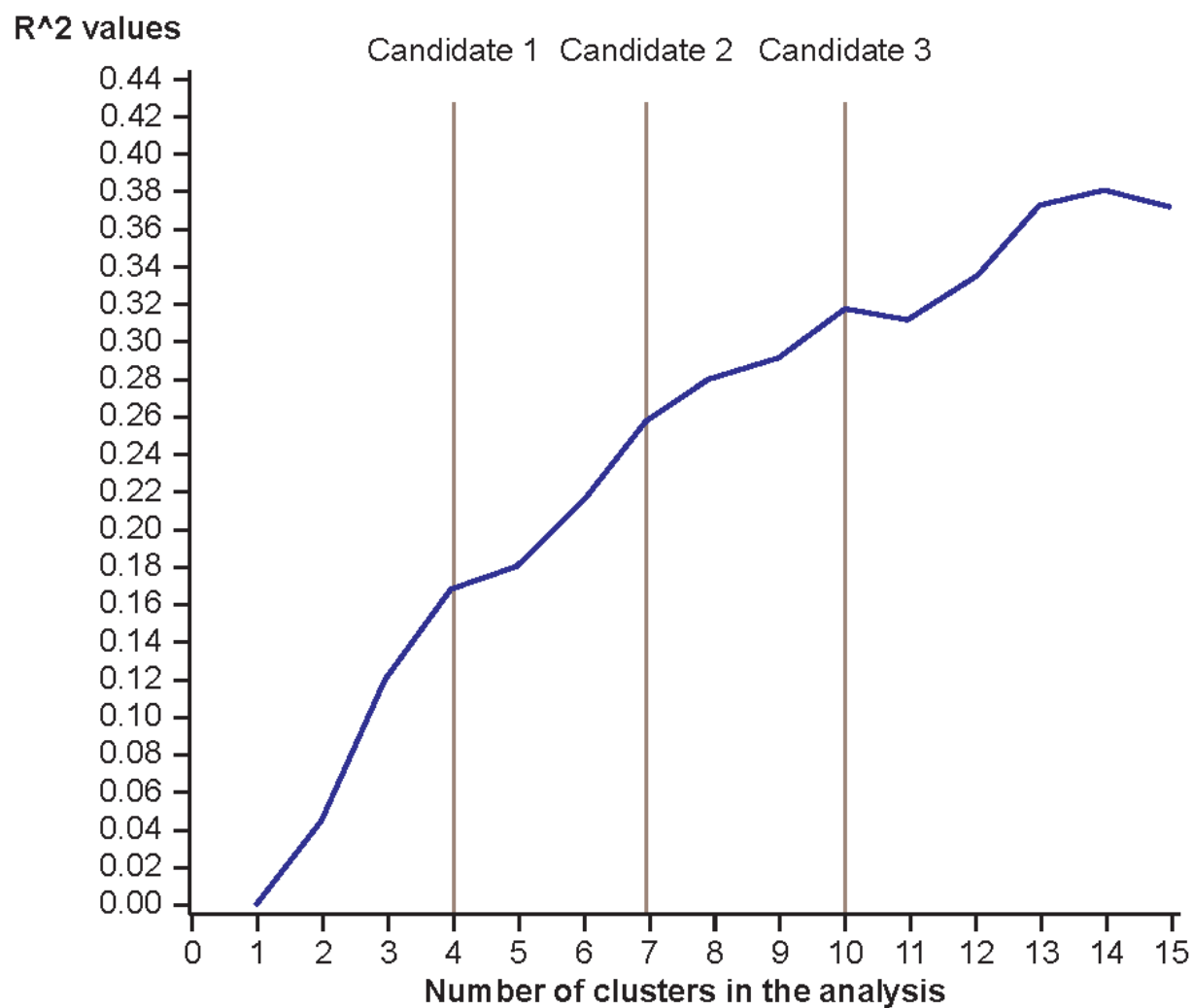
Correlation of cluster profiles with post-treatment parameters

After the cluster analysis, the correlations between the groups of patients (clusters) and some post-treatment parameters were examined through a multivariate analysis. Specifically, the aim was to analyze if there were any differences in response to treatment between the main clusters; therefore, the two smaller ones were excluded from this study

SUPPLEMENTARY MATERIAL

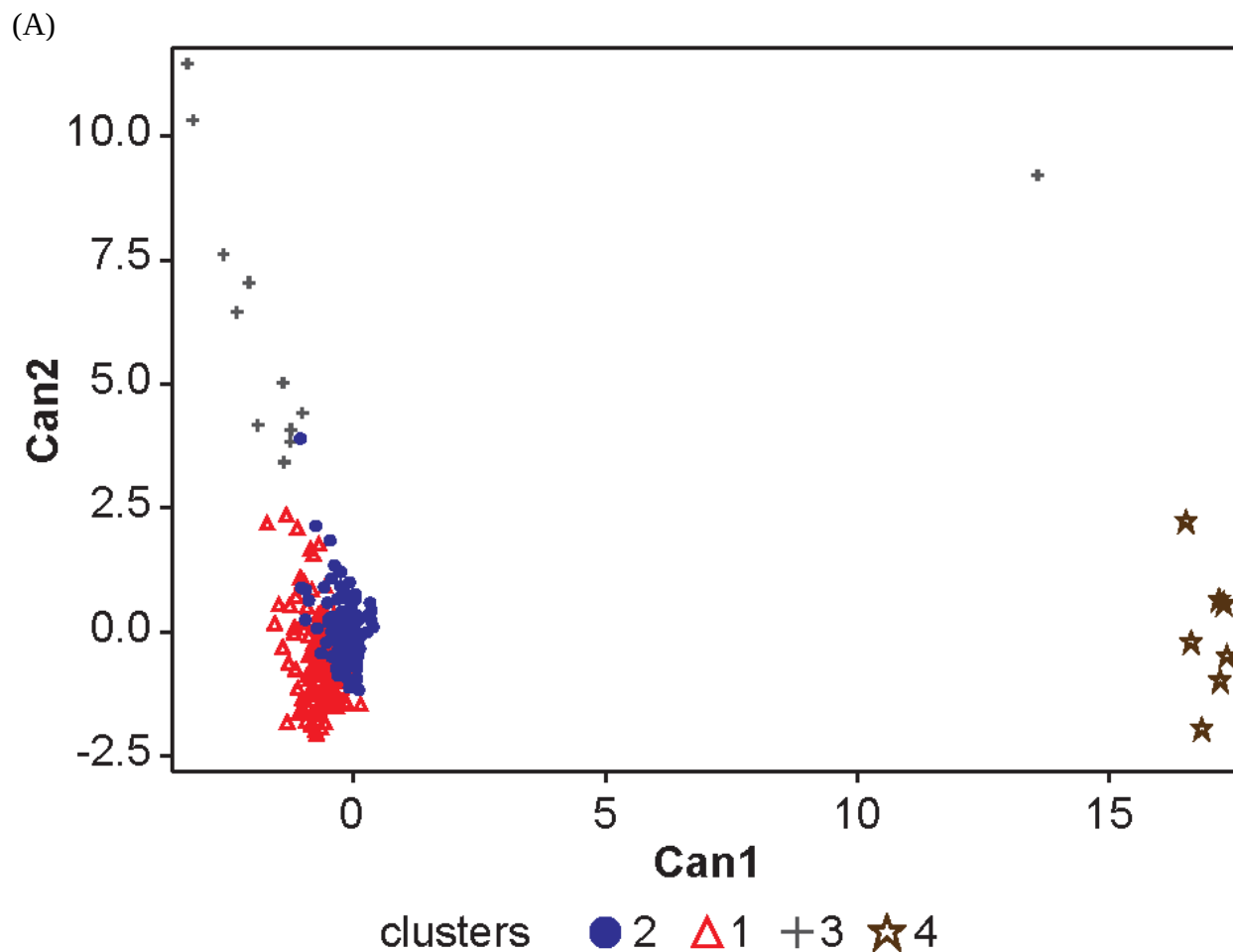
Supplementary Figures

Supplementary Figure 1. Number of clusters vs. explained variance: optimal number of clusters

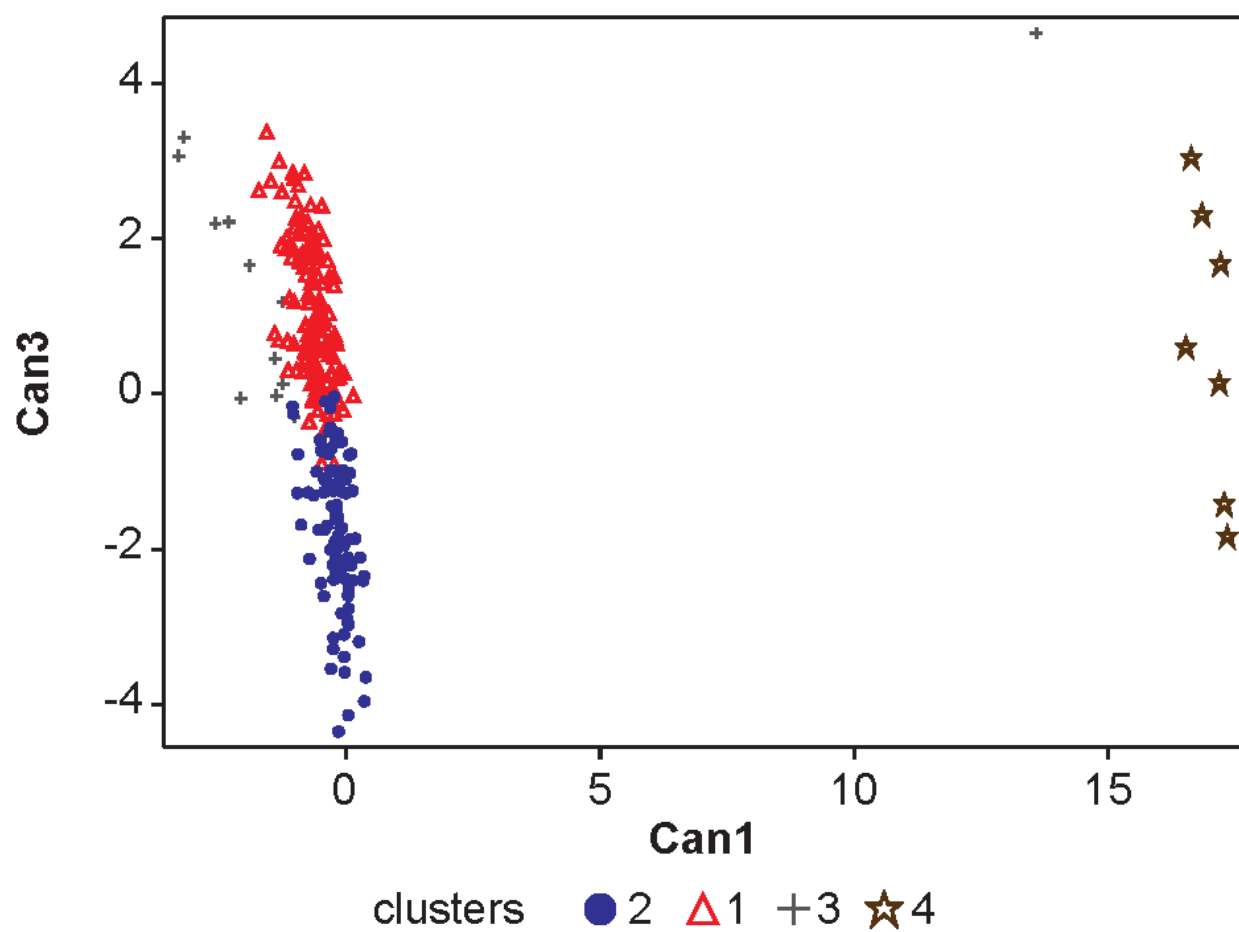


R², explained variance

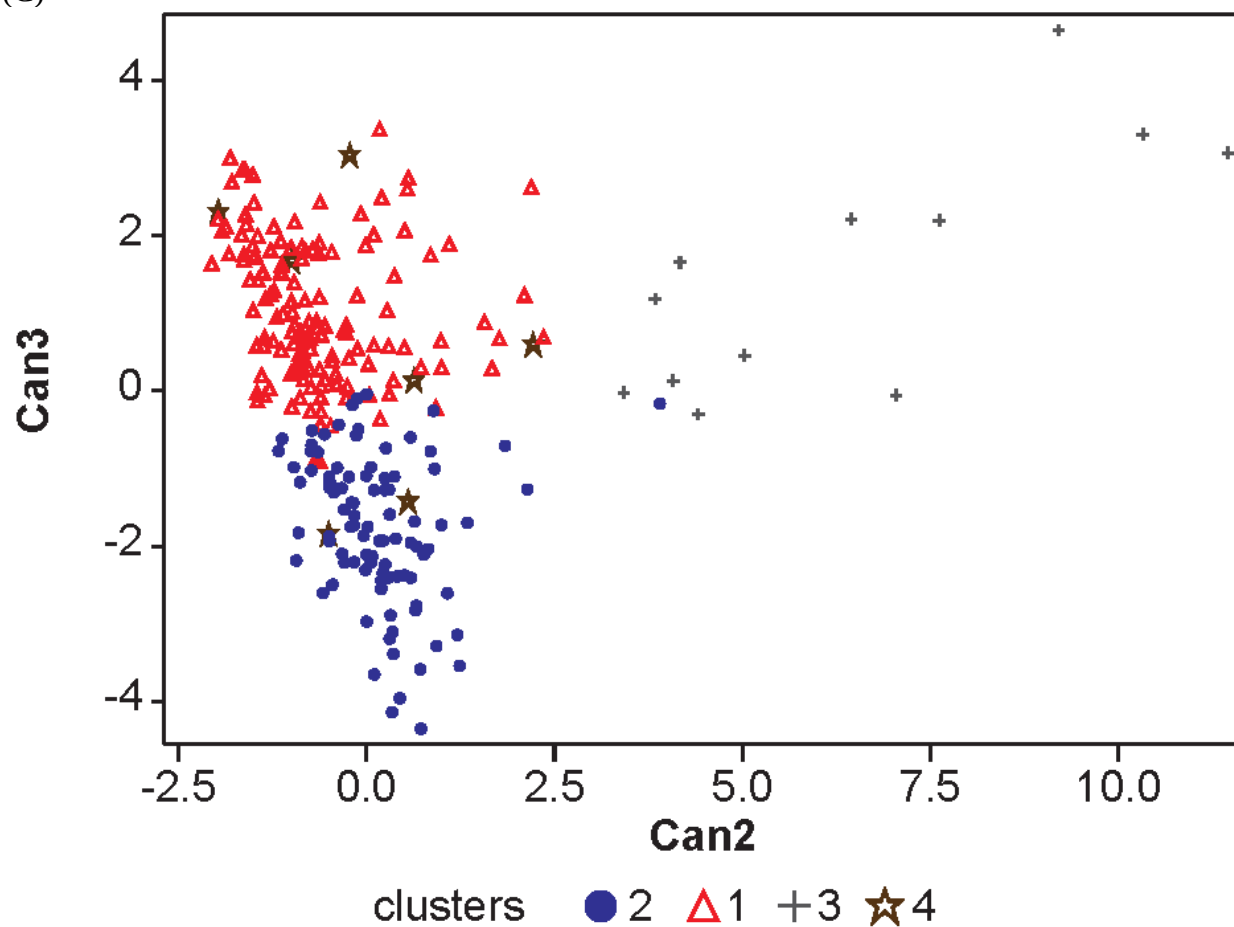
Supplementary Figure 2. Graphic representation of the canonical vectors. (A) Canonical vector 1 vs. canonical vector 2. (B) Canonical vector 1 vs. canonical vector 3. (C) Canonical vector 2 vs. canonical vector 3



(B)



(C)



Can1, canonical vector 1; Can2, canonical vector 2; Can3, canonical vector 3

SUPPLEMENTARY MATERIAL

Supplementary Tables

Supplementary Table 1. Cluster analysis

Clusters	Patients	Cluster characteristics
C1	141	• More females (75.2%) with a median age of 55 (48.0, 65.0) years • Reduced lung function: 86.5% had $FEV_1 \leq 80\%$ • Clinically significant exacerbations (median, 3.0 [2.0, 4.0]) • Elevated total IgE (median, 246.0 [106.0, 517.0] IU/mL) • FeNO levels: (43.0 [25.0, 52.0] ppb) • Blood eosinophils: 81.6% of patient with $\geq 3\%$ • Mostly received ICS high dose (85.8%) and treated with OCS (74.5%) • ER visits due to the asthma exacerbations (median, 3.0 [2.0, 4.0]) • 68.1% reported positive skin tests • Only 27.7% had family history of atopy
C2	96	• More females (56.3%) with younger age (median, 40.5 [26.5, 51.0] years) than C1 cluster • Better lung function: 42.7% had a $FEV_1 \leq 80\%$ • Less clinically significant exacerbations (median, 2.0 [1.0, 4.0]) • Elevated FeNO levels and higher blood eosinophil percentages • Total IgE values higher than C1 cluster • Mostly receiving ICS high doses but fewer patients treated with OCS (45.8%) than C1 cluster • Less ER visits due to asthma exacerbations (median, 1.0 [0.0, 3.0]) • More patients reported positive skin tests (89.6%) than C1 cluster • Almost half of the patients had a family history of atopy
C3	12	• More patients reported positive skin tests 91.7% (11/12) and all were poorly controlled • Greater proportion of patients had atopy • Median time of 2.6 (0.0, 6.6) years from asthma diagnosis to severe asthma diagnosis, much shorter ($P = 0.0073$) elapsed time than C1, C2 and C4 clusters

		• Median time from asthma diagnosis to start of treatment with omalizumab was 20.0 (1.5, 28.9) years, >20 times the median time in C1, C2 and C4 clusters ($P<0.0001$) • One patient (8.3%) had been admitted to ICU within the previous year
C4	7	• Smallest cluster, mostly characterized by high rate (3.0 [2.0, 3.5]) and the severity of the exacerbations • All patients had been admitted to ICU at least once within the previous year • ER visits due to the asthma exacerbations (median, 5.0 [1.0, 6.0]; $P<0.0001$)

ER, emergency room; FEV₁, forced expiratory volume in one second; FeNO, fractional exhaled nitric oxide; ICS, inhaled corticosteroid; ICU, intensive care unit; OCS, oral corticosteroids

Non-severe asthma exacerbations were exacerbations that did not require oral corticosteroids, emergency assistance or hospitalization. If provider doubles the OCS dose after an episode, this was considered a severe or clinically significant asthma exacerbation.

Supplementary Table 2. Summary of the cluster calculation and patient distribution in each group

Cluster Summary						
Cluster	Frequency	RMS Std Deviation	Maximum Distance from Seed to Observation	Radius Exceeded	Nearest Cluster	Distance Between Cluster Centroids
1	141	0.8917	5.3017		1	2.4130
2	96	0.9345	6.3766		2	2.4130
3	12	1.0325	6.8262		2	4.3659
4	7	0.9607	4.7255		2	5.8553

RMS, root mean square

Supplementary Table 3. Mean values of canonical vectors for each cluster found

Class Means on Canonical Variables			
Cluster	Can1	Can2	Can3
1	-0.65422160	-0.64221837	1.04065998
2	-0.19494051	0.14360993	-1.76731366
3	-0.67037699	6.42119806	1.54153741
4	17.00057973	-0.04116290	0.63294354

Can1, canonical vector 1; Can2, canonical vector 2; Can3, canonical vector

Supplementary Table 4. Clusters demographics and clinical characteristics

		C1 n=141	C2 n=96	C3 n=12	C4 n=7	P-value test
Age (years)	Median (Q1, Q3)	55.0 (48.0, 65.0)	40.5 (26.5, 51.0)	44.0 (36.0, 51.5)	41.0 (30.0, 65.0)	<0.0001 [†]
Female	n (%)	106 (75.2)	54 (56.3)	6 (50.0)	6 (85.7)	0.0058 ^ζ
Smoking status						
Non-smoker	n (%)	113 (80.2)	76 (79.2)	10 (83.3)	6 (85.7)	0.9594 ^ζ
Former smoker (without smoking ≥1)	n (%)	23 (16.3)	14 (14.6)	2 (16.7)	1 (14.3)	
Smoker	n (%)	5 (3.6)	6 (6.3)	0 (0.0)	0 (0.0)	
Number of comorbidities	Median (Q1, Q3)	1.0 (0.0, 1.0)	1.0 (1.0, 2.0)	1.5 (1.0, 2.0)	1.0 (0.0, 1.0)	<0.0001 [†]
Family history of atopy	n (%)	39 (27.7)	45 (46.9)	4 (33.3)	2 (28.6)	0.0162 ^ζ
Time from asthma diagnosis to severe asthma diagnosis (years)	Median (Q1, Q3)	10.0 (3.0, 19.4)	6.8 (2.2, 14.3)	2.6 (0.0, 6.6)	9.7 (1.6, 26.0)	0.0073 [†]
Duration of severe asthma until therapy (years)	Median (Q1, Q3)	1.2 (0.4, 2.8)	0.8 (0.1, 2.0)	20.0 (1.5, 28.9)	2.0 (0.2, 4.9)	<0.0001 [†]
BMI (kg/m²)	Median (Q1, Q3)	29.0 (25.6, 32.5)	23.6 (20.6, 26.8)	25.7 (23.8, 28.0)	29.3 (26.8, 31.8)	<0.0001 [†]
Daytime symptoms						
None or ≤ 2 days/week	n (%)	0 (0.0)	5 (5.2)	0 (0.0)	0 (0.0)	<0.0001 ^ζ
> 2 days/week	n (%)	21 (14.9)	49 (51.0)	3 (25.0)	2 (28.6)	
Daily symptoms	n (%)	82 (58.2)	36 (37.5)	8 (66.7)	5 (71.4)	
Continuous symptoms (several times a day)	n (%)	38 (27.0)	6 (6.3)	1 (8.3)	0 (0.0)	
Rescue medication						
None or ≤ 2 days/week	n (%)	1 (0.7)	5 (5.2)	0 (0.00)	1 (14.3)	<0.0001 ^ζ
>2 days/week (but not daily)	n (%)	34 (24.1)	49 (51.0)	4 (33.3)	2 (28.6)	
Every day	n (%)	74 (52.5)	39 (40.6)	8 (66.7)	4 (57.1)	
Several times a day	n (%)	32 (22.7)	3 (3.1)	0 (0.0)	0 (0.0)	

		C1 n=141	C2 n=96	C3 n=12	C4 n=7	P-value test
Nighttime symptoms						
None	n (%)	7 (5.0)	9 (9.4)	0 (0.0)	1 (14.3)	0.0540 [§]
≤ 2 times/month	n (%)	11 (7.8)	15 (15.6)	2 (16.7)	2 (28.6)	
> 2 times/month	n (%)	22 (15.6)	22 (22.9)	1 (8.3)	1 (14.3)	
More than once a week	n (%)	54 (38.3)	35 (36.5)	6 (50.0)	2 (28.6)	
Common	n (%)	47 (33.3)	15 (15.6)	3 (25.0)	1 (14.3)	
ACT score	Median	13.0	15.00	13.00	15.00	0.2307 [‡]
	(Q1, Q3)	(10.0, 15.0)	(11.00, 18.00)	(12.00, 16.00)	(15.00, 15.00)	
ACQ score	Median	3.0 (2.0, 3.6)	1.8 (1.4, 2.2)	3.0 (3.0, 3.0)	1.5 (1.5, 1.5)	0.1051 [‡]
	(Q1, Q3)					
Positive skin prick test	n (%)	96 (68.1)	86 (89.6)	11 (91.7)	3 (42.9)	<0.0001 [§]
Blood eosinophils						
<3%	n (%)	26 (18.4)	16 (16.7)	4 (33.33)	2 (28.57)	0.7189 [§]
3-<5%	n (%)	31 (22.0)	16 (16.7)	1 (8.33)	0 (0.00)	
5%-<8%	n (%)	40 (28.4)	27 (28.1)	3 (25.00)	3 (42.86)	
≥8%	n (%)	44 (31.2)	37 (38.5)	4 (33.33)	2 (28.57)	
FEV₁ ≤ 80%	n (%)	122 (86.5)	41 (42.7)	10 (83.3)	6 (85.7)	<0.0001 [§]
FeNO (ppb)	Median	43.0	34.5	38.0	22.0	0.3414 [‡]
	(Q1, Q3)	(25.0, 52.0)	(21.0, 60.0)	(16.0, 56.0)	(14.0, 28.0)	
Serum IgE (IU/mL)	Median	246.0	397.5	364.0	358.0	0.0095 [‡]
	(Q1, Q3)	(106.0, 517.0)	(184.5, 825.5)	(68.0, 1361.0)	(144.0, 730.0)	
Number of non-severe asthma episodes	Median	5.0 (3.0, 9.0)	4.0 (2.0, 6.0)	6.5 (4.5, 18.5)	5.0 (1.0, 12.0)	0.0108 [‡]
	(Q1, Q3)					
No. of clinically significant and/or severe exacerbations	Median	3.0 (2.0, 4.0)	2.0 (1.0, 4.0)	3.0 (2.0, 3.5)	5.0 (1.0, 6.0)	0.0120 [‡]
	(Q1, Q3)					
No. of visits to the emergency room due to asthma exacerbation	Median	3.0 (2.0, 4.0)	1.0 (0.0, 3.0)	2.5 (1.5, 4.0)	5.0 (1.0, 6.0)	<0.0001 [‡]
	(Q1, Q3)					
No. of hospitalizations due to exacerbations	Median	0.0 (0.0, 1.0)	0.0 (0.0, 0.0)	0.5 (0.0, 1.5)	3.0 (1.0, 5.0)	<0.0001 [‡]
	(Q1, Q3)					

		C1 n=141	C2 n=96	C3 n=12	C4 n=7	P-value test
No. of admissions to ICU due to exacerbations	Median (Q1, Q3)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	1.0 (1.0, 3.0)	<0.0001 [†]
No. of admissions to ICU due to exacerbations (ranges)						
0	n (%)	141 (100.0)	96 (100.0)	11 (91.7)	0 (0.0)	<.0001 [§]
≥1	n (%)	0 (0.0)	0 (0.0)	1 (8.3)	7 (100.0)	
Oral corticosteroids	n (%)	105 (74.5)	44 (45.8)	7 (58.3)	5 (71.4)	<0.0001 [§]
Dose of oral corticosteroids (mg)	Median (Q1, Q3)	10.0 (0.0, 50.0)	10.0 (0.0, 30.0)	50.0 (45.0, 50.0)	30.0 (0.0, 50.0)	0.4691 [†]

ACT: Asthma Control Test; ACQ: Asthma Control Questionnaire; BMI: Body mass index; FeNO: Fractional exhaled nitric oxide; FEV₁: Forced expiratory volume in 1 second; ICU: Intensive care unit

‡ ANOVA; * Chi-square test; § Fisher's exact test; † Kruskal-Wallis test; § Wilcoxon signed-rank test

Non-severe asthma exacerbations were exacerbations that did not require oral corticosteroids, emergency assistance or hospitalization. If provider doubles the OCS dose after an episode, this was considered a severe or clinically significant asthma exacerbation.

Supplementary Table 5. Comparison of Clusters 1 and 2

		C1 n=141	C2 n=96	P-value test
Age (years)	Median (Q1, Q3)	55.0 (48.0, 65.0)	40.5 (26.5, 51.0)	<0.0001 [§]
Female	n (%)	106 (75.2)	54 (56.3)	0.0023*
Smoking status				
Non-smoker	n (%)	113 (80.1)	76 (79.2)	0.6018*
Former smoker (without smoking ≥1 years)	n (%)	23 (16.3)	14 (14.6)	
Smoker	n (%)	5 (3.6)	6 (6.3)	
Number of comorbidities	Median (Q1, Q3)	1.0 (0.0, 1.0)	1.0 (1.0, 2.0)	<0.0001 [§]
Family history of atopy	n (%)	39 (27.7)	45 (46.9)	0.0023 ^ζ
Time from asthma diagnosis to severe asthma diagnosis (years)	Median (Q1, Q3)	10.0 (3.0, 19.4)	6.8 (2.2, 14.3)	0.0635 [§]
Duration of severe asthma until therapy (years)	Median (Q1, Q3)	1.2 (0.4, 2.8)	0.8 (0.1, 2.0)	0.0083 [§]
BMI (kg/m²)	Median (Q1, Q3)	29.0 (25.6, 32.5)	23.6 (20.6, 26.8)	<0.0001 [§]
Daytime symptoms				
None or ≤ 2 days/week	n (%)	0 (0.00)	5 (5.2)	<0.0001 ^ζ
> 2 days/week	n (%)	21 (14.9)	49 (51.1)	
Daily symptoms	n (%)	82 (58.2)	36 (37.5)	
Continuous symptoms (several times a day)	n (%)	38 (27.0)	6 (6.3)	
Rescue medication				
None or ≤ 2 days/week	n (%)	1 (0.7)	5 (5.2)	<0.0001 ^ζ
> 2 days/week (but not daily)	n (%)	34 (24.1)	49 (51.0)	
Every day	n (%)	74 (52.5)	39 (40.6)	
Several times a day	n (%)	32 (22.7)	3 (3.1)	
Night time symptoms				
None	n (%)	7 (4.96)	9 (9.4)	0.0096*
≤ 2 times/month	n (%)	11 (7.8)	15 (15.6)	
> 2 times/month	n (%)	22 (15.6)	22 (22.9)	
More than once a week	n (%)	54 (38.3)	35 (36.5)	
Common	n (%)	47 (33.3)	15 (15.6)	
Control as per GEMA				
Partially controlled asthma	n (%)	6 (4.3)	20 (20.8)	<0.0001*
Poorly controlled asthma	n (%)	135 (95.7)	76 (79.2)	
Positive skin prick test	n (%)	96 (68.1)	86 (89.6)	0.0001*
Blood eosinophils count				
<3%	n (%)	26 (18.4)	16 (16.7)	0.6113*

		C1 n=141	C2 n=96	P-value test
	3-<5%	n (%)	31 (22.0)	16 (16.7)
	5%-<8%	n (%)	40 (28.4)	27 (28.1)
	≥8%	n (%)	44 (31.2)	37 (38.5)
FEV₁				
	≤ 80%	n (%)	122 (86.5)	41 (42.7)
	>80%	n (%)	19 (13.5)	55 (57.3)
FeNO (ppb)	Median	43.0	34.5	0.5129 [§]
	(Q1, Q3)	(25.0, 52.0)	(21.0, 60.0)	
Serum IgE (IU/mL)	Median	246.0 (106.0,	397.5 (184.5,	0.0007 [§]
	(Q1, Q3)	517.0)	825.5)	
Number of non-severe asthma episodes	Median	5.0 (3.0, 9.0)	4.0 (2.0, 6.0)	0.0027 [§]
	(Q1, Q3)			
No. of clinically significant and/or severe exacerbations	Median	3.0 (2.0, 4.0)	2.0 (1.0, 4.0)	0.0020 [§]
	(Q1, Q3)			
No. of visits to the emergency room due to asthma exacerbation	Median	3.0 (2.0, 4.0)	1.0 (0.0, 3.0)	<0.0001 [§]
	(Q1, Q3)			
No. of hospitalizations due to exacerbations	Median	0.0 (0.0, 1.0)	0.0 (0.0, 0.0)	0.3005 [§]
	(Q1, Q3)			
Oral corticosteroids	n (%)	105 (74.5)	44 (45.8)	<0.0001*
Dose of oral corticosteroids (mg)	Median	10.0	10.0	0.9074 [§]
	(Q1, Q3)	(0.0, 50.0)	(0.0, 30.0)	
Short-acting β_2 agonists, as needed	n (%)	137 (97.2)	92 (95.8)	0.7181 ^ζ

ACT: Asthma Control Test; ACQ: Asthma Control Questionnaire; BMI: Body mass index; FeNO: Fractional exhaled nitric oxide; FEV₁: Forced expiratory volume in 1 second. *, Chi-square test; ζ , Fisher's exact test; †, Kruskal-Wallis test; §, Wilcoxon signed-rank test

Non-severe asthma exacerbations were exacerbations that did not require oral corticosteroids, emergency assistance or hospitalization. If provider doubles the OCS dose after an episode, this was considered a severe or clinically significant asthma exacerbation.

Supplementary Table 6. Summary of results from multivariate analysis

		Cluster 1 (n=141)	Cluster 2 (n=96)	P-value test
Inhaled corticosteroids?				
	<i>Missing</i> n	0	0	
	<i>Valid</i> n	141	96	
No change	n (%)	133 (94.33)	81 (84.38)	.0111*
Yes→No	n (%)	8 (5.67)	15 (15.63)	
Was the dose of inhaled corticosteroids decreased?				
	<i>Missing</i> n	10	16	
	<i>Valid</i> n	131	80	
No	n (%)	65 (49.62)	47 (58.75)	.2046 ^ζ
Yes	n (%)	66 (50.38)	33 (41.25)	
Oral corticosteroids?				
	<i>Missing</i> n	0	0	
	<i>Valid</i> n	141	96	
No change	n (%)	52 (36.88)	58 (60.42)	.0005 ^ζ
No→Yes	n (%)	1 (0.71)	0 (0.00)	
Yes→No	n (%)	88 (62.41)	38 (39.58)	
Did the number of non-severe asthma episodes decrease?				
	<i>Missing</i> n	0	2	
	<i>Valid</i> n	141	94	
No	n (%)	3 (2.13)	9 (9.57)	.0150 ^ζ
Yes	n (%)	138 (97.87)	85 (90.43)	
Did asthma severity improve as per GEMA?				
	<i>Missing</i> n	1	0	
	<i>Valid</i> n	140	96	
No	n (%)	1 (0.71)	0 (0.00)	1.0000 ^ζ
Yes	n (%)	139 (99.29)	96 (100.00)	
Was rescue medication reduced?				
	<i>Missing</i> n	0	0	
	<i>Valid</i> n	141	96	
No	n (%)	2 (1.42)	1 (1.04)	1.0000 ^ζ
Yes	n (%)	139 (98.58)	95 (98.96)	

GEMA: Spanish Guidelines on the Management of Asthma.

*Chi-square test; ^ζ, Fisher's exact test