SUPPLEMENTARY MATERIAL

Supplementary Tables

Supplementary Table 1. Cluster analysis

Clusters	Patients	Cluster characteristics
C1 • **Exacerbations** • **OCS** • **Eosinophils**	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 ≥ 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 • **Lung function** • **FeNO** • **IgE**	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 • **Positive skin tests** • **Atopy**	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

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		• 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 • **ICU** • **ER visit**	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; FEV_1, 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.

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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

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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

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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)	0.0058ζ
Smoking status						
Non-smoker	n (%)	113 (80.2)	76 (79.2)	10 (83.3)	6 (85.7)	0.9594ζ
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)	0.0162ζ
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/m^2)	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)	<0.0001ζ
> 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)	<0.0001ζ
>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)	

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		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[ζ]
≤ 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 (Q1, Q3)	13.0 (10.0, 15.0)	15.00 (11.00, 18.00)	13.00 (12.00, 16.00)	15.00 (15.00, 15.00)	0.2307[‡]
ACQ score	Median (Q1, Q3)	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[‡]
Positive skin prick test	n (%)	96 (68.1)	86 (89.6)	11 (91.7)	3 (42.9)	<0.0001[ζ]
Blood eosinophils						
<3%	n (%)	26 (18.4)	16 (16.7)	4 (33.33)	2 (28.57)	0.7189[ζ]
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)	
$FEV_1 \leq 80\%$	n (%)	122 (86.5)	41 (42.7)	10 (83.3)	6 (85.7)	<0.0001[ζ]
FeNO (ppb)	Median (Q1, Q3)	43.0 (25.0, 52.0)	34.5 (21.0, 60.0)	38.0 (16.0, 56.0)	22.0 (14.0, 28.0)	0.3414[†]
Serum IgE (IU/mL)	Median (Q1, Q3)	246.0 (106.0, 517.0)	397.5 (184.5, 825.5)	364.0 (68.0, 1361.0)	358.0 (144.0, 730.0)	0.0095[†]
Number of non-severe asthma episodes	Median (Q1, Q3)	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[†]
No. of clinically significant and/or severe exacerbations	Median (Q1, Q3)	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[†]
No. of visits to the emergency room due to asthma exacerbation	Median (Q1, Q3)	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[†]
No. of hospitalizations due to exacerbations	Median (Q1, Q3)	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[†]

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		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)	<.0001ζ
≥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)	<0.0001ζ
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; FEV_1: Forced expiratory volume in 1 second; ICU: Intensive care unit

‡ ANOVA; * 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.

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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)	0.0023ζ
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/m^2)	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)	<0.0001ζ
> 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)	<0.0001ζ
> 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*

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		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)	
FEV_1				
≤ 80%	n (%)	122 (86.5)	41 (42.7)	<.0001*
>80%	n (%)	19 (13.5)	55 (57.3)	
FeNO (ppb)	Median (Q1, Q3)	43.0 (25.0, 52.0)	34.5 (21.0, 60.0)	0.5129§
Serum IgE (IU/mL)	Median (Q1, Q3)	246.0 (106.0, 517.0)	397.5 (184.5, 825.5)	0.0007§
Number of non-severe asthma episodes	Median (Q1, Q3)	5.0 (3.0, 9.0)	4.0 (2.0, 6.0)	0.0027§
No. of clinically significant and/or severe exacerbations	Median (Q1, Q3)	3.0 (2.0, 4.0)	2.0 (1.0, 4.0)	0.0020§
No. of visits to the emergency room due to asthma exacerbation	Median (Q1, Q3)	3.0 (2.0, 4.0)	1.0 (0.0, 3.0)	<0.0001§
No. of hospitalizations due to exacerbations	Median (Q1, Q3)	0.0 (0.0, 1.0)	0.0 (0.0, 0.0)	0.3005§
Oral corticosteroids	n (%)	105 (74.5)	44 (45.8)	<0.0001*
Dose of oral corticosteroids (mg)	Median (Q1, Q3)	10.0 (0.0, 50.0)	10.0 (0.0, 30.0)	0.9074§
Short-acting β_2 agonists, as needed	n (%)	137 (97.2)	92 (95.8)	0.7181ζ

ACT: Asthma Control Test; ACQ: Asthma Control Questionnaire; BMI: Body mass index; FeNO: Fractional exhaled nitric oxide; FEV_1: 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.

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Supplementary Table 6. Summary of results from multivariate analysis

			Cluster 1 (n=141)	Cluster 2 (n=96)	P-value test
Inhaled corticosteroids?					
	Missing	n	0	0	
	Valid	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?					
	Missing	n	10	16	
	Valid	n	131	80	
No		n (%)	65 (49.62)	47 (58.75)	.2046ζ
Yes		n (%)	66 (50.38)	33 (41.25)	
Oral corticosteroids?					
	Missing	n	0	0	
	Valid	n	141	96	
No change		n (%)	52 (36.88)	58 (60.42)	.0005ζ
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?					
	Missing	n	0	2	
	Valid	n	141	94	
No		n (%)	3 (2.13)	9 (9.57)	.0150ζ
Yes		n (%)	138 (97.87)	85 (90.43)	
Did asthma severity improve as per GEMA?					
	Missing	n	1	0	
	Valid	n	140	96	
No		n (%)	1 (0.71)	0 (0.00)	1.0000ζ
Yes		n (%)	139 (99.29)	96 (100.00)	
Was rescue medication reduced?					
	Missing	n	0	0	
	Valid	n	141	96	
No		n (%)	2 (1.42)	1 (1.04)	1.0000ζ
Yes		n (%)	139 (98.58)	95 (98.96)	

GEMA: Spanish Guidelines on the Management of Asthma.

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

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