Original Article

Response to Biologics Along a Gradient of T2 Involvement in Patients With Severe Asthma: A Data-Driven Biomarker Clustering Approach

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What is already known about this topic? Asthma with low levels of type 2 (T2) biomarkers is poorly defined, phenotyped, and managed. Whether asthma phenotypes should be categorized as distinct T2-high/T2-low or exist on a spectrum of T2 involvement is a subject of debate.

What does this article add to our knowledge? We have identified 5 biomarker clusters along a gradient of T2 involvement in a large global, real-life, severe asthma population using a data-driven approach and showed a differential response to biologics along this gradient.

How does this study impact current management guidelines? Our findings suggest a change in paradigm from the dichotomous T2-high/T2-low nomenclature to a "T2-spectrum" approach and call for greater understanding of and more effective therapies for patients at the lower end of the T2 spectrum.

BACKGROUND: Asthma with low levels of type 2 (T2) biomarkers is poorly understood.
OBJECTIVE: To characterize severe asthma phenotypes and compare changes in asthma outcomes from pre- to postbiologic treatment along a gradient of T2 involvement.
METHODS: This was a registry-based cohort study including data from 24 countries. Biomarker distribution (blood eosinophil count, fractional exhaled nitric oxide, and IgE) was quantified before biologic initiation. Clusters were identified using a 5-component Gaussian finite mixture model and phenotypically characterized. Changes in asthma and health care utilization outcomes between 1-year pre- and postbiologic initiation were compared between clusters and by biologic class.
RESULTS: Among 3675 patients, 5 biomarker clusters were identified along a gradient of T2 involvement: cluster A with the lowest T2 involvement (16.4%), cluster B (20.4%), cluster C (22.9%), cluster D (30.3%), and cluster E with the highest T2 involvement (10.0%). In multivariable analysis, biologic use was associated with improved outcomes in all clusters but tended to be better at the higher end of the T2 spectrum. For example, patients in cluster C had a significantly greater

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Abbreviations used

ACT- Asthma Control Test
ACQ- Asthma Control Questionnaire
BEC- Blood eosinophil count
CI- Confidence interval
CRS- Chronic rhinosinusitis
ED- Emergency department
FeNO- Fractional exhaled nitric oxide
FEV_1- Forced expiratory volume in 1 second
FMSMSN- Finite mixture models with components belonging to the class of scale mixtures of the skew-normal distribution
GERD- Gastroesophageal reflux disease
GFMM- Gaussian finite mixture models
GINA- Global Initiative for Asthma
HCRU- Health care resource utilization
ISAR- International Severe Asthma Registry
LTOCS- Long-term oral corticosteroid
NP- Nasal polyps
OCS- Oral corticosteroid
$ppFEV_1$- Percent predicted FEV_1
T2- Type 2

increase in forced expiratory volume in 1 second compared with cluster A (difference 0.16 L [95% confidence interval: 0.08, 0.25]; $P < .001$). The odds of uncontrolled asthma were approximately 0.6 for all clusters compared with cluster A. Overall, exacerbation rates were lower, and greater improvements in lung function and asthma control were noted for anti−IL-5/5 receptor (R) (but not anti-IgE or anti−IL-4Rα) for all clusters compared with cluster A.

CONCLUSION: T2-targeting biologics have utility in the management of asthma with low T2 involvement, but more effective therapies are needed. Further research is warranted to identify specific pathogenic pathways at the lower end of the T2 spectrum that can be effectively targeted by biologics. **(J Allergy Clin Immunol Pract 2025;13:3296-315)**

Key words: *BEC; Benralizumab; Dupilumab; Effectiveness; FeNO; IgE; Mepolizumab; Omalizumab; Real-life; Reslizumab*

Asthma is a heterogeneous disease commonly categorized according to its pathogenesis (ie, allergic or nonallergic), its inflammation type or pattern (ie, eosinophilic or non-eosinophilic), and most recently, according to a continuum of underlying immunopathological mechanisms (ie, from type 2 [T2]-high to T2-low).[1] Most patients with severe asthma have T2-high asthma, ranging from 45% to 84% by recent estimates.[2-4] The reported prevalence of T2-low asthma (ie, low levels of T2 biomarkers) varies depending on definition, cohort, and methodology used,[3,5-12] but is estimated to be 49% of the general asthma population, when all levels of severity are considered,[13] 16% to 31% in other cohorts,[9,12] and more recently estimated at 8% of patients included in the International Severe Asthma Registry (ISAR).[2] Clinically, patients with a T2-low phenotype tend to be older, treated with long-term oral corticosteroids (LTOCS), and have later asthma onset, a smoking history, higher body mass index, and peripheral neutrophilia compared with those with T2-high disease.[4,10,14] They also tend to have less chronic rhinosinusitis (CRS) and more

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arterial hypertension, myocardial infarction, obesity, gastroesophageal reflux disease (GERD), sleep apnea, and depression/anxiety.[3,4]

Much remains unknown about T2-low asthma; whether it constitutes a distinct diagnosis or exists on a spectrum of T2 involvement is the subject of continued debate.[6] Currently, there is no agreed-on definition or signature clinical biomarker profile for T2-low asthma other than the absence of T2 inflammation,[15] but many standard-of-care asthma therapies, including inhaled and systemic corticosteroids, suppress T2 biomarkers, thus confounding T2-low categorization.[16,17] This definition of exclusion represents a challenge for both diagnosis and research into effective therapies.[6,15] Consequently, there are limited effective treatment options for T2-low asthma and no defined personalized treatment pathways.[6,14] Typically, T2-low asthma is less responsive to available biologics, which target T2 asthma-related pathways.[18,19]

A better understanding of the T2-low biomarker profile and phenotype characterization along a spectrum of T2 involvement would be useful to help predict differential response to current biologic therapy and potentially improve management of this less well-understood endotype. The International Severe Asthma Registry (ISAR) (https://www.isaregistries.opcglobal.org/) is the largest real-life data repository of severe asthma cases (n > 17,000). It currently includes data from 25 countries and offers a unique opportunity to investigate T2-low asthma and changes in asthma outcomes from pre- to postbiologic treatment.[20-22] Using a data-driven approach instead of predefined clinical biomarker cutoffs, we aimed to (1) describe distributions of biomarkers in patients with severe asthma along a gradient of T2 involvement, (2) phenotypically characterize patients along this gradient, and (3) compare changes in both asthma outcomes and associated health care resource utilization (HCRU) from pre- to postbiologic initiation across the gradient.

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METHODS

Study design and data source

This was a registry-based cohort study using data from ISAR.[20,21] Patients with severe asthma included in ISAR have been well characterized[23] and phenotyped,[2] and details of the registry are described elsewhere (see this article's Online Repository at www.jaci-inpractice.org).[21] Here, we have included data from 24 countries (Argentina, Australia, Bulgaria, Canada, Colombia, Denmark, Greece, India, Ireland, Italy, Japan, Korea, Kuwait, Mexico, New Zealand, Poland, Portugal, Saudi Arabia, Singapore, Spain, Taiwan, United Arab Emirates, United Kingdom, and United States) that shared data with ISAR between May 1, 2017, and February 15, 2023. Distribution of biomarkers (ie, blood eosinophil count [BEC], fractional exhaled nitric oxide [FeNO], and total serum IgE) was assessed before biologic initiation using the highest biomarker concentrations measured at any time (for those who did not subsequently initiate biologics, because all values were prebiologic) or in the 1-year period before biologic initiation (for those who did subsequently initiate biologics) (Figure E1, *A*, available in this article's Online Repository at www.jaci-inpractice.org). Asthma-related and HCRU outcomes were assessed in the 1-year periods before and after biologic initiation according to the level of T2 involvement (Table I). For the assessment of biologic-associated changes in these outcomes, study entry corresponded to the date of biologic initiation (Figure E1, *B*, available in this article's Online Repository at www.jaci-inpractice.org).

Ethics and registration

This study fulfilled requirements outlined in the REal Life EVidence AssessmeNt Tool (RELEVANT) recommendations for comparative effectiveness research studies, including a priori development of both the protocol and statistical analysis plan.[24] The study complied with appropriate registration and ethics requirements (see this article's Online Repository at www.jaci-inpractice.org).

Patients

All patients enrolled into ISAR are required to be 18 years or older and have severe asthma (defined as receiving treatment at Global Initiative for Asthma [GINA] 2018 step 5 or with uncon-

employee of the OPRI. OPRI conducted this study in collaboration with Optimum Patient Care, a co-funder of the ISAR. T. Iwanaga received speaker bureau fees from Kyorin, GlaxoSmithKline, Novartis, Boehringer Ingelheim, AstraZeneca, and Sanofi. D. J. Jackson has received speaker fees and consultancy fees from AstraZeneca, GlaxoSmithKline, and Sanofi Regeneron; and research funding from AstraZeneca and GlaxoSmithKline. M. S. Koh reports grant support from AstraZeneca and honoraria for lectures and advisory board meetings paid to her hospital (Singapore General Hospital) from GlaxoSmithKline, AstraZeneca, Novartis, Sanofi, and Boehringer Ingelheim, outside the submitted work. K. Kostikas received honoraria for presentations and consultancy fees from AstraZeneca, Berlin Chemie, Boehringer Ingelheim, Chiesi, ELPEN, GSK, Guidotti, Menarini, Pfizer, Sanofi, and Specialty Therapeutics. 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Porsbjerg has attended advisory boards for AstraZeneca, Novartis, TEVA, and Sanofi-Genzyme; has given lectures at meetings supported by AstraZeneca, Novartis, TEVA, Sanofi-Genzyme, and GlaxoSmithKline; has taken part in clinical trials sponsored by AstraZeneca, Novartis, Merck Sharp & Dohme, Sanofi-Genzyme, GlaxoSmithKline, and Novartis; and has received educational and research grants from AstraZeneca, Novartis, TEVA, GlaxoSmithKline, ALK, and Sanofi-Genzyme. F. Puggioni reports having received lectures or advisory board fees from Menarini, Mundipharma, Chiesi, Alk Abello, AstraZeneca, Boehringer Ingelheim, Guidotti, Malesci, GlaxoSmithKline, Hal Allergy, Novartis, Sanofi, Regeneron, Stallergenes Greer, Valeas, and Almirall. A. Quinton is an employee of AstraZeneca and may own stock or stock options in AstraZeneca. AstraZeneca is a co-funder of ISAR. C. K. Rhee received consulting/lecture fees from Merck Sharp & Dohme, AstraZeneca, GlaxoSmithKline, Novartis, Takeda, Mundipharma, Boehringer-Ingelheim, Teva, Sanofi, and Bayer. M. Sadatsafavi has received honoraria from AstraZeneca, Boehringer Ingelheim, Teva, and GlaxoSmithKline for purposes unrelated to the content of this paper and has received research funding from AstraZeneca and Boehringer Ingelheim directly into his research account from AstraZeneca for unrelated projects. S. Salvi declares research support and speaker fees from Cipla, Glenmark, and GlaxoSmithKline. C.-C. Sheu has received advisory board and speaker fees from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, and Pfizer; and has acted as an investigator for trials sponsored by AstraZeneca, Novartis, Roche, Sanofi-Regeneron, Galapagos, Shionogi, Aridis, Bristol Myers Squibb, Insmed, United Therapeutics, Enanta Pharmaceuticals, Areteia Therapeutics, Meiji, and Horizon Therapeutics. C. Taillé has received lecture or advisory board fees and grants to her institution from AstraZeneca, Sanofi,

TABLE I. Timing of pre- and postbiologic asthma outcomes

Label	Prebiologic	Postbiologic
Annualized exacerbation rate (count per year)	Number of exacerbations requiring rescue corticosteroids in the 12 months preceding biologic initiation	Number of exacerbations per year requiring rescue steroids after biologic initiation during the available 12-month follow-up period (minimum 48 weeks)
Postbronchodilator, FEV_1 (L)*	Highest reading in the 12 months preceding biologic initiation	Assessed closest to 1 year after biologic initiation (minimum 24 weeks)
Asthma control†	Well-controlled, partly controlled, or uncontrolled in the 12 months preceding biologic initiation	
HCRU	Asthma-related hospitalizations, ED visits, and invasive ventilations in the 12 months preceding biologic initiation	In the 12-month period after biologic initiation (minimum 24 weeks)

*For FEV_1, postbronchodilator measures were used if available, and prebronchodilator measures otherwise, while ensuring that both pre- and postbiologic measures were either pre- or postbronchodilator. In the subpopulation of patients included in the lung function analysis (n = 2929), postbronchodilator measurements were used for 44.0% patients.
†Categories defined by GINA 2023 update.[1] For countries providing ACQ score or ACT score instead of GINA control categories, conversions were performed as follows: mean ACQ score ≤0.75 = well-controlled, mean ACQ score >0.75 to <1.5 = partly controlled, and mean ACQ score ≥1.5 = uncontrolled; total ACT score >19 = well-controlled; total ACT score >15 to ≤19 = partly controlled, and total ACT score ≤15 = uncontrolled. In cases in which results from more than 1 control assessment were recorded, the prioritization was (1) GINA control category, (2) ACT score, and (3) ACQ score. *ACT*, Asthma Control Test; *ACQ*, Asthma Control Questionnaire; *ED*, emergency department; *FEV_1*, forced expiratory volume in one second; *GINA*, Global Initiative for Asthma; *HCRU*, health care resource utilization.

trolled asthma at GINA step 4).[25] Subsequent inclusion criteria differed by analysis. For the assessment of biomarker distributions, patients were also required to be biologic-naïve at the time of the assessment and to have available prebiologic information for all 3 biomarkers (BEC, FeNO, and IgE). For the assessment of changes in outcomes from pre- to postbiologic initiation (ie, biologic population), patients were also required to have received a biologic and have pertinent information on at least 1 asthma outcome assessed with ≥24 weeks of follow-up. Those with missing outcome data were excluded, but only from analyses from which their outcome data were missing, as were those with outlier biomarker values (BEC >5000 cells/μL, FeNO >500 ppb, IgE >10,000 IU/mL) (see this article's Online Repository at www.jaci-inpractice.org).

Variables

Collected variables included prebiologic demographic and clinical characteristics, highest prebiologic biomarker values (BEC [cells/μL], FeNO [ppb], and IgE [IU/mL]), and asthma outcomes before and after biologic initiation. Asthma outcomes included annual exacerbation rate, highest postbronchodilator forced expiratory volume in 1 second (FEV_1, L), and asthma control (Table I). An exacerbation was defined as an asthma-related hospital attendance/admission, an asthma-related emergency department (ED) attendance, and/or an acute oral corticosteroid (OCS) course of ≥3 days. Asthma control was categorized as well-controlled, partly controlled, or uncontrolled according to GINA 2023 criteria,[1] Asthma Control Test (ACT),[26] or Asthma Control Questionnaire (ACQ).[27] For countries providing ACQ or ACT scores instead of GINA control categories, conversions were performed as follows: mean ACQ score ≤0.75 = well-controlled, mean ACQ score >0.75 to <1.5 = partly controlled, mean ACQ score ≥1.5 = uncontrolled; total ACT score >19 = well-controlled, total ACT score >15 to ≤19 = partly controlled, total ACT score ≤15 = uncontrolled. In cases in which results from more than 1 asthma

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TABLE II. Prebiologic demographic and clinical characteristics of patients with severe asthma for each biomarker cluster

Cluster	Total	A (T2-low)	B	C	D	E	*P* value (intercluster)	*P* value (adjusted)*
N (%)	3675	602 (16.4)	751 (20.4)	840 (22.9)	1114 (30.3)	368 (10.0)		
Sex								
Female, n (%)	2225 (60.5)	431 (71.6)	421 (56.1)	496 (59.0)	689 (61.8)	188 (51.1)	<.001	<.001
Ethnicity, n (%)	N = 3558	N = 586	N = 726	N = 809	N = 1079	N = 358	<.001	<.001
White	2503 (70.3)	437 (74.6)	500 (68.9)	559 (69.1)	794 (73.6)	213 (59.5)		
Southeast Asian	246 (6.9)	33 (5.6)	53 (7.3)	52 (6.4)	66 (6.1)	42 (11.7)		
Northeast Asian	200 (5.6)	38 (6.5)	40 (5.5)	39 (4.8)	50 (4.6)	33 (9.2)		
African	133 (3.7)	15 (2.6)	32 (4.4)	36 (4.4)	38 (3.5)	12 (3.4)		
Mixed	19 (0.5)	0 (0.0)	4 (0.6)	9 (1.1)	4 (0.4)	2 (0.6)		
Other	174 (4.9)	11 (1.9)	39 (5.4)	48 (5.9)	58 (5.4)	18 (5.0)		
Unknown	283 (8.0)	52 (8.9)	58 (8.0)	66 (8.2)	69 (6.4)	38 (10.6)		
Age at enrollment (y)							<.001	<.001
Median (Q1, Q3)	54.0 (42.8, 64.0)	54.0 (43.0, 66.0)	52.0 (41.0, 63.0)	54.0 (42.0, 62.0)	55.0 (45.0, 64.2)	51.9 (38.0, 64.9)		
18-40, n (%)	809 (22.0)	129 (21.4)	180 (24.0)	191 (22.8)	203 (18.2)	106 (28.8)		
41-64, n (%)	2091 (56.9)	317 (52.7)	428 (57.0)	505 (60.2)	663 (59.5)	178 (48.4)		
65+, n (%)	774 (21.1)	156 (25.9)	143 (19.0)	143 (17.0)	248 (22.3)	84 (22.8)		
BMI, n (%)							<.001	<.001
Underweight (<18.5)	54 (1.6)	5 (0.9)	11 (1.6)	16 (2.1)	14 (1.4)	8 (2.3)		
Health weight (18.5-24.9)	949 (28.0)	162 (29.3)	176 (25.5)	245 (31.7)	241 (23.4)	125 (36.7)		
Overweight (25-29.9)	1120 (33.1)	162 (29.3)	218 (31.6)	269 (34.8)	349 (33.9)	122 (35.8)		
Obese (30+)	1265 (37.3)	223 (40.4)	285 (41.3)	244 (31.5)	427 (41.4)	86 (25.2)		
Smoking status, n (%)	N = 2907	N = 443	N = 593	N = 696	N = 886	N = 289	.132	.161
Current smoker	147 (5.1)	28 (6.3)	32 (5.4)	21 (3.0)	44 (5.0)	22 (7.6)		
Ex-smoker	867 (29.8)	131 (29.6)	167 (28.2)	201 (28.9)	279 (31.5)	89 (30.8)		
Never smoker	1893 (65.1)	284 (64.1)	394 (66.4)	474 (68.1)	563 (63.5)	178 (61.6)		
Age at onset (y), n (%)	N = 1857	N = 244	N = 402	N = 425	N = 591	N = 195	.014	.022
<18	636 (34.2)	83 (34.0)	166 (41.3)	120 (28.2)	191 (32.3)	76 (39.0)		
18-29	380 (20.5)	47 (19.3)	73 (18.2)	97 (22.8)	127 (21.5)	36 (18.5)		
≥30	841 (45.3)	114 (46.7)	163 (40.5)	208 (48.9)	273 (46.2)	83 (42.6)		
Biomarkers								
BEC (cells/μL)							<.001	<.001
Median (Q1, Q3)	340.0 (180.0, 680.0)	120.0 (100.0, 200.0)	300.0 (130.0, 500.0)	780.0 (406.0, 1100.0)	300.0 (200.0, 510.0)	895.0 (400.0, 1600.0)		
<150, n (%)	860 (23.4)	327 (54.3)	199 (26.5)	65 (7.7)	231 (20.7)	38 (10.3)		
150-300, n (%)	934 (25.4)	240 (40.0)	223 (29.7)	94 (11.2)	335 (30.1)	42 (11.4)		
>300, n (%)	1881 (51.2)	35 (5.8)	329 (43.8)	681 (81.1)	548 (49.2)	288 (78.3)		
FeNO (ppb)							<.001	<.001
Median (Q1, Q3)	32.0 (16.0, 66.0)	14.0 (10.0, 21.0)	28.0 (15.0, 46.0)	93.0 (59.0, 131.3)	32.0 (17.0, 49.0)	48.0 (21.0, 102.3)		
<25, n (%)	1521 (41.4)	520 (86.4)	341 (45.4)	87 (10.4)	458 (41.1)	115 (31.2)		
25-50, n (%)	903 (24.6)	82 (13.6)	251 (33.4)	95 (11.3)	399 (35.8)	76 (20.7)		

>50, n (%)	1251 (34.0)	0 (0.0)	159 (21.2)	658 (78.3)	257 (23.1)	177 (48.1)		
IgE (IU/mL)							<.001	<.001
Median (Q1, Q3)	161.0 (54.5, 452.0)	27.6 (12.4, 52.0)	580.0 (420.0, 879.0)	191.0 (95.0, 307.3)	103.0 (48.4, 158.0)	1770.0 (820.0, 2795.0)		
<150, n (%)	1762 (47.9)	602 (100.0)	0 (0.0)	339 (40.4)	798 (71.6)	23 (6.2)		
150-400, n (%)	637 (17.3)	0 (0.0)	33 (4.4)	278 (33.1)	316 (28.4)	10 (2.7)		
>400, n (%)	1276 (34.7)	0 (0.0)	718 (95.6)	223 (26.5)	0 (0.0)	335 (91.0)		
Prebiologic asthma-related outcomes								
LTOCS		N = 599	N = 749	N = 839	N = 1110	N = 365	<.001	<.001
Yes, n (%)	925 (25.2)	123 (20.4)	164 (21.8)	277 (33.0)	282 (25.3)	79 (21.5)		
Exacerbation rate, n (%)	N = 3472	N = 577	N = 709	N = 799	N = 1045	N = 342	<.001	<.001
0	1464 (42.2)	324 (56.2)	297 (41.9)	269 (33.7)	450 (43.1)	124 (36.3)		
1	729 (21.0)	112 (19.4)	144 (20.3)	192 (24.0)	202 (19.3)	79 (23.1)		
2	382 (11.0)	46 (8.0)	89 (12.6)	95 (11.9)	103 (9.9)	49 (14.3)		
3+	897 (25.8)	95 (16.5)	179 (25.2)	243 (30.4)	290 (27.8)	90 (26.3)		
$ppFEV_1$†	N = 2929	N = 473	N = 611	N = 660	N = 885	N = 300	.002	.004
<80%, n (%)	1829 (62.4)	267 (56.4)	414 (67.8)	425 (64.4)	543 (61.4)	182 (60.7)		
FEV_1/FVC†	N = 3067	N = 490	N = 631	N = 710	N = 917	N = 319	<.001	.001
<0.7, n (%)	1640 (53.5)	218 (44.5)	346 (54.8)	397 (55.9)	514 (56.1)	172 (53.9)		
Asthma control‡, n (%)	N = 2050	N = 281	N = 445	N = 465	N = 669	N = 190	.031	.040
Well-controlled	303 (14.8)	50 (17.8)	72 (16.2)	60 (12.9)	88 (13.2)	33 (17.4)		
Partly controlled	426 (20.8)	72 (25.6)	95 (21.3)	84 (18.1)	132 (19.7)	43 (22.6)		
Uncontrolled	1321 (64.4)	159 (56.6)	278 (62.5)	321 (69.0)	449 (67.1)	114 (60.0)		
Asthma treatment								
Add on to ICS/LABA, n (%)	N = 3626	N = 592	N = 740	N = 835	N = 1093	N = 366		
LAMA	1290 (35.6)	213 (36.0)	266 (35.9)	292 (35.0)	377 (34.5)	142 (38.8)	.639	.656
LTRA	1562 (43.1)	268 (45.3)	317 (42.8)	349 (41.8)	464 (42.5)	164 (44.8)	.672	.672
Theophylline	301 (8.3)	47 (7.9)	60 (8.1)	58 (6.9)	109 (10.0)	27 (7.4)	.175	.207
Macrolide	34 (1.0)	5 (0.8)	6 (0.8)	5 (0.6)	13 (1.2)	5 (1.4)	.621	.655
Biologic, n (%)	N = 2276	N = 249	N = 484	N = 602	N = 681	N = 260	<.001	<.001
Anti-IgE	651 (28.6)	63 (25.3)	226 (46.7)	116 (19.3)	179 (26.3)	67 (25.8)		
Anti−IL-5/5R	1337 (58.7)	135 (54.2)	205 (42.4)	420 (69.8)	424 (62.3)	153 (58.8)		
Anti−IL-4Rα	288 (12.7)	51 (20.5)	53 (11.0)	66 (11.0)	78 (11.5)	40 (15.4)		
Phenotype as defined using previously published methodology[2]								
Eosinophilic phenotype gradient§, n (%)	N = 3187	N = 351	N = 636	N = 840	N = 1000	N = 355	<.001	<.001
Grade 0	64 (2.0)	25 (7.1)	18 (2.8)	0 (0.0)	16 (1.6)	5 (1.4)		
Grade 1	502 (15.8)	136 (38.7)	113 (17.8)	65 (7.7)	160 (16.0)	28 (7.9)		
Grade 2	257 (8.1)	65 (18.5)	61 (9.6)	23 (2.7)	96 (9.6)	12 (3.4)		
Grade 3	2359 (74.1)	125 (35.6)	444 (69.8)	752 (89.5)	728 (72.8)	310 (87.3)		

Predominant biomarker pattern by cluster: A (triple-biomarker-low), B (high IgE + intermediate BEC), C (high BEC + FeNO), D (triple-biomarker-intermediate), and E (triple-biomarker-high).

ACT, Asthma Control Test; *ACQ*, Asthma Control Questionnaire; *BEC*, blood eosinophil count; *BMI*, body mass index; *FeNO*, fractional exhaled nitric oxide; *FEV_1*, forced expiratory volume in one second; *FVC*, forced vital capacity; *GINA*, Global Initiative for Asthma; *ICS*, inhaled corticosteroid; *LABA*, long-acting β_2-agonist; *LAMA*, long-acting muscarinic antagonist; *LTOCS*, long-term oral corticosteroid; *LTRA*, leukotriene receptor antagonist; *OCS*, oral corticosteroid; *ppFEV$_1$*, percent predicted forced expiratory volume in 1 second.
*P values adjusted for multiple comparisons using the Benjamini-Hochberg procedure.
†For FEV_1, postbronchodilator measures were used if available, and prebronchodilator measures otherwise, while ensuring that both pre- and postbiologic measures were either pre- or postbronchodilator. In the subpopulation of patients included in the lung function analysis (N = 2929), postbronchodilator measurements were used for 44.0% patients.
‡Categories defined by GINA 2023 update.[1] For countries providing ACQ or ACT scores instead of GINA control categories, conversions were performed as follows: mean ACQ score ≤0.75 = controlled, mean ACQ score >0.75 to <1.5 = partly controlled, and mean ACQ score ≥1.5 = uncontrolled; total ACT score >19 = well-controlled, total ACT score >15 to ≤19 = partly controlled, and total ACT score ≤15 = uncontrolled. In cases in which results from more than 1 control assessment were recorded, the prioritization was: (1) GINA control category, (2) ACT score, and (3) ACQ score.
§Categorized according to the likelihood of eosinophilic phenotype using a previously published gradient eosinophilic algorithm, predefined and agreed by expert consensus and based on highest BEC, long-term oral corticosteroid use, elevated fractional exhaled nitric oxide, nasal polyps, and adult-onset asthma.[2]

control assessment were recorded, the prioritization was (1) GINA control category, (2) ACT score, and (3) ACQ score. HCRU outcomes included asthma-related hospitalizations, ED visits, and invasive ventilations.

Study outcomes and statistics

The statistical analysis plan was predefined. STATA version 18 (StataCorp LLC, College Station, Texas) and R version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria) were used to conduct all statistical analyses, except the model-based clustering, which was performed using the R package mclust.[28]

Biomarker cluster distribution. Gaussian finite mixture models (GFMM) were first fitted to the biomarker data for a range of covariance parameterizations, with the number of mixture components (clusters) increased from 1 to 9 (Figure E2, *A*, available in this article's Online Repository at www.jaci-inpractice.org). A 5-cluster solution was selected to avoid overfitting, corresponding to the number of clusters for which there was flattening of the Bayesian Information Criterion gradient for the volume, shape, and orientation model variables (Figure E2, *B*, available in this article's Online Repository at www.jaci-inpractice.org). Biomarker clusters (for those with data for all 3 biomarkers) were then identified using a 5-component GFMM (see this article's Online Repository at www.jaci-inpractice.org).[29] Patients were assigned to the data-derived cluster that they were "closest to," from cluster A (low T2 invovlement) to cluster E, and described according to predominant biomarker patterns and median biomarker levels agreed on by working group consensus.

Sensitivity analyses were conducted to assess the robustness of the clustering to distributional assumptions about the mixture components. In the first approach, GFMM were fitted to the log-transformed biomarkers, to reduce the impact of outliers and skewness in the biomarker distributions. In the second approach, finite mixture models with components belonging to the class of scale mixtures of the skew-normal distribution (FMSMSN models) were fitted to the standardized biomarkers to allow for non-Gaussian mixture components.[30] Biomarker cluster distribution excluding IgE was also assessed.

Pre- to postbiologic changes in asthma and HCRU outcomes by cluster and relative to T2-low. Changes in asthma and HCRU outcomes from pre- to postbiologic initiation were assessed by cluster in those who subsequently initiated biologics. Initially, univariate analyses were conducted in which descriptive statistics were presented before and after biologic therapy along the T2-involvement gradient. Continuous outcome variables that were not skewed (ie, exacerbation rate and FEV_1) were summarized as means and standard deviations. Categorical variables (ie, uncontrolled asthma) were summarized as numbers and percentages. Multivariable analysis was conducted with cluster A (ie, T2-low) as reference. Annual exacerbation rate and FEV_1 (L) were analyzed with linear regression models, asthma control with logistic regression for odds of uncontrolled asthma, and HCRU outcomes with negative binominal regression, as there was evidence of overdispersion. Goodness-of-fit was measured using the coefficient of determination (R-squared) for the linear regression models and the Hosmer-Lemeshow test for logistic regression. A likelihood ratio χ^2 test was used to compare the goodness-of-fit of the negative binomial regression model with a Poisson regression model. Residual analysis was used to test the assumptions of the regression models. All models were adjusted for

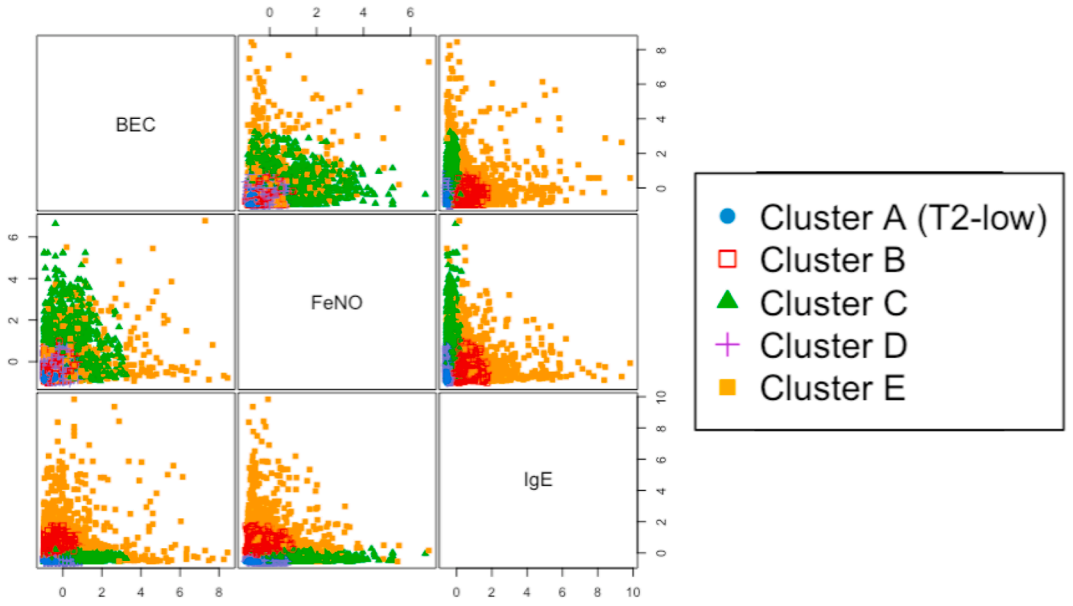

FIGURE 1. Biomarker clusters identified using the Gaussian finite mixture model (n = 3675). Clusters were ordered along a gradient from A (T2-low) to E (T2-high) and described by expert consensus according to the predominant biomarker pattern: cluster A (triple-biomarker-low), cluster B (high IgE + intermediate BEC), cluster C (high BEC + FeNO), cluster D (triple-biomarker-intermediate), and cluster E (triple-biomarker-high). Cluster D was described as triple-biomarker-intermediate as median biomarker levels for patients assigned to this cluster were generally somewhere between those in clusters A and E. Pairwise scatter plot for the 3 biomarkers. The vertical axis is BEC in the first row, FeNO in the second row, and IgE in the third row. The horizontal axis is BEC in the first column, FeNO in the second column, and IgE in the third column. For example, the top-right panel shows a plot of BEC measurements on the vertical axis against IgE values on the horizontal axis. Each biomarker is represented by a *Z*-score so that all biomarker scores are on the same scale. This ensures that equal weighting is given to each biomarker. Cluster membership is displayed with a color coding (as defined in the legend). The naming convention for the 5 clusters is the same as in Tables II and III. *BEC*, Blood eosinophil count; *FeNO*, fractional exhaled nitric oxide.

prebiologic outcome, age, sex, prebiologic LTOCS use, and country. Results were also stratified by biologic class (anti-IgE, anti−IL-5/5 receptor [R], and anti−IL-4Rα). *P* values <.05 were considered statistically significant. We accounted for multiplicity, when conducting cluster comparisons of prebiologic demographic and clinical characteristics and comorbidities by calculating adjusted *P* values to control the false discovery rate using the Benjamini-Hochberg procedure. Our analyses were based on complete cases assuming that biomarker data were missing completely at random.

Power. Statistical power for our primary outcome analysis using finite mixture models was estimated in a simulation study. First, data for the 3 preselected biomarkers (blood eosinophils, FeNO, and IgE) were simulated from multivariate Gaussian distributions with overlapping means and variances. The simulations were based on 4 underlying severe asthma clusters (conceptualized as "low T2," "high blood eosinophils," "high FeNO," and "triple biomarker high"). This choice was based on prior studies that provide evidence for 3 to 5 underlying phenotypes.[10,31] The standardized cluster means were (0, 0, 0), (2, 1, 1), (1, 2, 0), and (2, 2, 2), respectively. It was further assumed that there was moderate overlap between clusters (not perfectly separable) to reflect realistic biomarker patterns. The covariance matrix was $\begin{bmatrix} 1 & 0.4 & 0.3 \\ 0.4 & 1 & 0.4 \\ 0.3 & 0.4 & 1 \end{bmatrix}$. Power was estimated based on how frequently the "mclust" model in R was able to recover 3 to 4 clusters across varying sample sizes. Our simulations showed that 80% power was achieved for sample sizes of >2000, considerably below the available sample of n = 3675 eligible patients in ISAR.

RESULTS

Subject disposition and characteristics

As of March 2023, ISAR included data on 15,174 adult patients with severe asthma. Most patients were excluded from this analysis because of missing data for at least 1 biomarker; however, 3675 patients were eligible (female: 60.5%, median age at enrollment: 54.0 years) and included in the analysis of biomarker clusters, and 2276 were included in the analysis of pre- to postbiologic changes in asthma outcomes (Table E1 and Figure E3, available in this article's Online Repository at www.jaci-inpractice.org). Prebiologic demographic and clinical characteristics are presented in Table II and Table E2 (available in this article's Online Repository at www.jaci-inpractice.org).

Distributions: biomarker clusters

Five biomarker clusters were identified by our model (clusters A-E) and described according to predominant biomarker pattern and median biomarker levels: cluster A (T2-low, triple-biomarker-low), cluster B (high IgE + intermediate BEC),

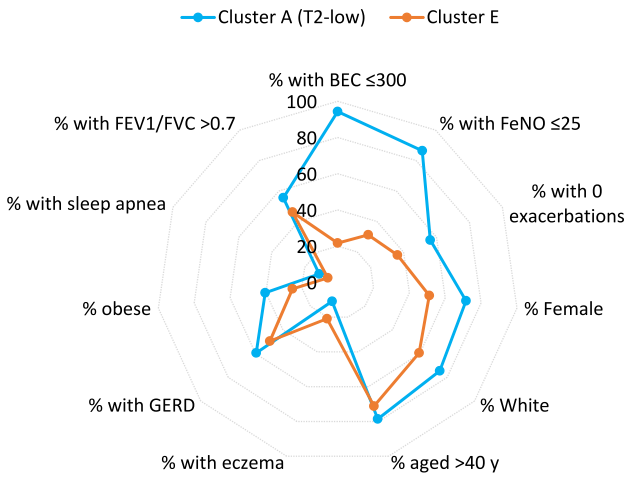

FIGURE 2. Clinical variable distribution pattern for cluster A (T2-low; n = 602) and cluster E (n = 368). Cluster A (T2-low): predominantly low median values for BEC, FeNO, and IgE. cluster E: predominantly high median values for BEC, FeNO, and IgE. *BEC*, Blood eosinophil count; *FeNO*, fractional exhaled nitric oxide; *FEV_1*, forced expiratory volume in 1 second; *FVC*, forced vital capacity; *GERD*, gastroesophageal reflux disease.

cluster C (high BEC + FeNO), cluster D (triple-biomarker-intermediate), and cluster E (triple-biomarker-high) (Figure 1). Cluster D was best described as triple-biomarker-intermediate as median levels for all 3 biomarkers for patients assigned to this cluster were generally intermediate between cluster A and cluster E (ie, 300 cells/μL, 32 ppb, and 103 IU/mL for BEC, FeNO and IgE, respectively). Similar results were noted, when IgE was excluded from the analysis (Figure E4, available in this article's Online Repository at www.jaci-inpractice.org).

Sensitivity analysis

Although log-transformation of biomarker distributions reduced skewness (Figure E5, *A-C*, available in this article's Online Repository at www.jaci-inpractice.org), the resulting 5 GFMM clusters were of limited clinical utility for studying the triple-biomarker-low phenotype (Figure E6, available in this article's Online Repository at www.jaci-inpractice.org). Using FMSMSN models to allow for non-Gaussian mixture components provided a similar 5-cluster solution as that provided by GFMM (Figure E7, available in this article's Online Repository at www.jaci-inpractice.org). Cluster structures were broadly similar, when stratified according to LTOCS status at index date (Figures E8 and E9, available in this article's Online Repository at www.jaci-inpractice.org). A similar biomarker profile was also noted in the triple-biomarker-low cluster (ie, cluster A) in both LTOCS users and nonusers at index date (Table E3, available in this article's Online Repository at www.jaci-inpractice.org).

Demographic and clinical characteristics of biomarker clusters

Of 3675 patients included in the analysis, 16.4% (n = 602), 20.4% (n = 751), 22.9% (n = 840), 30.3% (n = 1114), and 10.0% (n = 368) were in clusters A, B, C, D, and E, respectively (Table II). The prevalence of LTOCS use ranged from

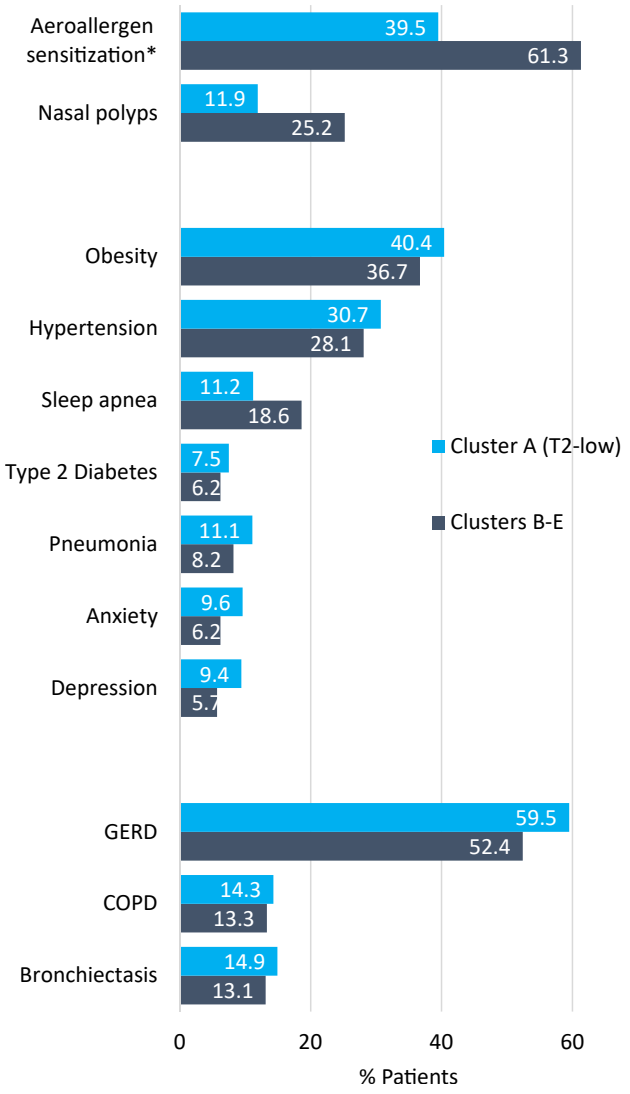

FIGURE 3. Comorbidity footprint of cluster A (T2-low) versus other clusters. See Table III for N numbers. *By skin prick test or serum allergy testing. Other clusters include cluster B (high IgE + intermediate BEC), cluster C (high BEC + FeNO), cluster D (triple-biomarker-intermediate), and cluster E (triple-biomarker-high). Cluster D was described as triple-biomarker-intermediate as median biomarker levels for patients assigned to this cluster were generally between those in clusters A and E. *COPD*, Chronic obstructive pulmonary disease; *GERD*, gastroesophageal reflux disease.

20.4% (n = 123/599) in cluster A to 33.0% (n = 277/839) in cluster C.

Those in cluster A (T2-low) tended to be female and White, have a percent predicted FEV_1 ($ppFEV_1$) >80%, and have a lower exacerbation rate in the previous year than those in the other clusters. This cluster had the highest proportion of those who subsequently initiated anti—IL-4Rα biologic therapy (Table II; Figure 2). They were also more likely than the other clusters to have GERD and certain other potentially OCS-related comorbidities, but were less likely to have any

TABLE III. Prebiologic prevalence of comorbidities of patients with severe asthma for each biomarker cluster

Cluster	A (T2-low)	B	C	D	E	*P* value (intercluster)	*P* value (adjusted)*
Comorbidities mimicking asthma exacerbations							
GERD, n (%)	N = 412 245 (59.5)	N = 418 228 (54.6)	N = 501 243 (48.5)	N = 630 348 (55.0)	N = 208 103 (49.5)	.015	.022
Bronchiectasis, n (%)	N = 423 63 (14.9)	N = 419 64 (15.3)	N = 511 61 (11.9)	N = 645 68 (10.5)	N = 209 41 (19.6)	.006	.009
COPD, n (%)	N = 421 60 (14.3)	N = 417 56 (13.4)	N = 500 57 (11.4)	N = 646 94 (14.6)	N = 212 29 (13.7)	.608	.655
Potentially T2-related comorbidities							
Allergic rhinitis, n (%)	N = 528 230 (43.6)	N = 573 333 (58.1)	N = 639 321 (50.2)	N = 857 437 (51.0)	N = 313 179 (57.2)	<.001	<.001
CRS ± NP, n (%)	N = 598 225 (37.6)	N = 748 299 (40.0)	N = 833 473 (56.8)	N = 1108 520 (46.9)	N = 364 187 (51.4)	<.001	<.001
NP, n (%)	N = 587 70 (11.9)	N = 726 134 (18.5)	N = 816 261 (32.0)	N = 1076 266 (24.7)	N = 362 91 (25.1)	<.001	<.001
Eczema, n (%)	N = 588 64 (10.9)	N = 726 91 (12.5)	N = 819 76 (9.3)	N = 1078 109 (10.1)	N = 363 76 (20.9)	<.001	<.001
Aeroallergen sensitization by SPT or serum allergy testing, n (%)	N = 324 128 (39.5)	N = 406 295 (72.7)	N = 425 223 (52.5)	N = 595 342 (57.5)	N = 204 139 (68.1)	<.001	<.001
Dust mite, n (%)	N = 323 76 (23.5)	N = 403 167 (41.4)	N = 424 97 (22.9)	N = 92 190 (32.1)	N = 204 95 (46.6)	<.001	<.001
Pollens, n (%)	N = 324 65 (20.1)	N = 406 160 (39.4)	N = 425 119 (28.0)	N = 595 185 (31.1)	N = 204 71 (34.8)	<.001	<.001
Mold, n (%)	N = 324 30 (9.3)	N = 406 88 (21.7)	N = 425 50 (11.8)	N = 595 78 (13.1)	N = 204 44 (21.6)	<.001	<.001
Animals, n (%)	N = 324 58 (17.9)	N = 406 154 (37.9)	N = 425 127 (29.9)	N = 595 169 (28.4)	N = 204 61 (29.9)	<.001	<.001
Potentially OCS-related comorbidities							
Type 2 diabetes, n (%)	N = 560 42 (7.5)	N = 692 45 (6.5)	N = 771 38 (4.9)	N = 1002 63 (6.3)	N = 344 27 (7.8)	.269	.300
Depression, n (%)	N = 562 53 (9.4)	N = 697 45 (6.5)	N = 782 46 (5.9)	N = 1012 52 (5.1)	N = 341 19 (5.6)	.019	.026
Anxiety, n (%)	N = 562 54 (9.6)	N = 698 40 (5.7)	N = 779 41 (5.3)	N = 1011 71 (7.0)	N = 341 22 (6.5)	.022	.030
Pneumonia, n (%)	N = 504 56 (11.1)	N = 535 38 (7.1)	N = 602 48 (8.0)	N = 785 67 (8.5)	N = 299 29 (9.7)	.191	.219
Hypertension, n (%)	N = 391 120 (30.7)	N = 378 111 (29.4)	N = 474 102 (21.5)	N = 571 183 (32.1)	N = 194 58 (29.9)	.003	.005
Sleep apnea, n (%)	N = 579 65 (11.2)	N = 717 125 (8.5)	N = 809 142 (7.8)	N = 1049 225 (10.4)	N = 351 52 (6.0)	.024	.031
Obesity, n (%)	N = 552 223 (40.4)	N = 690 285 (41.3)	N = 774 244 (31.5)	N = 1031 427 (41.4)	N = 341 86 (25.2)	<.001	<.001

Predominant biomarker pattern by cluster: A (triple-biomarker-low), B (high IgE + intermediate BEC), C (high BEC + FeNO), D (triple-biomarker-intermediate), and E (triple-biomarker-high).

BEC, Blood eosinophil count; *COPD*, chronic obstructive pulmonary disease; *CRS*, chronic rhinosinusitis; *FeNO*, fractional exhaled nitric oxide; *GERD*, gastroesophageal reflux disease; *NP*, nasal polyps; *OCS*, oral corticosteroid; *SPT*, skin prick test.

**P* values adjusted for multiple comparisons using the Benjamini-Hochberg procedure.

diagnosed allergy (aeroallergen sensitization by skin prick testing or serum allergy testing), allergic rhinitis, nasal polyps (NP), or CRS with or without NP (Figure 3; Table III). A full summary of all comorbidities by cluster is provided in Table E4 (available in this article's Online Repository at www.jaci-inpractice.org). Characteristics of the other clusters are presented in Tables II and III and Figure 2.

Pre- to postbiologic changes in asthma outcomes by cluster and relative to cluster A (T2-low)

Improvements from pre- to postbiologic initiation were noted for exacerbation rates, lung function, and asthma control, irrespective of the degree of T2 involvement, as assessed by univariate analysis (Figure E10, *A-C*; Table E5, available in this article's Online Repository at www.jaci-inpractice.org).

The degree of improvement in the other clusters compared with cluster A (as assessed by multivariable analyses) varied by cluster and by asthma outcome (Figure 4, *A-C*). Reductions in exacerbation rates (assessed by the linear regression model) were not significantly different for any of clusters with evidence of T2 involvement (ie, clusters B-E) compared with cluster A (Figure 4, *A*). However, patients in cluster C (ie, high BEC + FeNO) had a significantly greater increase in FEV_1 than those in cluster A (difference 0.16 L [95% confidence interval (CI): 0.08,

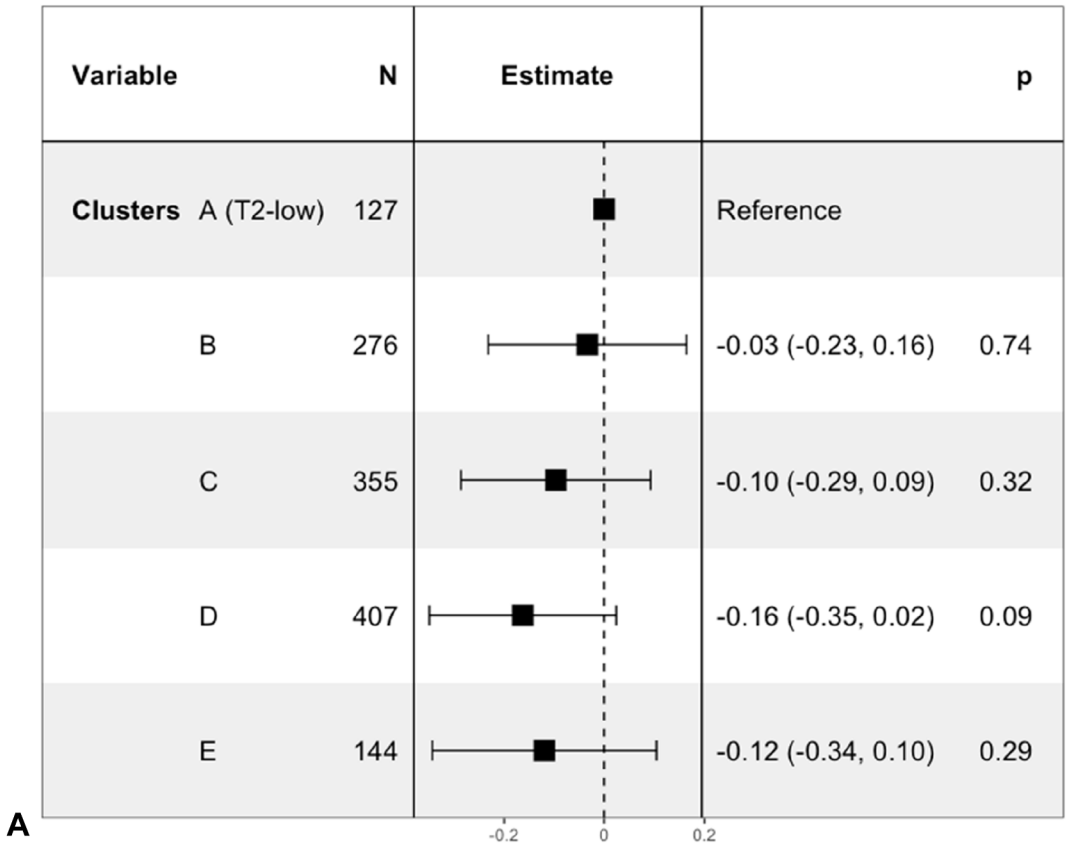

FIGURE 4. Change in (**A**) annualized exacerbation rate, (**B**) forced expiratory volume in 1 second (FEV_1, L), (**C**) uncontrolled asthma status, and annualized (**D**) asthma-related hospitalization (**E**) emergency department visit, and (**F**) invasive ventilation rates from pre- to postbiologic initiation relative to cluster A (T2-low). The data are presented as relative risk with 95% confidence intervals adjusted for prebiologic outcome, age, sex, country (except F as some countries had no patients who had an invasive ventilation), and prebiologic long-term oral corticosteroid. Clusters identified using the 5-component Gaussian finite mixture model (GFMM). See the section on biomarker cluster distribution above for more details. Clusters were from A (T2-low) to E and described by expert consensus according to the predominant biomarker pattern and median concentration: cluster A (T2-low, triple-biomarker-low), cluster B (high IgE + intermediate BEC), cluster C (high BEC + FeNO), cluster D (triple-biomarker intermediate), and cluster E (triple-biomarker-high). Cluster D was described as triple-biomarker-intermediate as median biomarker levels for patients assigned to this cluster were generally between those in clusters A and E. Changes in asthma and health care resource utilization (HCRU) outcomes from pre- to postbiologic initiation were assessed by cluster, with cluster A as reference. Annual exacerbation rate and FEV_1 (L) were analyzed with linear regression models, asthma control with logistic regression for odds of uncontrolled asthma, and HCRU outcomes with negative binominal regression, as there was evidence of overdispersion. Control categories were defined by GINA 2023 update.[1] For countries providing ACQ or ACT scores instead of GINA control categories, conversions were performed as follows: mean ACQ score $\leq$0.75 = well-controlled, mean ACQ score >0.75 to <1.5 = partly controlled, and mean ACQ score $\geq$1.5 = uncontrolled; total ACT score >19 = well-controlled, total ACT score >15 to $\leq$19 = partly controlled, and total ACT score $\leq$15 = uncontrolled. In cases in which results from more than 1 control assessment were recorded, the prioritization was (1) GINA control category, (2) ACT score, and (3) ACQ score. *ACT*, Asthma Control Test; *ACQ*, Asthma Control Questionnaire; *BEC*, blood eosinophil count; *FeNO*, fractional exhaled nitric oxide; *GINA*, Global Initiative for Asthma.

0.25]; $P < .001$, linear regression model); that is, the expected increase in FEV_1 was 0.16 L higher for cluster C compared with cluster A after accounting for baseline FEV_1, age, sex, and LTOCS use, and country (Figure 4, *B*). A similar pattern of greater improvement in lung function was also noted in cluster E (ie, triple-biomarker-high) compared with cluster A (difference: 0.10 L [95% CI: 0.00, 0.20]; $P = .05$). The odds of having uncontrolled asthma (assessed by logistic regression) were lower (approximately 0.6) for all clusters compared with cluster A, although reduced risk was not statistically significant (Figure 4, *C*). Broadly similar patterns were observed for each biologic class (Figures E11-E13, available in this article's Online Repository at www.jaci-inpractice.org). However, there was a trend for a greater reduction in exacerbation rates and greater

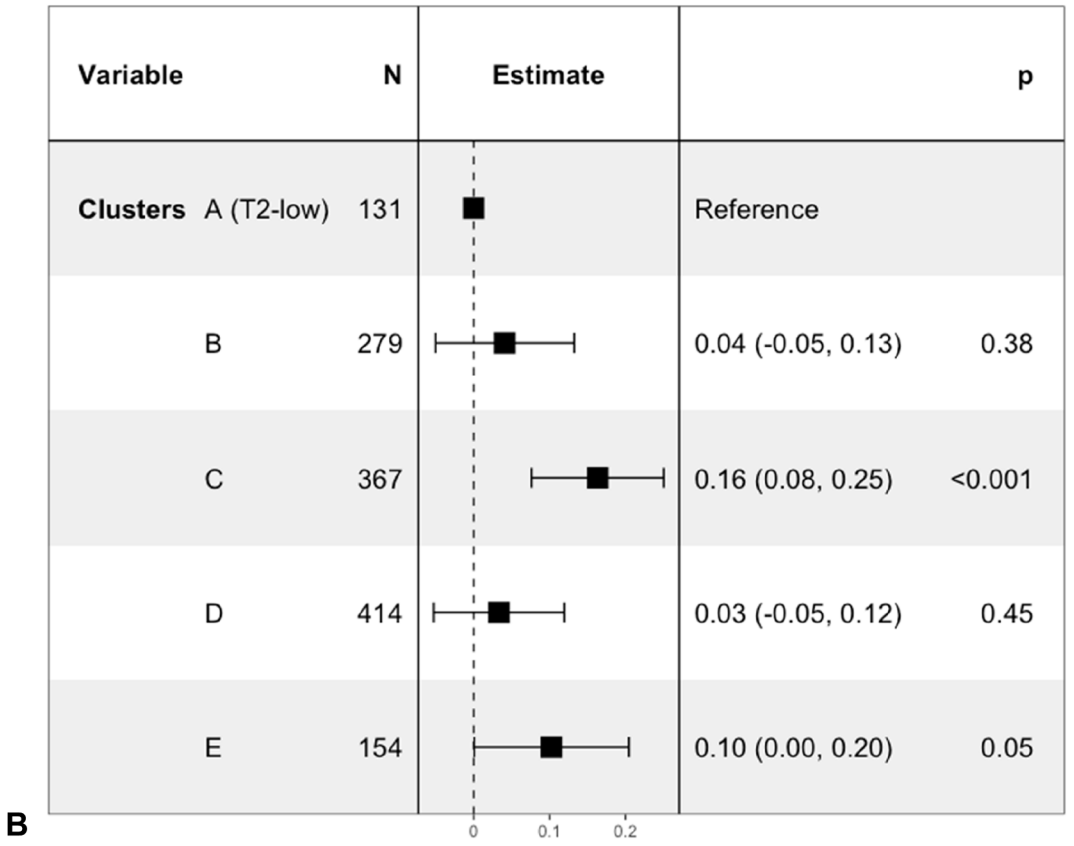

FIGURE 4. (*CONTINUED*).

improvements in lung function and asthma control status for anti—IL-5/5R for all clusters compared with cluster A (ie, across the T2 spectrum).

Pre- to postbiologic initiation changes in health care utilization by cluster and relative to cluster A (T2-low)

Although HCRU was low for all clusters after biologic initiation, reductions from pre- to postbiologic initiation were noted for hospitalizations, ED visits, and rates of invasive ventilation, as assessed by negative binomial regression (Figure E14, *A-C*; Table E6, available in this article's Online Repository at www.jaci-inpractice.org).

However, the degree of reduction in HCRU in the other clusters tended to be greater compared with cluster A, particularly for hospitalizations and ED visits, as assessed by multivariable analyses and adjusting for baseline values, age, sex, and LTOCS use (Figure 4, *D-F*). Patients in clusters B, C, D, and E experienced 46%, 37%, 25%, and 43% greater reductions in hospital admissions for asthma, respectively, compared with cluster A, which were statistically significant for all (Figure 4, *D*). A similar pattern of greater reductions in ED visits was observed for all T2 clusters versus cluster A, a 47%, 32%, 40%, and 63% reduction for clusters B, C, D, and E, respectively (Figure 4, *E*). There was also a general trend for greater reductions in the need for invasive ventilation for clusters B, C, and E, although being not significant compared with cluster A (Figure 4, *F*).

DISCUSSION

Our results identified a triple-T2-biomarker-low asthma cluster in a large, global, real-life, adult severe asthma population. A hypothesis-free, data-driven approach to phenotypic classification could provide added insight into conventional methods based on predefined thresholds of biomarkers, informed by randomized clinical trials and biologic prescribing criteria. Our results also feed into the ongoing debate of the utility of artificial intelligence in diagnostics. Using a data-driven approach, we found that asthma phenotypes presented along a continuum of T2-involvement, from triple-biomarker-low to triple-biomarker-high, and identified distinct phenotypic characteristics associated with these clusters. Although available biologics considered in this study targeting the T2-inflammatory pathway had a positive impact along the entire gradient of T2 involvement, the pre- to postbiologic effects varied by outcome, cluster, and biologic class and were lower in the triple-biomarker-low cluster (ie, differential response). There was a trend for greater pre- to postbiologic improvements in all asthma outcomes after anti—IL-5/5R biologic initiation for all clusters compared with cluster A (ie, T2-low), which were not observed for anti-IgE or anti—IL-4Rα therapies. These findings highlight the importance of characterizing

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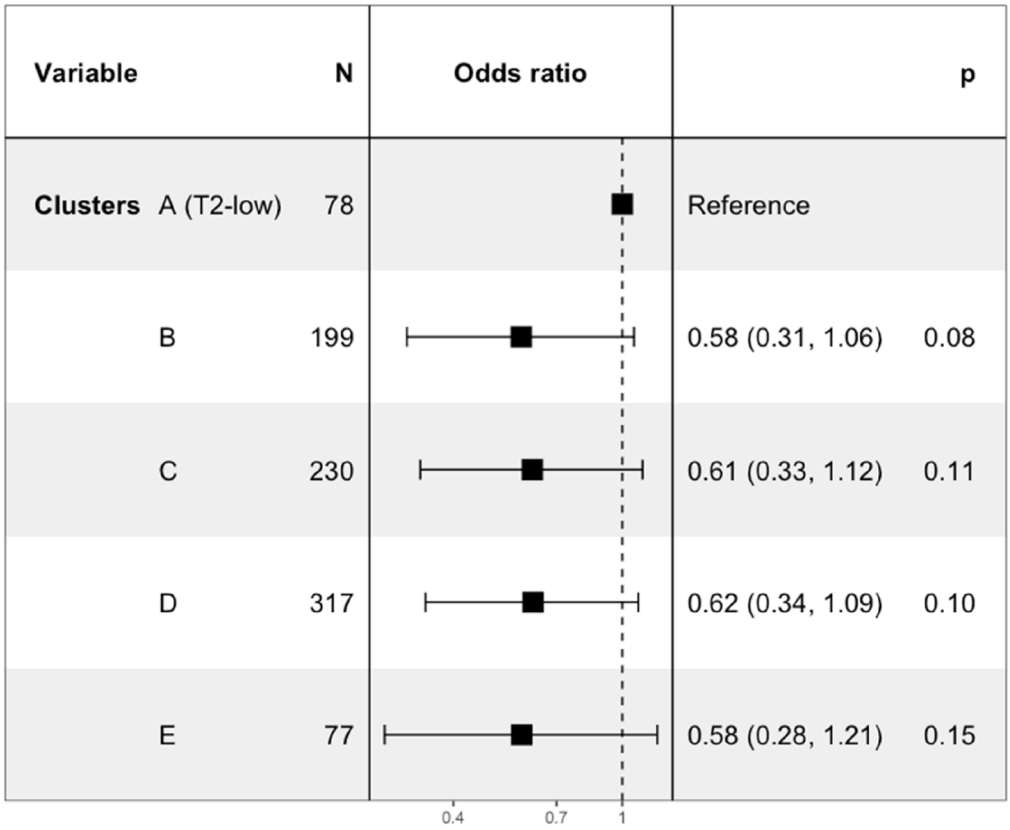

FIGURE 4. (*CONTINUED*).

phenotypes along a gradient of T2 involvement as part of a personalized approach to disease management, emphasize the need to align available treatment options with goals of care due to phenotype-specific responses to available biologics, and call for treatments specifically tailored for the triple-biomarker-low phenotype.

Overall, 16% of patients included in our severe asthma cohort were in the T2-low cluster (cluster A) as indicated by low median values of each biomarker assessed. Interestingly, 5.8% of patients allocated to cluster A had a BEC >300 cells/μL. Because our clusters were constructed using a data-driven (and arguably a more unbiased) approach rather than empirically using predefined clinical thresholds, patients were assigned to clusters along a spectrum of T2 involvement according to how closely their biomarker values aligned with the center point of each cluster. Notably, no patients in cluster A in our study had a BEC >500 cells/μL, an FeNO >50 ppb, or an IgE >150 IU/mL. Moreover, studies at the national level using predefined BEC and FeNO cutoffs reported a similar prevalence of T2-low asthma as that reported for cluster A in the current analysis.[4,11,32] It is worth noting that real-world T2 biomarker distributions vary between registries.[33-35] This may be due to differences in registry entry criteria (eg, some registries contain only biologic-treated patients), differences in asthma treatment patterns, or use of single biomarker measurements, the former potentially biasing toward T2-high and the latter likely biasing toward T2-low disease.

Binary stratification of asthma as T2-high and T2-low is perhaps an oversimplification of this highly complex and heterogeneous disease. In an effort to more precisely define the asthma phenotype, Heaney and et al[2] developed an algorithm to describe asthma phenotype along a gradient of eosinophil involvement and reported an 82.7% prevalence of eosinophilic phenotype among patients with severe asthma. The remaining 17.3% could be categorized according to a gradient of eosinophilic involvement; 8.5% described as "likely" and 8.7% described as "least likely" or "unlikely" to have eosinophilic asthma.[2] This prevalence of patients at the lower likelihood of eosinophilic gradient (8.7%) is slightly lower than the prevalence of triple-biomarker-low asthma reported in the current study (cluster A: 16%) and most likely reflects differences in categorization criteria; patients with noneosinophilic asthma in the Heaney et al study were required to have a BEC <150 cells/μL, FeNO <25 ppb, and no incidence of NP, adult onset asthma, or LTOCS use.[2] Our data, therefore, substantiate the prevalence rate of T2-low asthma in a global severe asthma population, further building on the eosinophilic gradient approach of Heaney et al,[2] to define a spectrum of T2 involvement, based on the expanded biomarker profile that can be an adjunct to the eosinophil gradient approach.

As T2-low asthma is currently not well understood, knowledge of associated clinical characteristics aids in identification and management of this phenotype. In the current study, compared with other clusters, patients in cluster A were more

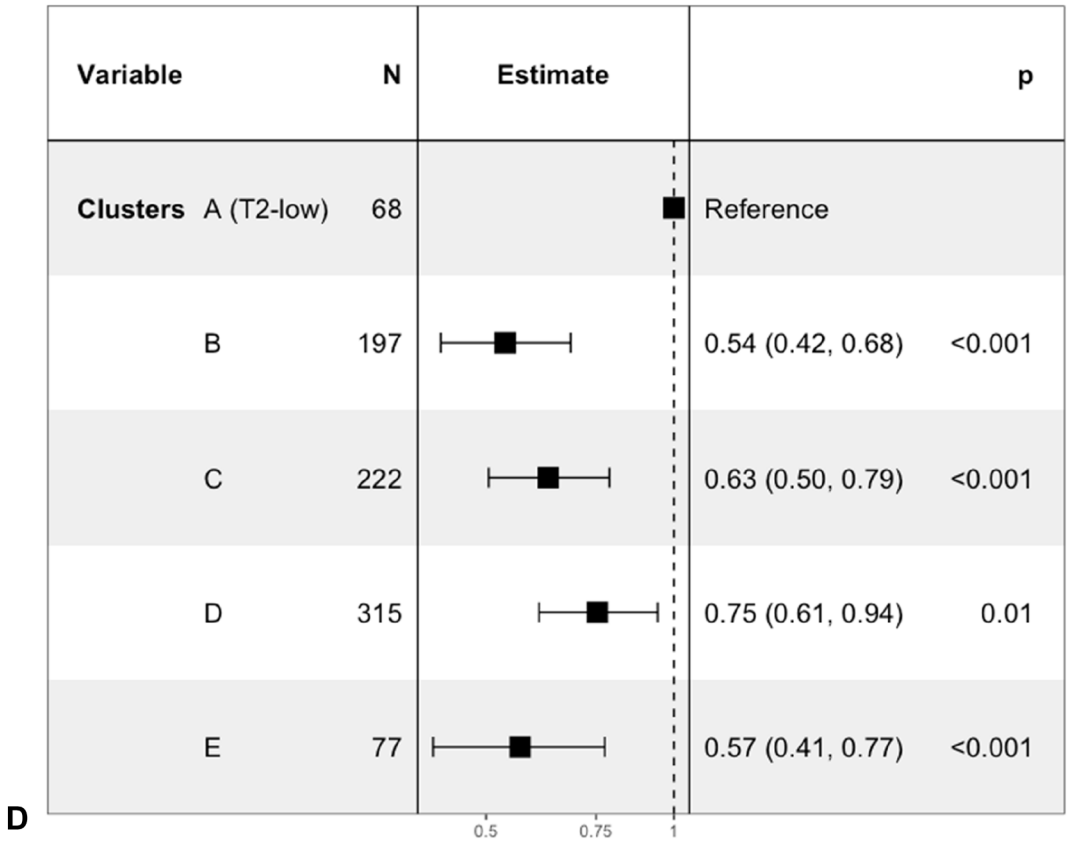

FIGURE 4. (*CONTINUED*).

likely to be female and White, have a ppFEV$_1$ >80%, have a lower exacerbation rate in the previous year, and present with GERD and other potentially OCS-related comorbidities, similar to characteristics reported by others.[12] Importantly, these key comorbidities can exacerbate or mimic asthma symptoms, thereby driving corticosteroid overuse, which may result in the appearance of a T2-low phenotype. An association with potentially OCS-related comorbidities has previously been reported by the FASE-CPHG study.[36] Likewise, others have reported more female patients (65.5% vs 36.2%) and patients with older age of asthma onset (47 vs 16 years) with nonatopic relative to atopic asthma[37] and a tendency of noneosinophilic disease in female patients, obese individuals, and those admitted to hospital for asthma.[38] Those in cluster A were also less likely to have any diagnosed allergy, allergic rhinitis, or NP, further supporting a comparably T2-low phenotype. Our study is arguably the most comprehensive phenotypic assessment of severe asthma, as it includes a wide range of demographic, biomarker, and clinical characteristics and considers both treatment and comorbidity profiles.

The lack of definitive characterization of a T2-low cluster and the current absence of specific biomarkers and molecular targets have made precision care challenging.[6] Notwithstanding these challenges—and somewhat surprisingly—our analysis showed benefits for anti-IgE, anti−IL-5/5R, and anti−IL-4Rα biologic treatment in cluster A, particularly for exacerbations (univariate analysis; see Figure E10 in this article's Online Repository at www.jaci-inpractice.org). Patients with minimal evidence of T2 inflammation may be prescribed a biologic therapy for various reasons, including potential T2-high masking effect of LTOCS, biologic indications for OCS-dependent asthma in certain countries, and suspicion for T2-driven asthma despite lower biomarkers. However, these findings may be indicative of regression toward the mean or could indicate that a proportion of patients in cluster A have some level of clinically relevant activation of T2-inflammatory pathways (ie, biologics are targeting residual T2 inflammation) or biologics are affecting a T2-low pathology or molecular pathway. Notably, those with evidence of greater T2 involvement tended to experience a greater improvement in lung function and had significantly greater reductions in asthma-related hospitalizations and ED visits, compared with patients in cluster A.

Although previous research has reported evidence of a strong association between prebiologic BEC and postbiologic improvement in exacerbations,[8,14] in our multivariable analysis, we found that exacerbation rate reductions associated with biologics overall were not different for any of T2-high clusters compared with cluster A (T2-low), although some differences in exacerbation rate were noted for clusters C and D relative to cluster A for those patients who received anti−IL-5/5R. Our results do not contradict previous findings but are a consequence of assessing the relationship between prebiologic biomarker concentration and exacerbations in a different way (ie, the reduction in exacerbation rate was relative to the prebiologic status, not compared with control).

In other studies, evidence of a beneficial effect of biologics for T2-low asthma is conflicting for omalizumab.[39,40] By contrast, benralizumab and dupilumab have been shown to significantly

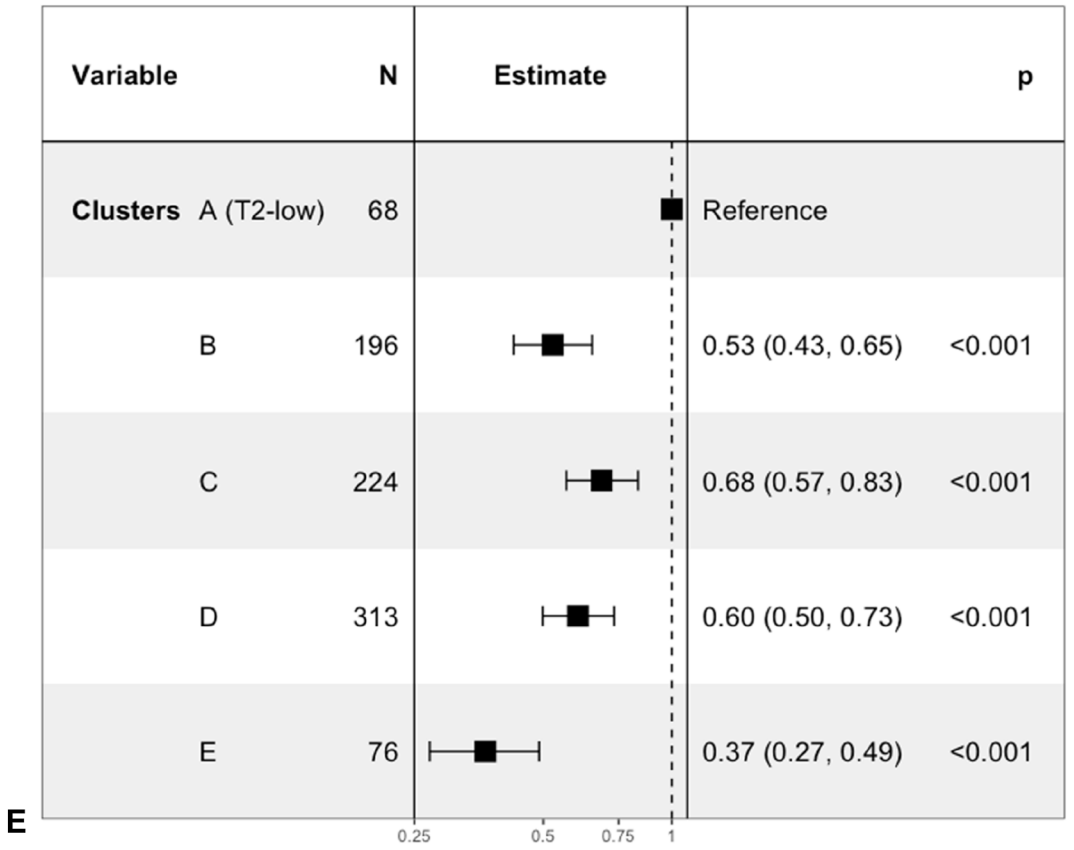

FIGURE 4. (*CONTINUED*).

decrease exacerbation rates in patients with BEC <300 cells/μL.[41-43] There was a higher prevalence of dupilumab users in our T2-low cluster compared with clusters with greater T2 involvement. In addition, in other studies, patients treated with tezepelumab experienced a significant reduction in annualized exacerbations rates compared with placebo, independent of BEC, FeNO, or T2 status, but it was more effective in those with increased BEC and FeNO levels.[18,19,44] As a newer biologic therapy, tezepelumab use has not yet been sufficiently captured by ISAR but will be included in future ISAR datasets. Other therapeutic targets for T2-low asthma include IL-33, IL-1β, IL-17, IL-6, IL-8, TNFα, PDE4, LTB_4, resolvins, apolipoproteins, and type 1 interferons.[14,45] Maintenance treatment with low-dose macrolides (eg, azithromycin)[46,47] has also shown some utility for the management of T2-low asthma, as well as other agents (eg, long-acting muscarinic antagonists), targeted co-morbidity management, and nonpharmacological interventions (eg, smoking cessation, weight reduction, avoidance of environmental/occupational agents, and bronchial thermoplasty).[14]

Limitations of our study include those common to all observational studies including missing data, regression to the mean, and referral bias. Missing biomarker data accounted for much of the attrition; more than 10,000 patients had no biomarker data recorded, highlighting the infrequent use of biomarkers for phenotyping in real life, even in tertiary care. Even in a database as large and comprehensive as ISAR, only single measurements of biomarkers were available for many patients, thus precluding an assessment of mean or median values, or cluster temporal stability. Our chosen approach to handling missing data relies on an assumption that the missing data mechanism is missing completely at random. Further studies are needed with more complete recording of biomarkers to help assess the wider generalizability of our findings. Although some biomarkers may be impacted by LTOCS, the exact timing of biomarker measurement was not captured relative to LTOCS use, and pre-LTOCS biomarker levels were unknown, we found that cluster structures were broadly similar, when stratified according to LTOCS status at index date. Models to assess the pre- to postbiologic changes in asthma and HCRU outcomes by cluster were also adjusted for LTOCS use. Furthermore, sputum eosinophilia was not captured, which may have resulted in more precise biomarker clustering, and all biomarkers were weighted equally in the clustering exercise (although a sensitivity analysis was conducted excluding IgE). Some covariates that could potentially affect biomarkers were not accounted for (eg, presence of atopy and CRS), although we did stratify clustering by LTOCS use, and analyses were adjusted by country. In addition, because our analyses were data-driven, the data may also have limited generalizability to the wider asthma population. We also acknowledge that there is likely some overlap between clusters (eg, some patients in cluster A have evidence of T2 inflammation). This is a consequence of the properties of the distributions for the 3 chosen biomarkers resulting in constraints on cluster separability. Therefore,

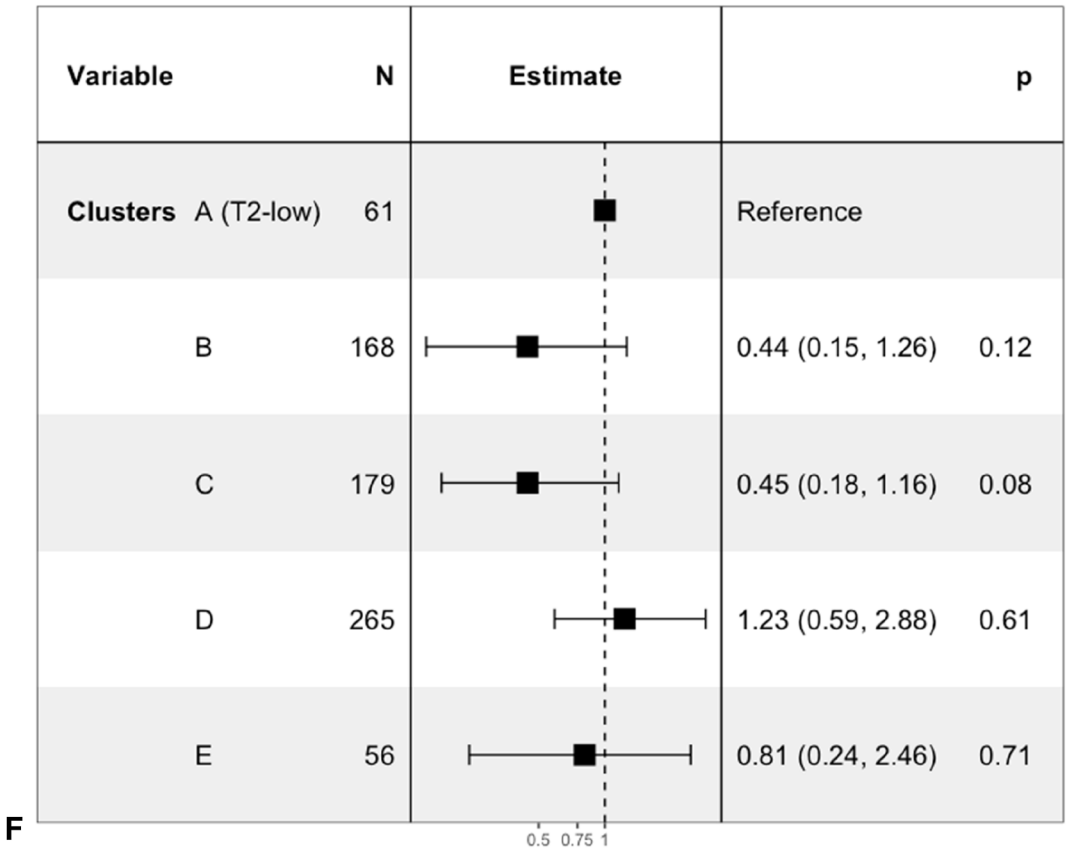

FIGURE 4. (*CONTINUED*).

replication of our clusters in a second cohort is warranted. Finally, as an exploratory research study designed to generate hypotheses, we acknowledge that false positives are possible due to multiple comparisons, but in our view, adjustment methods (eg, Bonferroni correction) were not necessary.[48] Our findings should be replicated in future independent studies.

Strengths of this study include inclusion of a large heterogeneous, real-life, severe asthma population encompassing patients from 24 countries. Furthermore, collection of a wide range of demographic and clinical phenotypes facilitated comprehensive phenotypic characterization. Our study was also designed to investigate differences across multiple asthma outcome and HCRU domains and across multiple T2 clusters. Use of the GFMM to identify clusters also provided a principled statistical approach to clustering that can assist a data-driven strategy for identifying biomarker-defined clusters in severe asthma. Further work is needed to include other indices (eg, presence of comorbidities) and biomarker weighting into the cluster model to produce sharper clustering, which could offer benefits over clinical-based algorithms and a more linear T2 spectrum/biologic-response relationship. Additional research to characterize temporal stability (persistence) and longer-term outcomes for the triple-biomarker-low phenotype and to further degranulate phenotypes more and less responsive to biologic therapy is also warranted.

In conclusion, our results highlight the complexity of T2 inflammatory involvement in severe asthma and support use of data-driven cluster analysis to define groups compared with using predefined clinical thresholds. More specifically, phenotypic characterization of clusters presented in our study could assist physicians in predicting the achievable response to biologics along the T2 spectrum; show that T2-targeted biologics have utility in the management of triple-biomarker-low disease, suggesting that treatment trials may be warranted in some patients; and emphasize the need for further research to identify pathways specific to triple-biomarker-low asthma that can be targeted by treatment.

Data sharing statement

The dataset supporting the conclusions of this article was derived from the ISAR. This study was approved by the Anonymised Data Ethics Protocols and Transparency committee—the independent scientific advisory committee for ISAR. The authors do not have permission to give public access to the study dataset; researchers may request access to ISAR data for their own purposes. ISAR research requests and proposals can be made via the ISAR website (https://www.isar.opcglobal.org/contact-us) or via the enquiries to info@isaregistries.org. In line with ISAR governance restrictions, sharing individual deidentified participant data is subject to the consent of the ISAR steering committee in accordance with patient consent, patient confidentiality, and ethical considerations. The study documents (protocol, statistical analysis plan, and clinical study report) will be made available in accordance with the criteria of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (EUPAS43785). Proposals should be

directed to info@isaregistries.org; to gain access, if approved by the regulatory boards, data requestors will need to sign a data access agreement.

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