CHEST

Eosinophilic and Noneosinophilic Asthma

An Expert Consensus Framework to Characterize Phenotypes in a Global Real-Life Severe Asthma Cohort

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ABBREVIATIONS: BEC = blood eosinophil count; EMR = electronic medical record; FENO = fractional exhaled nitric oxide; GINA = Global Initiative for Asthma; ISAR = International Severe Asthma Registry; LTRA = leukotriene receptor antagonist; mOCS = maintenance oral corticosteroid; OCS = oral corticosteroid; OPC = optimum patient care

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BACKGROUND: Phenotypic characteristics of patients with eosinophilic and noneosinophilic asthma are not well characterized in global, real-life severe asthma cohorts.

RESEARCH QUESTION: What is the prevalence of eosinophilic and noneosinophilic phenotypes in the population with severe asthma, and can these phenotypes be differentiated by clinical and biomarker variables?

STUDY DESIGN AND METHODS: This was an historical registry study. Adult patients with severe asthma and available blood eosinophil count (BEC) from 11 countries enrolled in the International Severe Asthma Registry (January 1, 2015-September 30, 2019) were categorized according to likelihood of eosinophilic phenotype using a predefined gradient eosinophilic algorithm based on highest BEC, long-term oral corticosteroid use, elevated fractional exhaled nitric oxide, nasal polyps, and adult-onset asthma. Demographic and clinical characteristics were defined at baseline (ie, 1 year before or closest to date of BEC).

RESULTS: One thousand seven hundred sixteen patients with prospective data were included; 83.8% were identified as most likely (grade 3), 8.3% were identified as likely (grade 2), and 6.3% identified as least likely (grade 1) to have an eosinophilic phenotype, and 1.6% of patients showed a noneosinophilic phenotype (grade 0). Eosinophilic phenotype patients (ie, grades 2 or 3) showed later asthma onset (29.1 years vs 6.7 years; $P < .001$) and worse lung function (postbronchodilator % predicted FEV_1, 76.1% vs 89.3%; $P = .027$) than those with a noneosinophilic phenotype. Patients with noneosinophilic phenotypes were more likely to be women (81.5% vs 62.9%; $P = .047$), to have eczema (20.8% vs 8.5%; $P = .003$), and to use anti-IgE (32.1% vs 13.4%; $P = .004$) and leukotriene receptor antagonists (50.0% vs 28.0%; $P = .011$) add-on therapy.

INTERPRETATION: According to this multicomponent, consensus-driven, and evidence-based eosinophil gradient algorithm (using variables readily accessible in real life), the severe asthma eosinophilic phenotype was more prevalent than previously identified and was phenotypically distinct. This pragmatic gradient algorithm uses variables readily accessible in primary and specialist care, addressing inherent issues of phenotype heterogeneity and phenotype instability. Identification of treatable traits across phenotypes should improve therapeutic precision.
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The knowledge that asthma represents a spectrum of diverse types is nothing new. In line with the Lancet Asthma Commission recommendations, asthma should be deconstructed into its various and heterogeneous types to answer the questions: What sort of asthma does the patient have?, What are the components of the airway disease?, and What are the treatable traits?[1,2] In particular, the term *severe asthma* includes many different phenotypes and endotypes that differ in their clinical presentation, underlying pathways, and response to treatment.[3]

Eosinophilic airways inflammation has emerged as the hallmark of one type of severe asthma, so much so that asthma is classified routinely as eosinophilic or noneosinophilic.[4] Brown[5] was the first to identify the corticosteroid-responsive eosinophilic asthma phenotype in 1958. This eosinophilic inflammation is

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Take-home Points

Study Question: What is the prevalence of eosinophilic and noneosinophilic phenotypes in the population with severe asthma, and can these phenotypes be differentiated by clinical and biomarker variables?

Results: Of 1,716 patients included, 83.8%, most likely had an eosinophilic phenotype. These patients were older, had later disease onset asthma, and showed worse lung function compared with those with a noneosinophilic phenotype (1.6%).

Interpretation: The severe asthma eosinophilic phenotype is more prevalent than previously thought and is phenotypically distinct when defined using variables readily accessible in real life.

driven predominantly by type 2 inflammation, including T-helper cells type 2 and group 2 innate lymphoid cells. It is mediated by IL-4, IL-5, IL-13, and granulocyte macrophage-colony stimulating factor and can be predicted (to some extent) from elevated fractional exhaled nitric oxide (FENO) concentration and sputum or blood eosinophilia.[6] Noneosinophilic asthma traditionally has been defined more arbitrarily as asthma without features of T-helper cell type 2 asthma and generally is based on the presence of neutrophils in sputum or the absence (or normal levels) of eosinophils or other T2 markers in sputum, biopsy samples, or blood.[7]

Knowledge of the presenting phenotype can help to predict asthma attack risk and health care resource use,[8,9] to inform targeted treatment, and to predict treatment response.[10,11] This eosinophil-targeted approach also has the advantage of reducing oral corticosteroid (OCS) use, which decreases risk of serious adverse events[12] and attenuates rates of severe exacerbations.[13] Noneosinophilic severe asthma needs to be characterized better if similar advancements in its treatment are to be made.

According to the Global Initiative for Asthma (GINA), the eosinophilic phenotype is found in approximately 50% of people with severe asthma.[14] Cluster analyses from different asthma cohorts have identified several asthma phenotypes (mostly eosinophilic) using a range of demographic and clinical characteristics to describe them.[15] However, substantial overlap was noted among phenotypes, most likely because of differences in sample population, geographic variation, variables assessed, and statistical methods used. Additionally, presence of comorbidities, exposures, OCS use, and FENO were not included in all cluster descriptions. Therefore, a need exists to characterize asthma phenotypes better in a large, multinational, real-life cohort of patients with severe asthma, considering the effect of steroids on type 2 biomarker concentrations and the importance of multiple blood eosinophil count (BEC) measurements when defining phenotypes. A more detailed deconstruction of asthma into its component types has the potential to make personalized treatment a reality for patients with asthma, effectively jump-starting the so-called stalled asthma outcomes and asthma mortality trends that have remained unchanged for years.[2]

A combination of clinical characteristics and biomarkers may be a better way to characterize asthma types. GINA recommends using different combinations of factors to identify type 2 inflammatory phenotypes, including BEC, FENO, sputum eosinophils, need for maintenance OCS (mOCS) and presence of multiple comorbidities.[16] Only one study previously proposed a diagnostic scheme to determine severe eosinophilic asthma, which was agreed by severe asthma expert consensus.[17] However, it has not yet been applied to a real-life clinical setting. The International Severe Asthma Registry (ISAR; http://isaregistries.org/), the largest adult severe asthma registry in the world, has sufficient power to investigate, characterize, quantify, and compare eosinophilic and noneosinophilic phenotypes and covers diverse jurisdictions, facilitating the generalizability of findings to the wider severe asthma population. ISAR captures BEC and many other variables associated with severe eosinophilic asthma (eg, FENO, age at onset, comorbidities, atopic status, and mOCS use),[18,19] enabling the development of a multicomponent, expert-endorsed algorithm for use in real life.

The aim of our study was (1) to describe an algorithm to characterize better severe eosinophilic and noneosinophilic asthma using both phenotype characteristics and biomarkers, (2) to quantify the proportion of patients with severe asthma with these phenotypes in the largest real-life severe asthma cohort in the world (ie, ISAR), and (3) to describe and compare their demographic and clinical characteristics.

Methods

Study Design and Data Source

This was a historical registry study to quantify and characterize eosinophilic and noneosinophilic severe asthma for patients enrolled in ISAR from January 1, 2015, through September 30, 2019.[19] Prospective, de-identified patient data incorporating standardized variables from new and pre-existing severe asthma registries were pooled from 11 countries (Bulgaria, Canada, Denmark, Greece, Italy, Japan, Kuwait, South Korea, Spain, the United Kingdom, and the United States). A full description of variables collected is provided in e-Table 1, including demographic variables (eg, age, age at onset, sex, race) as well as details on asthma attack rate, asthma control status, presence of atopy and comorbidities, biomarker concentrations (eg, IgE and FENO), lung function, and treatment regimen. A full description of how ISAR works has been published previously.[20] Details on compliance with local and international codes and regulations are provided in e-Appendix 1.

Patients

Patients were required to be aged 18 years of age or older at enrolment, to have severe asthma (ie, receiving treatment at GINA 2018 step 5 or with uncontrolled asthma at GINA step 4)[21] with ≥ 1 BEC recorded. A summary of how each registry diagnoses asthma and categorizes severe asthma is provided in e-Tables 2 and 3.

Development of Gradient Eosinophilic Phenotype Algorithm

A gradient eosinophilic phenotype algorithm was developed after an extensive literature review as well as discussions with and consensus of experts in the ISAR Steering Committee (comprising scientists, clinicians, and epidemiologists) (e-Fig 1). Consensus was achieved after several face-to-face meetings and via e-mail correspondence (e-Appendix 1). This group of experts selected variables used to inform the algorithm and agreed on cutoff values, based on published evidence and feasibility of availability in real-life clinical practice, but without knowledge of how selection of these variables (or their cutoffs) would influence eosinophil phenotype grading in the present cohort. These variables and cutoffs included highest BEC ever (≥ 300 cells/μL, ≥ 150-300 cells/μL, or <150 cells/μL), anti-IL-5/5 receptor treatment, long-term OCS use ever, elevated FENO (≥ 25 parts per billion) ever, nasal polyps diagnosis ever, and adult asthma onset (≥ 18 years) and were informed by the published evidence base and asthma management guidelines.[16,22-27] Phenotypes were classified as grade 3 (most likely eosinophilic), grade 2 (likely eosinophilic), grade 1 (least likely eosinophilic), and grade 0 (noneosinophilic) (Fig 1). Patients most likely to have an eosinophilic phenotype (grade 3) were those with highest BEC ever of ≥ 300 cells/μL or receiving anti-IL-5/anti-IL-5 receptor therapy, or with BEC of ≥ 150 to 300 cells/μL with (1) mOCS or (2) ≥ 2 of nasal polyps, elevated FENO, or late onset of disease. The noneosinophilic phenotype (grade 0) was defined by experts as highest BEC ever of < 150 cells/μL in

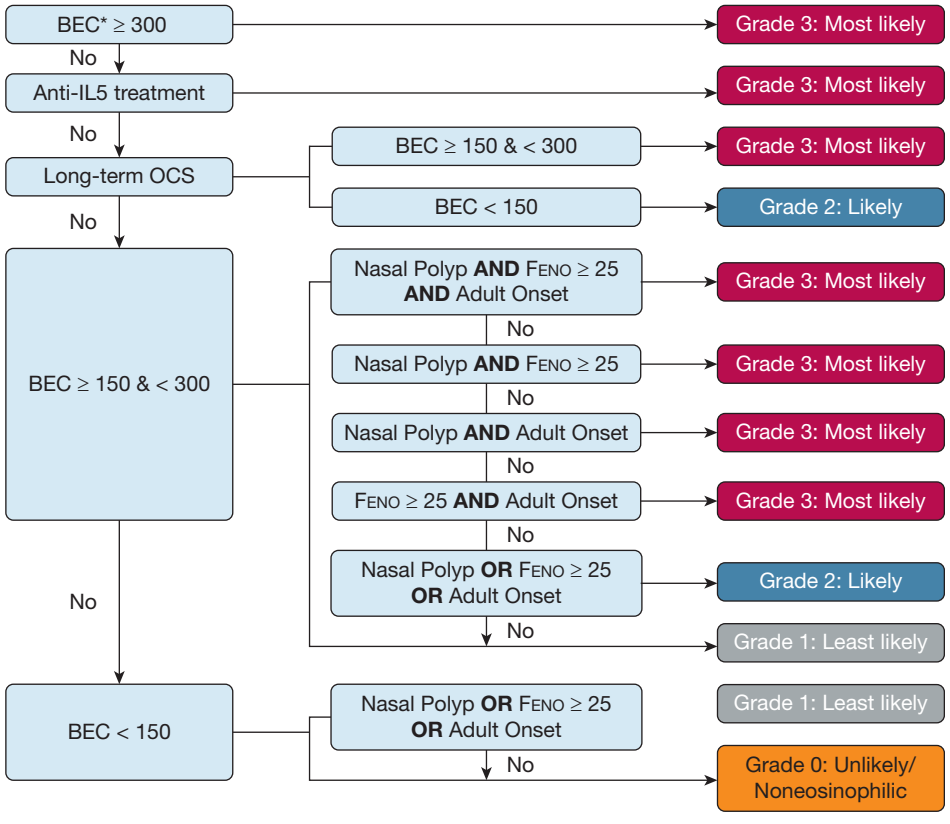

Figure 1 – *Flow chart showing original eosinophilic and noneosinophilic severe asthma phenotype algorithm. BEC = blood eosinophil count; FENO = fractional exhaled nitric oxide; OCS = oral corticosteroid.*

the absence of nasal polyps, elevated FENO, late onset, or mOCS. See Figure 1 for definitions of grade 1 and 2 eosinophilic phenotypes.

Description of Eosinophilic and Noneosinophilic Severe Asthma Phenotypes

Both demographic and clinical variables were used to describe eosinophilic and noneosinophilic severe asthma populations. All demographic and clinical characteristic were obtained within 1 year before or closest to the highest BEC recording (before anti-IL-5 therapy).

Statistical Analysis

The statistical analysis plan was predefined to reduce bias. Stata version 14.1 software (StataCorp) was used to conduct all statistical analyses. Descriptive statistics were computed for all demographic and clinical characteristics by phenotype (grades 0-3) as continuous variables or categorical measures as appropriate. For testing differences between groups, phenotypes were collapsed into an overall eosinophilic group (ie, grades 2 and 3) and a definitely noneosinophilic group (ie, grade 0). Grade 1 was excluded from the noneosinophilic group because patients in this group had at least one eosinophilic characteristic. Between-group differences in categorical variables were tested using the χ^2 test or Fisher exact test (if $n < 5$). The unpaired Student t test and Wilcoxon Mann-Whitney test were used to compare normally and nonnormally distributed data across groups, respectively. A two-sample test was used to compare proportions across groups. Statistical significance was defined as $P < .05$.

Sensitivity Post Hoc Analyses

The original gradient eosinophilic phenotype algorithm was reformulated without adult-onset asthma and without FENO as criteria. The number of patients (prospective ISAR data) in each eosinophilic and noneosinophilic phenotype was recalculated, and demographic and clinical characteristics for each group were reassessed. The number (percentage) of patients in each phenotype and a summary of their demographic and clinical characteristics also were assessed for retrospective electronic medical record (EMR) data captured for patients with severe asthma actively managed in routine care in the United States (ie, have at least two visits).

Results

Patients

The ISAR prospective population comprised 1,716 patients (United States, n = 70; United Kingdom, n = 712; Spain, n = 217; Italy, n = 163; Kuwait, n = 158; Denmark, n = 127; Bulgaria, n = 87; Canada, n = 85; Greece, n = 35; Japan, n = 34; and South Korea, n = 28). The ISAR retrospective population (using EMR data) included a further 1,891 patients with severe asthma actively managed with routine care in the United States.

Gradient Eosinophilic Phenotype Algorithm

For the ISAR prospective population (n = 1,716), 83.8% of patients were identified as most likely (grade 3) to have an eosinophilic phenotype, 8.3% were identified as likely (grade 2) to have an eosinophilic phenotype, and 6.3% were identified as least likely (grade 1) to have an eosinophilic phenotype, with 1.6% of patients being identified as having noneosinophilic asthma (grade 0) (Table 1). These phenotype classifications were rechecked for robustness by cross-examining their defining characteristics, showing an increase of age at onset, incidence of nasal polyps, and high FENO from grade 0 (noneosinophilic) to grade 3 (eosinophilic) phenotypes (e-Table 4). Grade 3 (most likely) eosinophilic phenotype predominated for patients with severe asthma in all countries, ranging from 64% of patients in South Korea to 93% of patients in Denmark (Fig 2). The eosinophilic phenotype distribution was similar when age at asthma onset and FENO were excluded from the gradient algorithm (Table 1, e-Figs 2, 3). For the ISAR retrospective population actively assessed in the United States (n = 1,891), 74.3%, 4.1%, and 11.5% most likely, likely, and least likely had an eosinophilic severe asthma phenotype, respectively; 10.1% of patients had a noneosinophilic phenotype.

Demographic and Clinical Characteristics

Original Algorithm (ISAR Prospective Population, n = 1,716): Patients in the severe asthma cohort, regardless of phenotype (ie, eosinophilic or noneosinophilic severe asthma) tended to be White (68.7% vs 74.1%), to be overweight or obese (70.5% vs 74.0%), to be atopic (ie, specific IgE testing or skin prick test; 88.3% vs 90.9%), to have elevated (> 150 International Units/mL) IgE concentrations (61.8% vs 70.0%), and to have high allergic rhinitis prevalence (65.5% vs 60.0%), with most exhibiting poor asthma control (59.9% vs 59.3%) and multiple exacerbations (≥ 2 in the previous year; 62.0% vs 59.1%) (Table 2). The prevalence of former smokers (28.4% vs 34.6%), ED visits (≥ 1 in the previous year; 33.9% vs 32.0%), and hospitalizations (≥ 1 in the previous year; 28.6% vs 24.0%) was high in both groups (Table 2). Although an adherence variable was not included in the current dataset, all patients were receiving background asthma therapy with evidence of persistence and good adherence (in the opinion of the clinician or based on other evidence, such as prescription refills).

Some differences were noted. Patients with an eosinophilic phenotype (ie, grades 2 or 3) tended to be older (52.4 years vs 38.8 years; $P < .001$), to have later asthma onset (29.1 years vs 6.7 years; $P < .001$), and to worse lung function (ie, FEV_1 to FVC

TABLE 1] Characterization of Eosinophilic and Noneosinophilic Phenotypes and the Proportion of Patients With Severe Asthma With These Phenotypes in ISAR

Highest BEC Available (cells/μL)[a]	Treatment or Clinical Characteristic	Eosinophilic Phenotype	Prospective ISAR Population (N = 1,716) [Original Algorithm]		Prospective ISAR Population (N = 1,716) [Original Algorithm Minus Age of Onset]		Prospective ISAR Population (N = 1,716) [Original Algorithm Minus FENO]	
			No. (%)	(%)	No. (%)	%	No. (%)	%
≥ 300		Grade 3: most likely	1,196 (69.7)		1,196 (69.7)		1,196 (69.7)	
Anti-IL5		Grade 3: most likely	178[b] (10.4)		178[b] (10.4)		178[b] (10.4)	
≥ 150-< 300	Long-term OCS	Grade 3: most likely	37 (2.2)	**83.8**	37 (2.2)	**82.6**	37 (2.2)	**82.7**
	Presence of ≥ 2 of the following: NP, FENO ≥ 25 ppb, or adult onset[c] (no long-term OCS)	Grade 3: most likely	27 (1.6)		7 (0.4)		8 (0.5)	
	Either NP, FENO ≥ 25 ppb or adult onset (no long-term OCS)	Grade 2: likely	67 (3.9)	**3.9**	45 (2.6)	**2.6**	71 (4.1)	**4.1**
	No NP, elevated FENO, adult onset, or long-term OCS	Grade 1: least likely	27 (1.6)	**1.6**	69 (4.0)	**4.0**	42 (2.4)	**2.4**
< 150	Long-term OCS	Grade 2: likely	75 (4.4)	**4.4**	75 (4.4)	**4.4**	75 (4.4)	**4.4**
	Either NP, FENO ≥ 25 ppb or adult onset (no long-term OCS)	Grade 1: least likely	81 (4.7)	**4.7**	40 (2.4)	**2.4**	64 (3.7)	**3.7**
	No NP, elevated FENO, adult onset, or long-term OCS	Grade 0: unlikely (non-eosinophilic)	28 (1.6)	**1.6**	69 (4.0)	**4.0**	45 (2.6)	**2.6**

BEC = blood eosinophil count; FENO = fractional exhaled nitric oxide; ISAR = International Severe Asthma Registry; NP = nasal polyps; OCS = oral corticosteroids; ppb = parts per billion.

[a]Independent criteria specified in each row; before anti-IL-5/5 receptor or long-term OCS treatment was used wherever possible.

[b]Of 178 patients receiving anti-IL-5, 125 patients showed BEC of < 150 cells/μL (88 patients receiving maintenance OCS; 37 patients never received maintenance OCS) and 53 patients showed BEC of ≥ 150 - < 300 cells/μL (38 receiving maintenance OCS; 15 patients never received maintenance OCS). Of the 37 with BEC of < 150 cells/μL without OCS, 26 patients did not have a BEC available from before anti-IL-5 treatment. Eleven patients (from Canada [n = 1] Denmark [n = 2], Spain [n = 3] and the United States [n = 5]) had a BEC available from before anti-IL-5 treatment.

[c]Onset of asthma: ≥ 18 y of age.

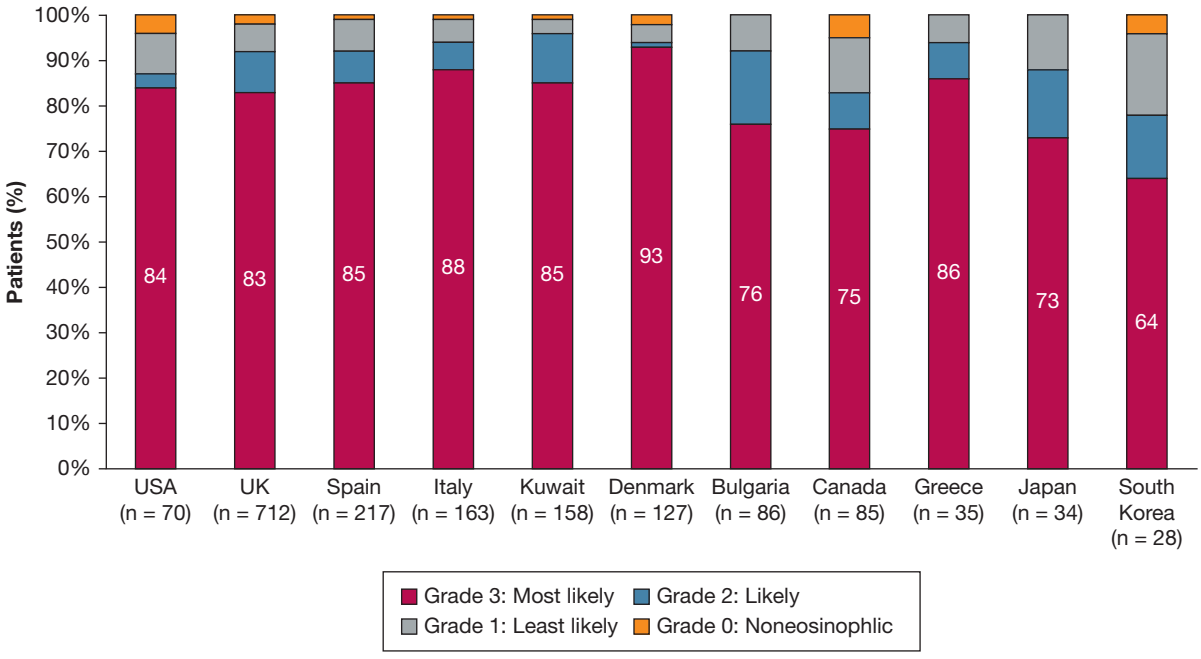

Figure 2 – *Bar graph showing eosinophilic severe asthma phenotype distribution by country for prospective International Severe Asthma Registry population (defined according to the original algorithm).*

ratio of < 0.7: 46.6% vs 16.7% [$P = .039$] and postbronchodilator % predicted FEV_1: 76.1% vs 89.3% [$P = .027$]) than those with a noneosinophilic phenotype (Table 2, Fig 3). Those with noneosinophilic severe asthma (ie, grade 0) were more likely to be women (81.5% vs 62.9%; $P = .047$), to have eczema (20.8% vs 8.5%; $P = .033$), and to use anti-IgE (32.1% vs 13.4%; $P = .004$) and leukotriene receptor antagonist (LTRA; 50.0% vs 28%; $P = .011$) as an add-on to inhaled corticosteroids plus long-acting β-agonist therapy than those patients with an eosinophilic phenotype (ie, grades 2 or 3) (Table 2, Fig 3). Demographic and clinical characteristics along the eosinophil phenotype gradient (ie, grades 0, 1, 2, and 3) are provided in e-Table 5.

Original Algorithm Without Age at Onset and FENO as Phenotype-Defining Criteria (ISAR Prospective Population, n = 1,716) and for Those Actively Managed in the United States (n = 1,891; EMR Data): A similar distribution of demographic and clinical characteristics was observed when age at onset and FENO were removed as defining criteria from the eosinophil gradient algorithm (e-Tables 6 and 7). When age at onset was excluded from the algorithm, those with noneosinophilic severe asthma still tended to be younger (49.6 years vs 52.3 years; $P = .145$), to have earlier asthma onset (27.4 years vs 28.9 years; $P = .637$), and to have eczema (12.5% vs 8.4%; $P = .291$), although the difference between noneosinophilic and eosinophilic phenotypes was less marked (e-Table 6). When FENO was removed from the gradient algorithm, those with noneosinophilic severe asthma still tended to be women (75.0 years vs 62.7 years; $P = .096$), to have eczema (13.9% vs 8.3%; $P = .229$), and to use add-on LTRA with inhaled corticosteroids plus long-acting β-agonist therapy (40.0% vs 28.0%; $P = .078$), but the difference was no longer significant compared with those with eosinophilic severe asthma (e-Table 7). The demographic and clinical characteristics for those patients with severe asthma assessed actively in the United States were slightly different from the ISAR prospective data (e-Table 8).

Discussion

We demonstrated that the eosinophilic severe asthma phenotype is larger than previously estimated (ie, > 80% vs approximately 50%)[14] and identified distinct eosinophilic and noneosinophilic severe asthma patterns based on a combination of clinical and biomarker variables. Our proposed multicomponent eosinophil phenotype classification algorithm is based on extensive literature review and expert consensus, uses variables readily accessible both in primary and specialist care, and is linked to morbidity and treatment response. Furthermore, the algorithm takes variability in BEC

TABLE 2] Demographic and Clinical Characteristics According to Eosinophilic (Grades 2 and 3) and Noneosinophilic (Grade 0) Phenotype, Categorized According to the Original Algorithm (ISAR Prospective Population; N = 1,716)

Characteristic	Noneosinophilic (Grade 0; n = 28)	Eosinophilic (Grades 2 or 3; n = 1,580)	*P* Value
Sex			
Nonmissing	27 (96.4)	1,571 (99.4)	**.047**[a,b]
Female	22 (81.5)	988 (62.9)	
Age, y			
Nonmissing	26 (92.9)	1,513 (95.8)	
Mean ± SD	38.8 ± 12.1	52.4 ± 13.8	**.000**[c,b]
18-34	10 (38.5)	177 (11.7)	
35-54	14 (53.8)	631 (41.7)	**.000**[d,b]
55-79	2 (7.7)	683 (45.1)	
≥ 80	0 (0)	22 (1.4)	
Ethnicity			
Nonmissing	27 (96.4)	1,549 (98.0)	
White	20 (74.1)	1,064 (68.7)	
Asian	3 (11.1)	140 (9.1)	
Black	0 (0)	55 (3.5)	.650[d]
Mixed	0 (0)	12 (0.8)	
Other	4 (14.8)	272 (17.6)	
Unknown	0 (0)	6 (0.4)	
BMI, kg/m^2[b]			
Nonmissing	27 (96.4)	1,546 (98.0)	
Underweight (< 18.5)	0 (0)	25 (1.6)	
Normal (≥ 18.5-< 25)	7 (25.9)	431 (27.9)	.943[d]
Overweight (≥ 25-< 30)	10 (37.0)	504 (32.6)	
Obese (≥ 30)	10 (37.0)	586 (37.9)	
Smoking status			
Nonmissing	26 (92.9)	1,540 (97.5)	
Current smokers	1 (3.8)	53 (3.4)	.570[d]
Former smoker	9 (34.6)	438 (28.4)	
Never smoker	16 (61.5)	1,049 (68.1)	
Age at asthma onset, y			
Nonmissing	23 (82.1)	1,493 (90.9)	
Mean ± SD	6.7 ± 4.1	29.1 ± 18.0	**.000**[c,b]
< 18	23 (100.0)	424 (29.5)	
18-29	0 (0.0)	283 (19.7)	—
≥ 30	0 (0.0)	729 (50.8)	
Comorbidities ever			
Nonmissing	24 (85.7)	1,493 (94.5)	
NP	0 (0.0)	492 (32.9)	—
Nonmissing	14 (50.0)	851 (53.9)	
CRS	6 (42.9)	448 (52.6)	.467[a]
Nonmissing	13 (46.4)	514 (32.5)	
CRS without NP	6 (46.1)	198 (38.5)	.577[a]

(Continued)

TABLE 2] *(Continued)*

Characteristic	Noneosinophilic (Grade 0; n = 28)	Eosinophilic (Grades 2 or 3; n = 1,580)	*P* Value
Nonmissing	—	314 (19.9)	—
CRS with NP	0 (0.0)	234 (74.5)	
Nonmissing	15 (53.6)	869 (55.0)	.658[a]
AR	9 (60.0)	569 (65.5)	
Nonmissing	24 (85.7)	1,275 (80.7)	**.033**[a,b]
Eczema	5 (20.8)	109 (8.5)	—
Atopy			
Nonmissing	22 (78.6)	1,362 (86.2)	.701[f]
Atopy	20 (90.9)	1,202 (88.3)	
Asthma control			
Asthma control, nonmissing	27 (96.4)	1,296 (82.0)	
Poorly controlled	16 (59.3)	776 (59.9)	.828[a]
Not well controlled	5 (18.5)	190 (14.7)	
Well controlled	6 (22.2)	330 (25.5)	
Asthma attacks, nonmissing	22 (78.6)	1,354 (85.7)	
Mean ± SD	3.2 ± 3.0	3.4 ± 3.7	.919[c]
0	5 (22.7)	350 (25.9)	
1	4 (18.2)	166 (12.3)	
2	1 (4.5)	180 (13.3)	.698[d]
3	2 (9.1)	129 (9.6)	
≥ 4	10 (45.5)	529 (39.1)	
Health care resource use			
Invasive ventilation, nonmissing	22 (78.6)	1,395 (88.3)	
Mean ± SD	0.1 ± 0.5	0.1 ± 0.6	.724[c]
0	20 (90.9)	1,294 (92·8)	
1	1 (4.5)	75 (5.4)	.442[d]
≥ 2	1 (4.5)	26 (1.9)	
ED visit, nonmissing	25 (89.3)	1,461 (92.5)	
Mean ± SD	1.6 ± 4.2	1.2 ± 3.2	.978[c]
0	17 (68.0)	965 (66.0)	
1	2 (8.0)	161 (11.0)	.912[d]
≥ 2	6 (24.0)	335 (22.9)	
Hospitalization, nonmissing	25 (89.3)	1,446 (91.5)	
Mean ± SD	0.6 ± 1.9	0.7 ± 1.5	.676[c]
0	19 (76.0)	1,033 (71.4)	
1	2 (8.0)	202 (14.0)	.808[d]
≥ 2	4 (16.0)	211 (14.6)	
Biomarkers			
IgE (International Units/mL), nonmissing	20 (71.4)	1,270 (80.4)	
< 150	6 (30.0)	485 (38.2)	
150-400	7 (35.0)	357 (28.1)	.709[a]
> 400	7 (35.0)	428 (33.7)	

(Continued)

TABLE 2] *(Continued)*

Characteristic	Noneosinophilic (Grade 0; n = 28)	Eosinophilic (Grades 2 or 3; n = 1,580)	*P* Value
FENO, nonmissing, ppb	23 (82.1)	1,080 (68.4)	
< 25	23 (100.0)	299 (27.7)	
≥ 25-< 50	0 (0.0)	338 (31.3)	—
≥ 50	0 (0.0)	443 (41.0)	
Lung function			
Post-BD FEV_1 nonmissing,% predicted	14 (50.0)	823 (52.1)	**.027**[b,e]
Mean ± SD	89.3 ± 18.2	76.1 ± 22.1	
Pre-BD FEV_1, % predicted	n = 21	n = 1,174	
Mean ± SD	77.1 ± 23.2	72.9 ± 24.1	.427[e]
Post-BD FEV_1 to FVC ratio, nonmissing	12 (42.9)	641 (40.6)	.429[e]
Mean ± SD	0.7 ± 0.1	0.7 ± 0.2	
< 0.7	2 (16.7)	299 (46.6)	**.039**[b,f]
Reversibility, nonmissing	11 (39.3)	616 (39.0)	.933[c]
Mean ± SD	7.5 ± 8.0	7.9 ± 8.6	
< 9%	7 (63.6)	616 (64.1)	.973[f]
Therapy ever			
Nonmissing	28 (100.0)	1,580 (100.0)	
Anti-IL-5/5 receptor	0 (0.0)	790 (50.0)	
Mepolizumab	0 (0.0)	638 (80.7)	
Benralizumab	0 (0.0)	129 (16.3)	—
Reslizumab	0 (0.0)	23 (2.9)	
Long-term OCS	0 (0.0)	697 (44.1)	
Baseline therapies			
Nonmissing	28 (100.0)	1,580 (100.0)	
Anti-IgE	9 (32.1)	212 (13.4)	**.004**[a,b]
Anti-IL-4	0 (0)	2 (0.1)	.576[a]
Long-term OCS	0 (0.0)	581 (36.7)	—
Macrolide	1 (3.6)	78 (4.9)	.596[d]
Add on to ICS and LABA			
LAMA	11 (39.3)	503 (31.8)	.402[a]
LTRA	14 (50.0)	443 (28.0)	**.011**[a,b]
LAMA and LTRA	7 (25.0)	237 (15.0)	.144[a]
Theophylline	2 (7.1)	188 (11.9)	.765[d]

Data are presented as No. (%) or mean ± SD. Statistically significant P values are shown in bold. BD = bronchodilator; CRS = chronic rhinosinusitis; — = not compared; FENO = fractional exhaled nitric oxide; ICS = inhaled corticosteroid; ISAR = International Severe Asthma Registry; LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic receptor antagonist; LTRA = leukotriene receptor antagonist; NP = nasal polyps; OCS = oral corticosteroid; ppb = parts per billion.

[a]χ^2 test.

[b]$P < .05$.

[c]Wilcoxon Mann-Whitney test.

[d]Fisher exact test.

[e]t Test.

[f]Two-sample test of proportions.

(using the highest ever value) and impact of OCS into account, both of which can confound phenotype classification. We proposed a gradient approach (ie, likelihood of eosinophilic asthma), rather than a dichotomous approach, to severe asthma phenotype classification in recognition of the inherent heterogeneity within phenotypes and the fact that they can occur in isolation or combination in any given patient and may change over time, either because of the natural history of the disease or as a consequence of

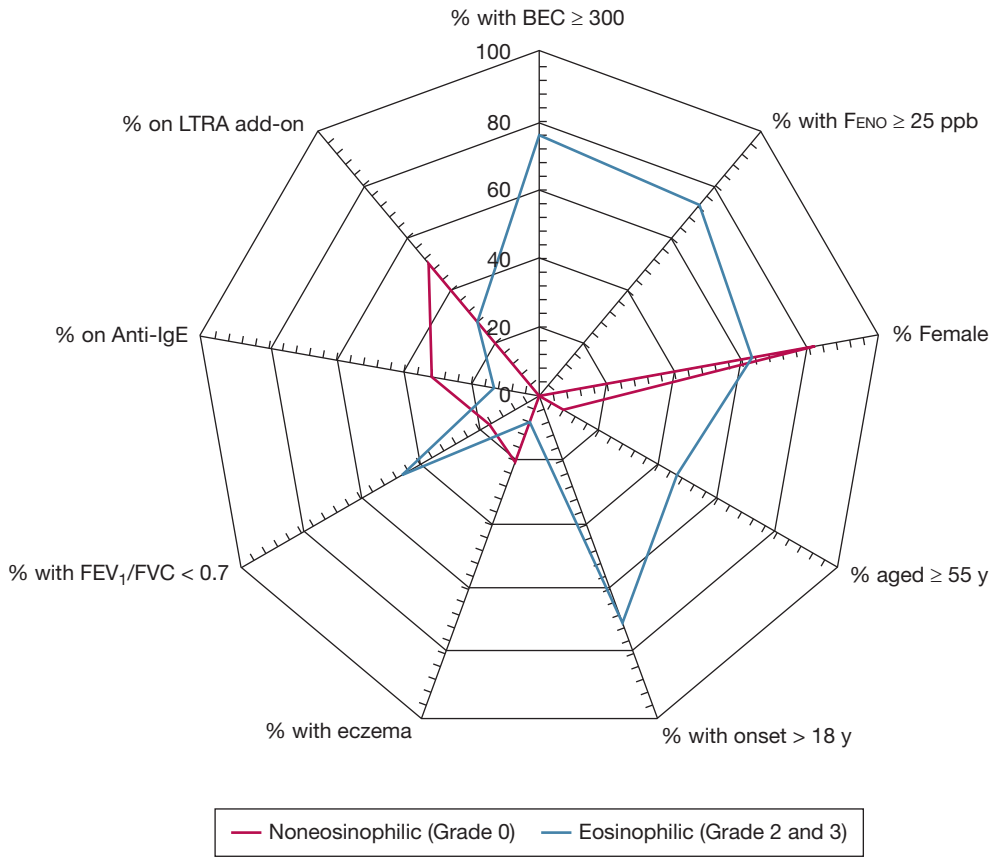

Figure 3 – *Spider plot showing the clinical and biomarker variable distribution pattern for the eosinophilic (n = 1,580) and noneosinophilic (n = 28) severe asthma phenotype for the International Severe Asthma Registry prospective population. BEC = blood eosinophil count; FENO = fractional exhaled nitric oxide; LTRA = leukotriene receptor antagonist (add-on to inhaled corticosteroids plus long-acting β-agonist therapy); ppb = parts per billion.*

treatment.[1] Finally, we pooled diverse data from large severe asthma registries to provide a real-life phenotype snapshot at the global and country levels, quantifying and characterizing both the severe eosinophilic phenotype and also the often-ignored noneosinophilic severe asthma phenotype, which historically has been a diagnosis of exclusion.

A gradient and multicomponent eosinophil classification algorithm is useful to reflect heterogeneity not only within severe asthma, but also within eosinophilic and noneosinophilic phenotypes. Use of elevated BEC as the sole marker for defining an eosinophilic phenotype may be misleading for several reasons. The amount of eosinophils in the blood is both time-dependent and treatment-dependent; eosinophil counts fluctuate in a circadian pattern and are also reduced during OCS therapy.[28,29] Additionally, a low BEC does not necessarily rule out the presence of airway eosinophilia. Its use as a single surrogate marker for airway eosinophilia in patients with asthma "will lead to a substantial number of false positives or false negatives."[30] A combination of clinical parameters and biomarkers may safeguard against phenotype misclassification and is one explanation for the > 80% of patients with severe eosinophilic asthma observed in the present study. Both the Severe Asthma Research Program and the Leicester cohorts have used this combination approach.[31]

Using a multicomponent gradient eosinophil algorithm to characterize eosinophilic and noneosinophilic phenotypes of severe asthma within ISAR (Fig 1) permitted us to take a phenotype snapshot.[1] We found that that the vast majority of patients (> 80%) in severe asthma centers globally have background eosinophilic asthma (regardless of the algorithm used) and that the proportion of patients with a completely noneosinophilic phenotype is very rare (only 1.6% in the current study). Others recently validated our findings, showing a similarly high prevalence of eosinophilic asthma (83.4%), defined as ≥ 300 cells/μL ever in the

past 10 years, in a real-life difficult-to-treat UK asthma population.[32] However, arguably the ISAR gradient eosinophil algorithm affords a more practical means of determining eosinophilic asthma status than reliance on protracted, sequential BEC.

The low prevalence of noneosinophilic phenotype in the present study could be the result of the strict noneosinophilic phenotype definition used, OCS overtreatment, possibly anti-IgE treatment and LTRA treatment, which may have suppressed some algorithm variables (eg, BEC), or a combination thereof.[33,34] This low-eosinophilic phenotype prevalence remained when age at onset and FENO were removed as criteria from the gradient algorithm. Those with an eosinophilic severe asthma phenotype have an elevated BEC (ie, ≥ 150 cells/μL), are more likely to have nasal polyps and FENO of ≥ 25 parts per billion (by algorithm definition), are older, and are more likely to have adult-onset asthma and worse lung function (than those with noneosinophilic severe asthma). Conversely, our preliminary findings, based on small numbers, found that those with a noneosinophilic severe asthma phenotype have a relatively low BEC (ie, < 150 cells/μL), no nasal polyps, low FENO (ie, < 25 parts per billion), and early-onset disease and are more likely to be women, to have eczema, and to be treated with anti-IgE and LTRA add-on to inhaled corticosteroids plus long-acting β-agonist therapy (presumably because of ineligibility for anti-IL-5/5 receptor treatment by virtue of low BEC). This finding highlights the lack of other treatment options and the need to develop treatments targeted at this often-overlooked subset of patients with severe asthma. The higher likelihood of eczema reported relative to patients with an eosinophilic phenotype may be the result of the greater prevalence of OCS and biologic use in the latter group, which may reduce the severity of both conditions so they are not active.

In common with most severe asthma cohorts, we found a clear predominance of women (regardless of phenotype). Interestingly, the prevalence of male sex seemed to be proportionately greater in the eosinophilic group (37.1% vs 18.5%), which in conjunction with older age and later disease onset seen in the eosinophilic group aligns with the findings of Azim and colleagues,[35] who recently identified a male, adult-onset, eosinophilic, difficult asthma phenotype that so far has received scant attention in the literature. Similarity of health care resource use for both eosinophilic and noneosinophilic severe asthma suggests comparable asthma severity across phenotypes. Similarity across phenotypes for asthma control and asthma attacks may be attributable to the fact that ISAR selects patients who are more likely to experience an asthma attack. However, this finding may suggest that despite complete suppression of eosinophilic inflammation (with corticosteroids or biologic therapy) in those with definite eosinophilic asthma, symptoms and asthma attacks can persist and that other factors (besides the eosinophil) are important (eg, comorbidities, health care access, and socioeconomic factors). Characterization of noneosinophilic mechanisms that persist when eosinophilic inflammation has been suppressed warrants further characterization. The relatively lower prevalence of the severe eosinophilic phenotype in the US retrospective population (74%) is attributed mainly to a lack of nasal polyps and age at asthma onset data and speaks to the benefit of the standardized, prospective data collection and coding used in ISAR as well as the importance of longitudinal assessment of BEC.

Table 3 compares this global view of eosinophilic phenotype description with cluster analyses from three large asthma cohorts (Severe Asthma Research Program, Unbiased Biomarkers for Prediction of Respiratory Disease, and Airways Disease Endotyping for Personalized Therapeutics).[15] All clusters identified a predominance of eosinophilic clusters, but differed in the size of the eosinophilic and noneosinophilic clusters identified, ranging from 49% to 56% and 16% to 31%, respectively,[36,37] and markedly differed from the results of the current study (Table 3). These differences in part may be the result of inclusion of mild asthma in these clusters (eg, the percentage of patients with an eosinophilic phenotype increases to 81.2% when patients with mild disease are discounted from the Severe Asthma Research Program cohort) because of differences in choice of variables and are complicated by the inclusion of a mixed granulocyte phenotype in the Unbiased Biomarkers for Prediction of Respiratory Disease and the Airways Disease Endotyping for Personalized Therapeutics cohorts, which include neutrophilic types. Indeed, Burgel and colleagues[38] argue that cluster analyses should be viewed as an exploratory analysis and that the results should be validated using clinically relevant end points in multiple cohorts of patients. Use of multiple clinical biomarkers, a well-characterized cohort, and variables that are treatable to define phenotypes (as in our

TABLE 3] Comparison of ISAR Eosinophilic Phenotypes vs Clinical Cluster Analyses From Three Large, Well-Phenotyped Asthma Cohorts

ISAR Cohort (N = 1,716)		SARP Cluster (n = 726)[37]		U-BIOPRED Cluster (n = 82)[36]		ADEPT Clusters (n = 156)[36]	
Characteristics	%	Characteristics	%	Characteristics	%	Characteristics	%
		Early onset, mild, atopic, eosinophilic (n = 110)		Mild asthma, good lung function, early onset, low inflammation (n = 25)		Mild, normal lung function, early onset, low inflammation (n = 28)	
Eosinophilic (BEC ≥ 150 cells/μL), adult onset, high FENO (> 25 ppb), nasal polyps, older, worse lung function	83.8	Early onset, moderate, atopic, eosinophilic (n = 321)	68.9	Moderate, hyperresponsive, eosinophilic (n = 32)	48.8	Moderate, atopic, mild reversible obstruction, hyperresponsive, eosinophilic (n = 44)	50.6
		Late onset, nonatopic, eosinophilic, female, obese (n = 59)		Severe uncontrolled, severe reversible obstruction, mixed granulocytic (n = 8)		Severe uncontrolled, severe reversible obstruction, mixed granulocytic (n = 35)	
		Early onset, severe atopic reversible, obstruction, eosinophilic (n = 120)					
Noneosinophilic (low BEC < 150 cells/μL), early onset, low FENO (< 25 ppb), no nasal polyps, female, eczema, better lung function	1.6	late onset, long duration, severe, fixed airflow obstruction (n = 116)	16.0	Mixed severity, mild reversible obstruction, noneosinophilic, neutrophilic (n = 17)	20.7	Mixed severity, mild reversible obstruction, noneosinophilic, neutrophilic (n = 49)	31.4

Table adapted from Carr et al[15] (2018). ADEPT = Airways Disease Endotyping for Personalized Therapeutics; BEC = blood eosinophilic count; FENO = fractional exhaled nitric oxide; ISAR = International Severe Asthma Registry; ppb = parts per billion; SARP = Severe Asthma Research Program; U-BIOPRED = Unbiased Biomarkers for the Prediction of Respiratory Disease.

study) may have a superior biological responsiveness predictive value.[3,39]

One limitation of the study includes a potential selection bias for the eosinophilic phenotype within ISAR. Although the ISAR population may be enriched for those with high BEC, frequent asthma attacks, and suitability for biologic prescription in some countries (eg, the United Kingdom), thus positively selecting for the severe eosinophilic phenotype, this is not true for all countries. Indeed, a recent study including data from 7 ISAR-participating countries (the United States, United Kingdom, South Korea, Italy, Australia, New Zealand, and Singapore) found that only 25.4% of patients with severe asthma were receiving biologic therapy (either anti-IgE or anti-IL-5).[40] A similarly high prevalence of eosinophilic asthma and low prevalence of noneosinophilic asthma also has been reported in a primary care cohort using the same eosinophil phenotype gradient algorithm[41] and in the actively managed US EMR population presented in the current study. Furthermore, a similarly low prevalence of noneosinophilic asthma has been reported in the Refractory Asthma Stratification Programme-UK asthma cohort using a different algorithm.[42] Our algorithm is intended to aid phenotype classification and does not capture all asthma subtypes, for instance, the subtype of asthmatics with low BEC and elevated FENO and nasal polyps who do respond well to anti-IL-4/13 therapy.[43] This phenotype can be explored more fully within ISAR when IL-4/13 use becomes more widespread. Additional limitations include a reliance on BEC rather than sputum eosinophil count, possibility of recall bias (eg, for onset of asthma), and the large imbalance in patient numbers between the groups when describing demographic and clinical characteristics. However, it should be noted that although sputum induced by hypertonic saline generally is considered a reliable, noninvasive method to assess and monitor eosinophilia, it can be problematic in patients with severe and uncontrolled asthma inducing airway narrowing, failure to produce an adequate sputum sample in about one-quarter of patients, or both.[44] Blood eosinophilia is an accurate surrogate marker for sputum eosinophils, with a reported ROC AUC of 89%.[45]

It is recommended that this gradient algorithm be applied in a different severe asthma study population with longitudinal BEC records to assess the specificity of the eosinophil phenotype definition and to assess the generalizability of the reported results. Future work could evaluate the internal and external validity of the gradient algorithm, could examine more fully the eosinophil phenotype characteristics by country, could characterize the ISAR cohort according to type 2 and non-type 2 endotypes, and could examine overlap between phenotypes and biomarkers.

Interpretation

This multicomponent, expert-endorsed, eosinophil gradient algorithm, using variables readily accessible in real life, has shown that the prevalence of the severe asthma eosinophilic phenotype is higher than previously thought and phenotypically distinct. Use of this algorithm may enable physicians to ascertain what type of asthma patients have, the components of the airway disease, and its treatable traits, bringing us one step closer to the practice of precision medicine and selection of targeted phenotype-specific treatments.

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Additional information: The e-Appendix, e-Figures, and e-Tables can be found in the Supplemental Materials section of the online article.

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