Original Article

Burden of Uncontrolled Severe Asthma With and Without Elevated Type-2 Inflammatory Biomarkers

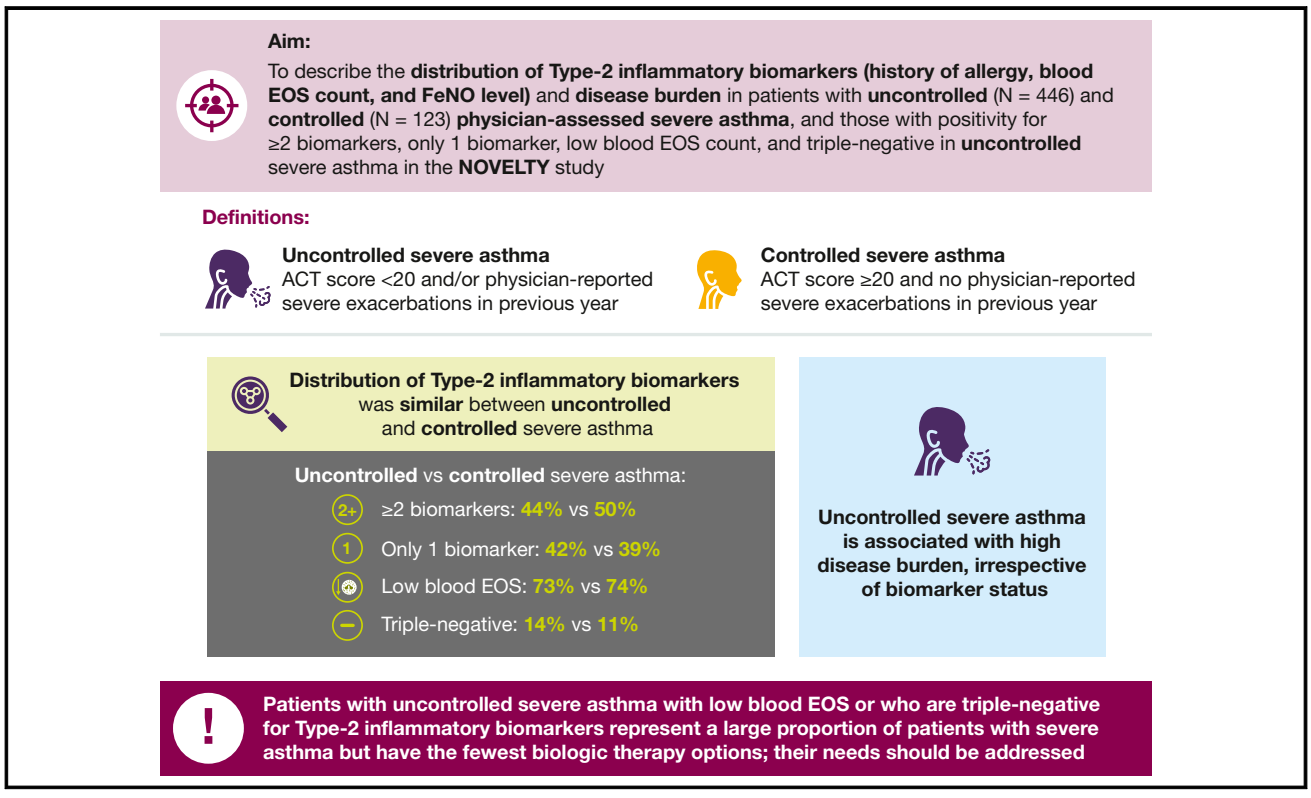
Bo Ding, PhD[a], Stephanie Chen, PhD[b], Eleni Rapsomaniki, PhD[c], Anna Quinton, MSc[d], William Cook, PhD[b], Helen K. Reddel, MBBS, PhD[e], and Alberto Papi, MD[f]; for the NOVELTY Scientific Community and the NOVELTY study investigators *Gothenburg, Sweden; Gaithersburg, Md; Cambridge, United Kingdom; Sydney, New South Wales, Australia; and Ferrara, Italy*

What is already known about this topic? Many patients with asthma have type-2 airway inflammation, identified by the presence of specific biomarkers, including atopy, high blood eosinophil count, and/or high fractional exhaled nitric oxide levels.

What does this article add to our knowledge? In uncontrolled severe asthma, disease burden is high, regardless of patients' biomarker status.

How does this study impact current management guidelines? Many patients with uncontrolled severe asthma have low blood eosinophil counts or are triple-negative for history of allergy, blood eosinophil counts, and fractional exhaled nitric oxide. These patients have few biologic therapy options, and their needs should be addressed.

VISUAL SUMMARY



Abbreviations used

ACT- Asthma Control Test
BD- bronchodilator
BMI- body mass index
COPD- chronic obstructive pulmonary disease
EOS- eosinophil
ER- emergency room
FeNO- fractional exhaled nitric oxide
FEV_1- forced expiratory volume in one second
GP- general practitioner
ICS- inhaled corticosteroid
IgE- immunoglobulin E
IL- interleukin
IL-4R- interleukin-4 receptor
IL-5- interleukin-5
IL-5R- IL-5 receptor
ISAR- International Severe Asthma Registry
LABA- long-acting β_2-agonist
LAMA- long-acting muscarinic antagonist
mMRC- modified Medical Research Council
NOVELTY- NOVEL observational longiTudinal studY
OCS- oral corticosteroid
ppb- parts per billion
SGRQ- St George's Respiratory Questionnaire
WHO- World Health Organization

BACKGROUND: Many patients with asthma have type-2 airway inflammation, identified by the presence of biomarkers, including history of allergy, high blood eosinophil (EOS) count, and high fractional exhaled nitric oxide levels.

OBJECTIVE: To assess disease burden in relation to type-2 inflammatory biomarker status (history of allergy, blood EOS count, and fractional exhaled nitric oxide level) in patients with uncontrolled and controlled severe asthma in the NOVEL observational longiTudinal studY (NOVELTY) (NCT02760329).

METHODS: Asthma diagnosis and severity were physician-reported. Control was defined using Asthma Control Test score (uncontrolled <20, controlled ≥20) and/or 1 or more severe physician-reported exacerbation in the previous year. Biomarker distribution (history of allergy, blood EOS count, and fractional exhaled nitric oxide level), symptom burden (Asthma Control Test score, modified Medical Research Council dyspnea scale), health status (St George's Respiratory Questionnaire score), exacerbations, and health care resource utilization were assessed.

RESULTS: Of 647 patients with severe asthma, 446 had uncontrolled and 123 had controlled asthma. Among those with uncontrolled asthma, 196 (44%) had 2 or more positive biomarkers, 187 (42%) had 1 positive biomarker, 325 (73%) had low blood EOS, and 63 (14%) were triple-negative. Disease burden was similarly high across uncontrolled subgroups, irrespective of biomarker status, with poor symptom control (Asthma Control Test score 14.9-16.6), impaired health status (St George's Respiratory Questionnaire total score 46.7-49.4), clinically important breathlessness (modified Medical Research Council grade ≥2 in 47.3%-57.1%), and 1 or more severe exacerbation (70.6%-76.2%).

CONCLUSIONS: Type-2 inflammatory biomarkers did not differentiate disease burden in patients with severe asthma. Patients with low type-2 inflammatory biomarker levels have few biologic therapy options; their needs should be addressed. **(J Allergy Clin Immunol Pract 2024;■:■-■)**

Key words: *Asthma; Allergy; Disease burden; Eosinophil; Exacerbations; Fractional exhaled nitric oxide; Health status; Health care resource utilization; Symptom control; Type-2 inflammatory biomarkers*

INTRODUCTION

Asthma is a heterogeneous inflammatory disease of the airways that is estimated to affect 1% to 29% of people in different countries.[1] Most patients have mild or moderate asthma, which is defined as asthma that can be controlled with low- or medium-

[a]BioPharmaceuticals Medical, AstraZeneca, Gothenburg, Sweden
[b]BioPharmaceuticals Medical, AstraZeneca, Gaithersburg, Md
[c]Real World Data Science, BioPharmaceuticals Medical, AstraZeneca, Cambridge, United Kingdom
[d]Global Health Economics and Payer Evidence, AstraZeneca, Cambridge, United Kingdom
[e]The Woolcock Institute of Medical Research and Macquarie University, Sydney, New South Wales, Australia
[f]Respiratory Medicine Unit, Department of Translational Medicine, Università di Ferrara, Ferrara, Italy

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Data availability statement: Data underlying the findings described in this article may be obtained in accordance with AstraZeneca's data-sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure. Data for studies directly listed on Vivli can be requested through Vivli at http://www.vivli.org/. Data for studies not listed on Vivli could be requested through Vivli at https://vivli.org/members/enquiries-about-studies-not-listed-on-the-vivli-platform/. AstraZeneca Vivli member page is also available outlining further details: https://vivli.org/ourmember/astrazeneca/. The NOVELTY protocol is available at https://astrazenecagrouptrials.pharmacm.com/.

Conflicts of interest: B. Ding is an employee of AstraZeneca. S. Chen is an employee of and holds shares in AstraZeneca. E. Rapsomaniki is an employee of and holds shares in AstraZeneca. A. Quinton is an employee of and holds shares in AstraZeneca. W. Cook is an employee of AstraZeneca. H. K. Reddel has participated in advisory boards for AstraZeneca, Chiesi, GlaxoSmithKline, Novartis, and Sanofi-Genzyme; received honoraria from Alkem, AstraZeneca, Boehringer Ingelheim, Chiesi, Getz, GlaxoSmithKline, Sanofi, and Teva Pharmaceuticals for independent medical educational presentations; received independent research funding from AstraZeneca, GlaxoSmithKline, and Novartis; received consulting fees from AstraZeneca and Novartis; and has a leadership role in the Global Institute for Asthma and a member of the Australian National Asthma Council Guidelines Committee. A. Papi has received research grants from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Pfizer, Sanofi, and Teva; consulting fees from AstraZeneca, Avillion, Chiesi, Elpen Pharmaceuticals, GlaxoSmithKline, IQVIA, Novartis, and Sanofi; and payment or honoraria from AstraZeneca, Avillion, Boehringer Ingelheim, Chiesi, Edmond Pharma, Elpen Pharmaceuticals, GlaxoSmithKline, IQVIA, Menarini, MSD, Mundipharma, Novartis, Sanofi, Teva, and Zambon.

For the video abstract, see Video E1 in this article's Online Repository at www.jaci-inpractice.org.

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Corresponding author: Bo Ding, PhD, AstraZeneca, Pepparedsleden 1, Gothenburg SE 431 83, Mölndal, Sweden. E-mail: Bo.Ding@astrazeneca.com.

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dose inhaled corticosteroids (ICSs) with or without long-acting β_2-agonists (LABAs).[1] However, patients with severe asthma have a substantial burden of exacerbations and associated health care resource utilization[2-4] despite treatment with medium- to high-dose ICS/LABA. Up to 81% of these patients continue to have uncontrolled symptoms,[5] leading to more exacerbations, greater symptom burden, lower health-related quality of life, and more oral corticosteroid (OCS) use, compared with patients with controlled asthma.[4,5] Although fewer than 5% of patients with asthma have uncontrolled severe disease despite medium- or high-dose ICS/LABA, these patients are estimated to incur nearly 40% of all asthma-related costs.[6] Indeed, it has been estimated that over the next 20 years, $300.6 billion in direct costs could be saved in the United States alone if all patients were able to achieve good asthma control during that time period.[7]

Patients with asthma can be categorized as having type-2 high or type-2 low airway inflammation, based on the presence or absence of specific biomarkers, including history of allergy, high blood eosinophil (EOS) count, and/or high fractional exhaled nitric oxide (FeNO) levels[8-10]; however, type-2 status is not fixed and may change over time, particularly following allergen exposure, corticosteroid treatment, or biologic therapy directed at type-2 inflammation.[11,12] A history of allergy, which is often associated with elevated serum immunoglobulin (IgE), has been associated with higher health care resource utilization and cost versus non-allergy-related asthma.[13] Patients with high blood EOS count (≥300 cells/μL) are known to be at a higher risk of exacerbations and poor asthma control versus patients with low blood EOS count (<300 cells/μL).[1,14,15] However, in one study, nearly 20% of patients with severe asthma who had a low blood EOS count, and had not been treated with biologics, also experienced exacerbations and had less than optimal asthma control within the 12 months following their most recent blood EOS count measurement.[16] Patients with uncontrolled moderate to severe asthma with high baseline FeNO levels (≥50 parts per billion [ppb]) were found to have a higher exacerbation rate compared with patients with lower FeNO levels (<25 ppb) in a *post hoc* analysis of a clinical trial.[17]

Clinical and immunologic phenotyping of patients has led to the development of several monoclonal antibody add-on therapies for patients with type-2 high severe asthma. High blood EOS count is a predictor of response to type-2-targeted biologic therapy and is therefore used as an eligibility criterion for these treatments.[1] Although the introduction of biological therapy can markedly improve outcomes for many patients with severe asthma, patient response to treatment can vary, with some patients seeing very little benefit at all.[18,19] Currently, 5 types of biologics are licensed in the United States for the treatment of severe asthma: anti-IgE (omalizumab),[20] anti-IL-5 (mepolizumab and reslizumab),[21,22] anti-IL-5 receptor-α (benralizumab),[23] anti-IL-4 receptor-α (dupilumab),[24] and anti-thymic stromal lymphopoietin (tezepelumab).[25] The first 4 of these are solely indicated for the treatment of patients with type-2 high severe asthma; thus, patients with type-2 low asthma have the fewest therapy options. In addition, because patients positive for more than 1 inflammatory pathway may be eligible for more than 1 biologic add-on therapy, there is a clinical need to better characterize this population and assess the disease burden in these patients.[9,10]

The aim of this analysis was to assess the burden of disease in relation to biomarker status by examining history of allergy, blood EOS count, and FeNO level in a cross-sectional analysis of patients with uncontrolled and controlled severe asthma recruited from primary care and specialist centers. Baseline data from the NOVEL observational longiTudinal studY (NOVELTY; NCT02760329),[26,27] a multicountry, prospective observational study of patients with a physician-assigned diagnosis of asthma and/or chronic obstructive pulmonary disease (COPD), were used in this analysis.

METHODS

Study design

Details of the NOVELTY design have been published previously.[26,27] Briefly, NOVELTY included patients aged 18 years or older (or ≥12 years in some countries) with a physician-assigned diagnosis of asthma, COPD, or both (asthma + COPD). Patients were enrolled at primary care and specialist centers in 19 countries in the Americas, Asia, Australia, and Europe. The NOVELTY protocol was approved in each participating country by the relevant independent ethics committees and institutional review boards, and all patients provided written informed consent.

Study population

Patients were included in this analysis if they had a physician-assigned diagnosis of asthma and physician-assessed severe asthma, and had completed the baseline study visit, which were conducted from July 2016 to March 2018.[26] To avoid the extreme selectivity of regulatory severe asthma trials and allow generalization of findings to patients in clinical practice,[28] no diagnostic or severity criteria were provided. Recruitment was stratified by physician-assigned diagnosis of asthma, COPD, or both (asthma + COPD) and physician-assessed severity (mild, moderate, or severe), to ensure sufficient patient numbers for subgroup analyses. Patients with physician-assigned diagnoses of both asthma and COPD (asthma + COPD) were included in a sensitivity analysis.

Study assessments

Physicians reported baseline and clinical characteristics, as detailed previously.[26] Symptom control over the previous 4 weeks was assessed using the Asthma Control Test (ACT), which comprises 5 items scored on a 1 to 5 scale; the total score (5-25) is the sum of all items, with higher scores indicating better asthma control.[29] Uncontrolled asthma was defined by an ACT score of less than 20 and/or 1 or more severe physician-reported exacerbation (requiring systemic corticosteroids, emergency room [ER] visit, or hospitalization during the 12-month period before the baseline visit). Controlled asthma was defined as an ACT score of 20 or more with no severe physician-reported exacerbations in the previous 12 months.[30]

The biomarkers assessed in this analysis were history of allergy (present or absent, restricted to seasonal allergic rhinitis/sinusitis; perennial allergic rhinitis/sinusitis; allergic conjunctivitis; atopic eczema; skin allergy; latex, mold, or animal allergy; or positive test for atopy), blood EOS count (high: ≥300 cells/μL; low: <300 cells/μL), and FeNO level (high: ≥25 ppb; low: <25 ppb). Subgroups comprised patients who (1) were positive for 2 or more biomarkers (any combination), (2) were positive for only 1 of the biomarkers, (3) had low blood EOS count, and (4) were triple-negative for biomarkers (no history of allergy, blood EOS count <300 cells/μL, and FeNO <25 ppb).

Shortness of breath was assessed using the modified Medical Research Council (mMRC) dyspnea scale,[31] which has 4 grades (0-4), with a higher grade indicating worse dyspnea; mMRC dyspnea grade 2 or higher is classified as clinically important dyspnea. Health status was evaluated using St George's Respiratory Questionnaire (SGRQ),[32] a

50-item questionnaire scored on a 0 to 100 scale, with higher scores indicating worse health status. Exacerbations, defined as episodes beyond the patient's usual day-to-day variance during the 12 months before baseline, were reported by physicians at the baseline visit. Severe exacerbations were defined as those requiring treatment with systemic corticosteroids, ER visits, or hospital admission during the 12-month period before baseline. Asthma-related health care resource utilization included asthma-related general practitioner, specialist, and ER visits, hospital admissions, and nights hospitalized due to exacerbations during the 12 months before baseline.

Statistical analysis

Descriptive results for continuous variables are presented using median and interquartile range; categorical variables are presented using frequency distributions. Differences in mMRC dyspnea grade, ACT and SGRQ scores, physician-reported exacerbations, and health care resource utilization between patients with uncontrolled and controlled severe asthma were compared using *t* tests for normally distributed data and Kruskal-Wallis tests for nonnormally distributed data. R statistical software (version 4.1.0, The R Foundation for Statistical Computing, Vienna, Austria) was used in the analysis.[33] The distribution of the 3 biomarkers (history of allergy, blood EOS count, and FeNO level) and their overlap is described in patients with severe asthma, uncontrolled severe asthma, and controlled severe asthma. Descriptive results are also reported for the 4 subsets of patients with uncontrolled severe asthma.

Since physicians may assess asthma severity differently than recommended in guidelines, sensitivity analyses were performed by repeating the main analyses in patients in NOVELTY with asthma (regardless of physician-assessed severity) who were treated with medium- or high-dose ICS + LABA with or without a long-acting muscarinic antagonist, or any biologic therapy or maintenance OCS. To further assess the generalizability of the findings in patients from this global, real-world population, sensitivity analyses were also performed in patients with physician-assessed severe asthma + COPD.

Further sensitivity analyses excluded patients treated with anti-IL-5/IL-5 receptor (IL-5R), patients treated with maintenance OCS, patients treated with anti-IgE, anti-IL-5/IL-5R, and/or maintenance OCS, and current smokers.

RESULTS

Patient characteristics

Overall, 647 patients with severe asthma and no missing data for history of allergy, blood EOS count, or FeNO level were included (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org). Of these, 446 (68.9%) had uncontrolled severe asthma (mean age, 54.0 years; 34.3% males) and 123 (19.0%) had controlled severe asthma (mean age, 55.3 years; 43.1% males). An additional 78 patients (12.1%) had missing ACT data and so could not be classified as having either controlled or uncontrolled asthma and were not included in this analysis (see Figure E2 in this article's Online Repository at www.jaci-inpractice.org).

The uncontrolled severe asthma group had a lower proportion of patients from North-East Asia (4.0% vs 15.4%), and a greater proportion of patients with higher body mass index (mean, 29.6 vs 27.4 kg/m^2; $P = .002$), treated with maintenance OCS (11.7% vs 7.8%; $P = .33$), or with 1 or more nonrespiratory comorbidities (69.7% vs 56.1%; $P = .005$) compared with the controlled severe asthma group, respectively (Table I). Postbronchodilator forced expiratory volume in one second was lower in patients with uncontrolled severe asthma compared with controlled severe asthma (75.4% vs 84.0% predicted; $P < .001$), but similar proportions were treated with type-2 high targeted biologic therapy (Table I).

Biomarker distribution

Among patients with uncontrolled severe asthma, 52 (11.7%) were positive for all 3 type-2 inflammatory biomarkers, 144 (32.3%) had 2 biomarkers, and 383 (85.9%) had 1 or more biomarker. Of the prespecified subgroups, 196 (43.9%) had 2 or more positive biomarkers (mean age, 53.5 years; 42.9% male), 187 (41.9%) had only 1 positive biomarker (mean age, 52.6 years; 28.9% male), 325 (72.9%) had low blood EOS count (mean age, 54.0 years; 31.1% male), and 63 (14.1%) were triple-negative (mean age, 59.8 years; 23.8% male; Table II; see Figure E3 in this article's Online Repository at www.jaci-inpractice.org). Patients who were triple-negative were more likely to be female, to have a body mass index equal to or higher than 30 kg/m^2, and have fewer respiratory comorbidities than those who were positive for 2 or more biomarkers, only 1 biomarker, or those with low blood EOS count (Table II).

A large proportion of patients in both the uncontrolled and controlled severe asthma groups had a history of allergy (67.9% and 74.8%, respectively). However, many patients in both the uncontrolled and controlled severe asthma groups had low blood EOS count (72.9% and 74.0%, respectively) or low FeNO levels (53.6% and 50.4%, respectively). A combination of history of allergy but low blood EOS count was seen in 49.6% and 54.5% of patients with uncontrolled and controlled severe asthma, respectively (see Table E1 in this article's Online Repository at www.jaci-inpractice.org).

Similar proportions of patients with uncontrolled and controlled severe asthma had 1 or more elevated biomarker (85.9% and 88.6%, respectively) and 1 elevated biomarker (41.9% and 39.0%, respectively). The proportion of patients who were triple-negative for the biomarkers was similar in the uncontrolled and the controlled severe asthma groups (14.1% and 11.4%, respectively; Figure 1; Table E1).

Symptom burden and health status

Two-thirds (67.9%) of patients with uncontrolled severe asthma were classified as having "not well controlled" or "very poorly controlled" asthma based on ACT score, representing their symptom control over the previous 4 weeks. Not surprisingly, patients with uncontrolled severe asthma had worse asthma symptom control, compared with patients with controlled severe asthma (ACT score 15.2 vs 22.4, respectively; $P < .001$; see Table E2 in this article's Online Repository at www.jaci-inpractice.org). Similarly, poor symptom control was seen within the uncontrolled subgroups, irrespective of their biomarker status. Mean mMRC dyspnea grades for patients with uncontrolled severe asthma were higher than for those with controlled severe asthma (1.61 vs 0.70, respectively; $P < .001$). Across the uncontrolled subgroups, mean mMRC dyspnea grades were similar (range, 1.57-1.83) regardless of biomarker status. Almost half the patients with uncontrolled severe asthma had clinically important breathlessness (mMRC dyspnea grade $\geq$2; 49.3%), versus few patients with controlled severe asthma (12.4%). The highest proportion of patients with mMRC dyspnea grade 2 or higher was in the subgroup who were triple-negative (57.1%; Table II).

TABLE I. Baseline demographic and clinical characteristics in patients with physician-assessed severe asthma, uncontrolled severe asthma, and controlled severe asthma

Variable	All severe asthma (N = 647)*	Controlled severe asthma (N = 123)	Uncontrolled severe asthma (N = 446)	*P* value (controlled vs uncontrolled severe asthma)
Age (y)				.38
Mean ± SD	54.0 ± 15.3	55.3 ± 15.2	54.0 ± 14.9	
Median (IQR)	56.0 (45.0-66.0)	58.0 (49.0-65.0)	56.0 (44.0-66.0)	
Age at diagnosis (y)				.06
N with data	626	117	434	
Mean ± SD	29.4 ± 20.8	32.8 ± 21.5	28.9 ± 20.4	
Median (IQR)	30.0 (9.0-46.0)	35.0 (14.0-50.0)	29.0 (9.0-45.0)	
Sex				.08
Male	240 (37.1)	53 (43.1)	153 (34.3)	
Ethnicity				<.001
N with data	639	120	443	
White†	485 (75.9)	82 (68.3)	352 (79.5)	
Black‡	16 (2.5)	3 (2.5)	9 (2.0)	
North-East Asian	39 (6.1)	19 (15.8)	18 (4.1)	
South-East Asian	19 (3.0)	5 (4.2)	13 (2.9)	
Other	80 (12.5)	11 (9.2)	51 (11.5)	
BMI (kg/m^2)				.002
N with data	641	121	443	
Mean ± SD	29.1 ± 7.0	27.4 ± 5.7	29.6 ± 7.1	
Median (IQR)	27.8 (24.2-32.8)	26.6 (23.6-30.4)	28.3 (24.9-33.3)	
BMI WHO categories				.05
N with data	641	121	443	
<18.5 kg/m^2	18 (2.8)	6 (5.0)	10 (2.3)	
≥18.5 to <25 kg/m^2	168 (26.2)	36 (29.8)	107 (24.2)	
≥25 to <30 kg/m^2	213 (33.2)	44 (36.4)	143 (32.3)	
≥30 kg/m^2	242 (37.8)	35 (28.9)	183 (41.3)	
Smoking status				.49
Current smoker	44 (6.8)	9 (7.3)	32 (7.2)	
Former smoker	198 (30.6)	43 (35.0)	132 (29.6)	
Never smoked	405 (62.6)	71 (57.7)	282 (63.2)	
Respiratory comorbidities				.33
Patients with ≥1 respiratory comorbidity	362 (56.0)	66 (53.7)	261 (58.5)	
Nonrespiratory comorbidities				.005
Patients with ≥1 nonrespiratory comorbidity	419 (64.8)	69 (56.1)	311 (69.7)	
mMRC dyspnea grade				<.001
N with data	632	121	438	
Mean ± SD	1.41 ± 1.01	0.70 ± 0.75	1.61 ± 0.99	
mMRC dyspnea grade ≥2	267 (42.2)	15 (12.4)	216 (49.3)	
Post-BD FEV_1 (% predicted)				<.001
N with data	608	112	421	
Mean ± SD	76.8 ± 23.6	84.0 ± 20.7	75.4 ± 24.0	
Medication				
N with data	580	115	401	
Maintenance OCS	60 (10.3)	9 (7.8)	47 (11.7)	.33
Anti-IgE (omalizumab)	152 (26.2)	34 (29.6)	103 (25.7)	.50
Anti-IL-5/IL-5R (mepolizumab, reslizumab, benralizumab)	60 (10.3)	9 (7.8)	47 (11.7)	.27
Anti-IL-4R (dupilumab)	7 (1.2)	2 (1.7)	5 (1.2)	.50

(continued)

TABLE I. *(Continued)*

Variable	All severe asthma (N = 647)*	Controlled severe asthma (N = 123)	Uncontrolled severe asthma (N = 446)	*P* value (controlled vs uncontrolled severe asthma)
History of allergy§				
Yes	479 (74.0)	103 (83.7)	322 (72.2)	.01
Blood EOS count (cells/μL)				.75
Mean ± SD	246.0 ± 216.8	241.0 ± 238.2	248.1 ± 210.9	
Median (IQR)	180.00 (110.00-300.00)	180.00 (120.00-300.00)	185.00 (110.00-310.00)	
FeNO (ppb)				.95
Mean ± SD	34.82 ± 33.33	35.44 ± 32.69	35.28 ± 35.29	
Median (IQR)	23.00 (14.00-41.50)	24.00 (14.00-43.00)	22.00 (13.25-41.00)	

ACT, Asthma control test; *BD*, bronchodilator; *BMI*, body mass index; *EOS*, eosinophil; *FeNO*, fractional exhaled nitric oxideo; *FEV_1*, forced expiratory volume in one second; *IgE*, immunoglobulin E; *IL-4R*, IL-4 receptor; *IL-5*, interleukin-5; *IL-5R*, interleukin-5 receptor; *IQR*, interquartile range; *mMRC*, modified Medical Research Council; *OCS*, oral corticosteroid; *ppb*, parts per billion; *SD*, standard deviation; *WHO*, World Health Organization.

Data are presented as n (%) unless otherwise stated.

*All severe asthma includes 78 patients whose asthma control status could not be classified.

†The term 'Caucasian' was used in the electronic case report form for recording patient ethnicity.

‡The term 'African American' was used in the electronic case report form for recording patient ethnicity.

§History of allergy was derived from the question in the electronic case report form: "Any current or past allergies or allergy?" with the exception of food allergy, drug allergy, and anaphylaxis. Biomarker positivity is defined as history of allergy (restricted to seasonal allergic rhinitis/sinusitis; perennial allergic rhinitis/sinusitis; allergic conjunctivitis; atopic eczema; skin allergy; latex, mold, or animal allergy; or positive test for atopy), blood EOS ≥300 cells/μL, and/or FeNO ≥25 ppb. Low blood EOS count is defined as blood EOS count of <300 cells/μL. Triple-negative biomarkers are defined as no history of allergy, blood EOS <300 cells/μL, and FeNO <25 ppb.

Mean SGRQ total scores were higher in patients with uncontrolled versus controlled severe asthma (48.1 vs 22.7, respectively; $P < .001$), and were similar across biomarker subgroups (46.7-49.4). Mean SGRQ impact scores (38.2 vs 14.7; $P < .001$), SGRQ symptom scores (58.8 vs 31.9; $P < .001$), and SGRQ activity scores (59.6 vs 31.9; $P < .001$) were higher in the uncontrolled severe asthma group compared with the controlled severe asthma group. SGRQ domain scores were similar across the biomarker subgroups of uncontrolled severe asthma (Figure 2; see Table E3 in this article's Online Repository at www.jaci-inpractice.org).

Exacerbations

Fewer patients with uncontrolled severe asthma had no physician-reported exacerbations in the 12 months before baseline compared with the controlled severe asthma group (23.4% vs 84.6%, respectively; $P < .001$, Figure 3, *A*). By definition, no patients with controlled severe asthma had any severe asthma exacerbations, whereas 72.6% with uncontrolled severe asthma had 1 or more severe exacerbation ($P < .001$). The proportion of patients with severe exacerbations was similar across the biomarker subgroups (Figure 3, *B*; see Table E4 in this article's Online Repository at www.jaci-inpractice.org).

Health care resource utilization

During the previous 12 months, patients with uncontrolled severe asthma had more asthma-related general practitioner visits (mean 2.6 visits/patient/y) compared with patients with controlled severe asthma (mean 1.2 visits/patient/y), with similar frequency in the uncontrolled severe asthma biomarker subgroups ($P < .001$; Figure 4, Table E4). Although the mean number of specialist visits was similar between patients with uncontrolled and controlled severe asthma (3.94 vs 3.84, respectively; $P = .81$), there was a slightly wider distribution across biomarker subgroups, ranging from 3.58 for patients with 1 biomarker to 4.49 for patients who were triple-negative. Asthma-related ER visits (range, 0.48-0.67; $P < .001$) and hospital admission visits (range, 0.23-0.29; $P < .001$) were similar among the uncontrolled subgroups although by definition, patients with controlled severe asthma had no asthma-related ER or hospital admission visits. The mean number of nights spent in hospital due to exacerbations was 1.16 nights/patient/y for patients with uncontrolled severe asthma.

Sensitivity analyses

Results for patients with asthma treated with a medium- or high-dose ICS + LABA, or a medium-dose ICS + LABA with a long-acting muscarinic antagonist or any biologic therapy or maintenance OCS (N = 1162), reflecting patients with medium- or high-intensity treatment, were similar in direction and magnitude to the main analysis, across the uncontrolled and controlled asthma patient groups and the uncontrolled asthma biomarker subgroups (see Tables E5-E8 and Figures E4, *A*, E5, and E6, *A*, in this article's Online Repository at www.jaci-inpractice.org).

For the severe asthma + COPD sensitivity analysis (N = 277; see Tables E9-E12 and Figures E4, *B*, E6, *B*, and E7 in this article's Online Repository at www.jaci-inpractice.org), more patients with controlled severe asthma + COPD had a history of allergy (74.8% vs 47.8%; Tables E1 and E12) and a combination of history of allergy/low blood EOS count (54.5% vs 34.8%; Tables E1 and E12) compared with the main analysis, respectively. In addition, more patients with controlled and uncontrolled severe asthma + COPD were triple-negative for biomarkers, compared with the main analysis (30.4% vs 11.4% and 23.5% vs 14.1%, respectively; Tables E1 and E12).

In the sensitivity analyses that excluded patients treated with anti-IL-5/IL-5R, patients treated with maintenance OCS, patients treated with anti-IgE, anti-IL-5/IL-5R, and/or maintenance OCS, and current smokers, biomarker distributions were similar to the main analysis (see Tables E13-E16 in this article's

TABLE II. Baseline demographic and clinical characteristics in patients with uncontrolled severe asthma with positivity for ≥2 biomarkers, only 1 biomarker, low blood ES count, and triple-negative biomarkers

Variable	Uncontrolled severe asthma with positivity for ≥2 biomarkers (N = 196)	Uncontrolled severe asthma with positivity for only 1 biomarker (N = 187)	Uncontrolled severe asthma with low blood EOS (N = 325)	Uncontrolled severe asthma with triple-negative biomarkers (N = 63)
Age (y)				
Mean ± SD	53.5 ± 14.6	52.6 ± 15.3	54.0 ± 14.8	59.8 ± 13.6
Median (IQR)	54.0 (45.0-64.0)	55.0 (43.0-64.0)	56.0 (44.0-66.0)	62.0 (52.5-69.0)
Age at diagnosis (y)				
N with data	190	181	316	63
Mean ± SD	29.8 ± 20.1	25.9 ± 20.0	27.8 ± 20.6	34.7 ± 21.3
Median (IQR)	30.0 (12.0-45.0)	25.0 (6.0-43.0)	26.5 (7.8-45.0)	36.0 (14.5-52.5)
Sex				
Male	84 (42.9)	54 (28.9)	101 (31.1)	15 (23.8)
Ethnicity				
N with data	195	185	323	63
White*	146 (74.9)	150 (81.1)	259 (80.2)	56 (88.9)
Black†	6 (3.1)	3 (1.6)	6 (1.9)	0
North-East Asian	10 (5.1)	5 (2.7)	12 (3.7)	3 (4.8)
South-East Asian	6 (3.1)	6 (3.2)	11 (3.4)	1 (1.6)
Other	27 (13.8)	21 (11.4)	35 (10.8)	3 (4.8)
BMI (kg/m^2)				
N with data	195	187	322	61
Mean ± SD	29.2 ± 6.5	29.6 ± 6.7	29.9 ± 7.4	31.0 ± 9.8
Median (IQR)	28.3 (24.5-32.7)	28.2 (25.3-33.3)	28.4 (25.0-33.9)	30.1 (24.1-34.7)
BMI WHO categories				
N with data	195	187	322	61
<18.5 kg/m^2	5 (2.6)	2 (1.1)	6 (1.9)	3 (4.9)
≥18.5 to <25 kg/m^2	51 (26.2)	43 (23.0)	75 (23.3)	13 (21.3)
≥25 to <30 kg/m^2	64 (32.8)	65 (34.8)	105 (32.6)	14 (23.0)
≥30 kg/m^2	75 (38.5)	77 (41.2)	136 (42.2)	31 (50.8)
Smoking status				
Current smoker	12 (6.1)	16 (8.6)	24 (7.4)	4 (6.3)
Former smoker	55 (28.1)	54 (28.9)	94 (28.9)	23 (36.5)
Never smoked	129 (65.8)	117 (62.6)	207 (63.7)	36 (57.1)
Respiratory comorbidities				
Patients with ≥1 respiratory comorbidity	132 (67.3)	108 (57.8)	183 (56.3)	21 (33.3)
Nonrespiratory comorbidities				
Patients with ≥1 nonrespiratory comorbidity	128 (65.3)	135 (72.2)	231 (71.1)	48 (76.2)
mMRC dyspnea grade				
N with data	193	182	320	63
Mean ± SD	1.57 ± 0.98	1.58 ± 1.0	1.63 ± 1.01	1.83 ± 0.96
mMRC dyspnea grade ≥2	94 (48.7)	86.0 (47.3)	158 (49.4)	36 (57.1)
Post-BD FEV_1 (% predicted)				
N with data	184	180	305	57
Mean ± SD	73.5 ± 23.0	77.6 ± 24.9	76.7 ± 24.3	74.4 ± 24.3
Medication				
Maintenance OCS	20 (11.6)	21 (12.4)	34 (11.6)	6 (10.2)
Anti-IgE (omalizumab)	48 (27.7)	50.0 (29.6)	72 (24.7)	5 (8.5)
Anti-IL-5/IL-5R (mepolizumab, reslizumab, benralizumab)	20 (11.6)	22 (13.0)	43 (14.7)	5 (8.5)
Anti-IL-4R (dupilumab)	4 (2.3)	0	2 (0.7)	1 (1.7)
History of allergy‡				
Yes	164 (83.7)	142 (75.9)	234 (72.0)	16 (25.4)

(continued)

TABLE II. *(Continued)*

Variable	Uncontrolled severe asthma with positivity for ≥2 biomarkers (N = 196)	Uncontrolled severe asthma with positivity for only 1 biomarker (N = 187)	Uncontrolled severe asthma with low blood EOS (N = 325)	Uncontrolled severe asthma with triple-negative biomarkers (N = 63)
Blood EOS count (cells/μL)				
Mean ± SD	353.1 ± 245.4	172.5 ± 143.9	149.4 ± 74.4	145.9 ± 69.7
Median (IQR)	320.00 (160.00-470.00)	140.00 (90.00-210.00)	140.00 (90.00-200.00)	130.00 (90.00-190.00)
FeNO (ppb)				
Mean ± SD	53.96 ± 38.18	22.81 ± 27.73	30.48 ± 33.13	14.21 ± 5.14
Median (IQR)	40.00 (29.00-69.00)	16.00 (10.00-22.00)	20.00 (12.00-35.00)	15.00 (10.50-18.00)

ACT, Asthma control test; *BD*, bronchodilator; *BMI*, body mass index; *EOS*, blood eosinophil; *FeNO*, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in one second; *IgE*, immunoglobulin E; *IL-4R*, IL-4 receptor; *IL-5*, interleukin-5; *IL-5R*, interleukin-5 receptor; *IQR*, interquartile range; *mMRC*, modified Medical Research Council; *OCS*, oral corticosteroid; *ppb*, parts per billion; *SD*, standard deviation; *WHO*, World Health Organization.
Data are presented as n (%) unless otherwise stated.
*The term 'Caucasian' was used in the electronic case report form for recording patient ethnicity.
†The term 'African American' was used in the electronic case report form for recording patient ethnicity.
‡History of allergy was derived from the question in the electronic case report form: "Any current or past allergies or allergy?" with the exception of food allergy, drug allergy, and anaphylaxis. Biomarker positivity is defined as history of allergy (restricted to seasonal allergic rhinitis/sinusitis; perennial allergic rhinitis/sinusitis; allergic conjunctivitis; atopic eczema; skin allergy; latex, mold, or animal allergy; or positive test for atopy), blood EOS ≥300 cells/μL, and/or FeNO ≥25 ppb. Low blood EOS count is defined as blood EOS count of <300 cells/μL. Triple-negative biomarkers are defined as no history of allergy, blood EOS <300 cells/μL, and FeNO <25 ppb.

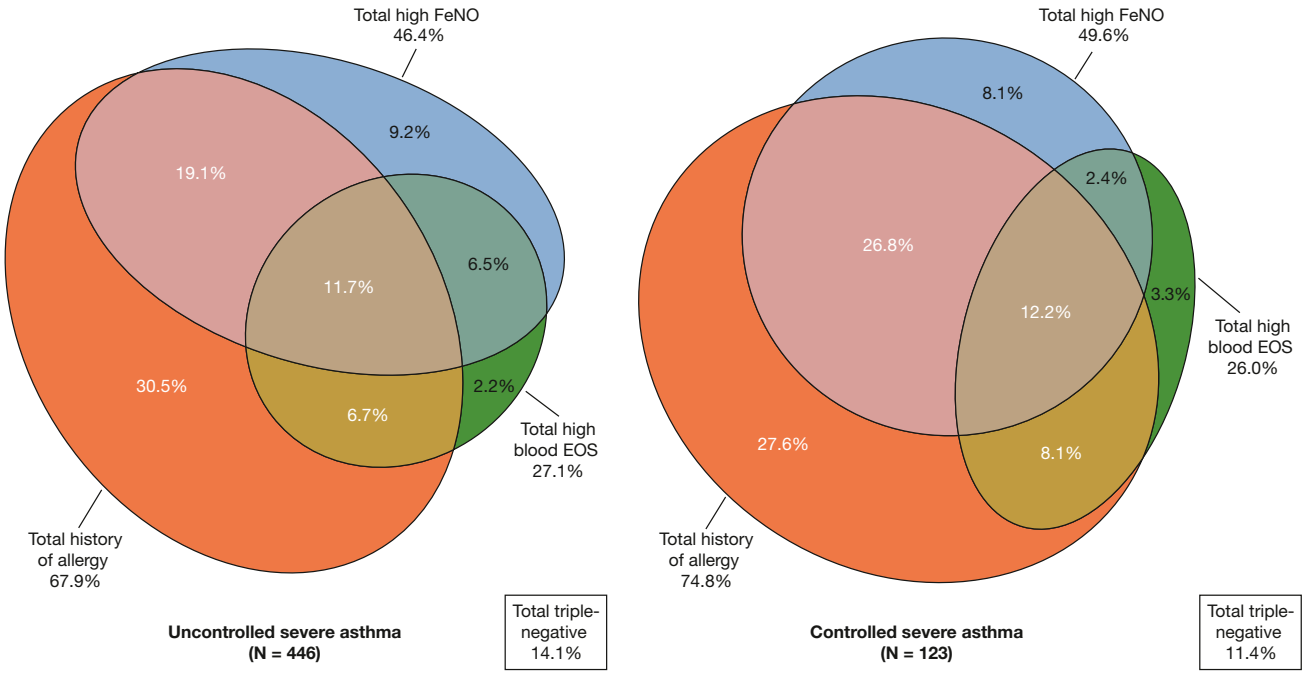

FIGURE 1. Type-2 inflammatory biomarker incidence across severe uncontrolled and controlled asthma. Data are presented as n (%). Areas in the Venn diagrams are proportional to the numbers. High EOS is defined as blood EOS count of greater than or equal to 300 cells/μL. High FeNO is defined as greater than or equal to 25 ppb; allergy is defined as history of allergy (restricted to seasonal allergic rhinitis/sinusitis; perennial allergic rhinitis/sinusitis; allergic conjunctivitis; atopic eczema; skin allergy; latex, mold, or animal allergy; or positive test for atopy). *EOS*, Blood eosinophil; *FeNO*, fractional exhaled nitric oxide; *ppb*, parts per billion.

Online Repository at www.jaci-inpractice.org). Overall, 39.5% of patients with uncontrolled severe asthma were treated with anti-IgE, anti-IL-5/IL-5R, and/or maintenance OCS; when excluding these patients, the proportion of patients with uncontrolled severe asthma with low EOS count was similar when compared with the main analysis (70.5% vs 72.9%, respectively).

DISCUSSION

This global analysis of patients with physician-reported diagnosis of severe asthma provides novel data on the disease burden and distribution of type-2 inflammatory biomarkers (history of allergy, blood EOS count, FeNO level) in patients with uncontrolled or controlled severe asthma. The disease burden of uncontrolled severe asthma is substantial, with worse symptom

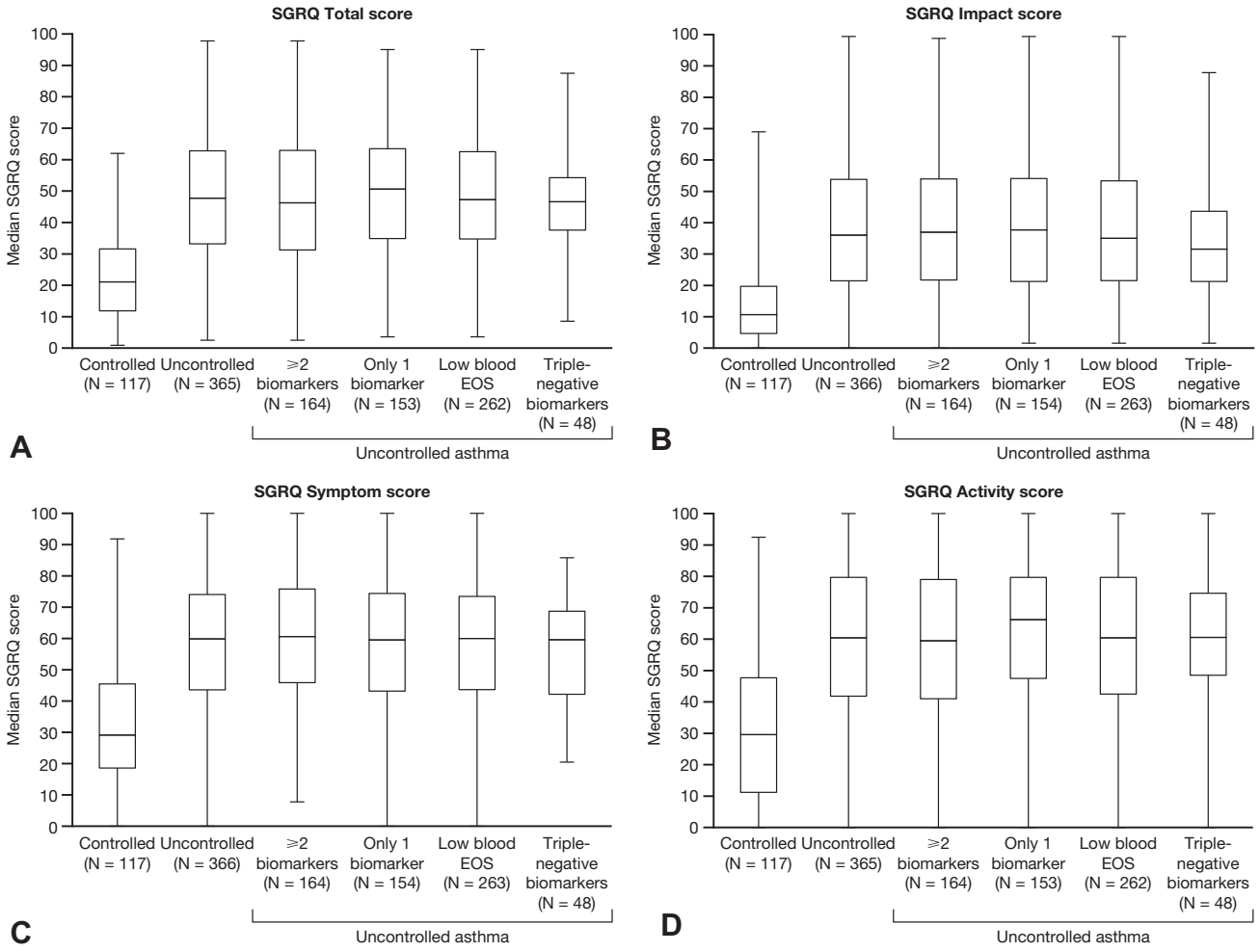

FIGURE 2. Patient health status across severe uncontrolled and controlled asthma using SGRQ by (**A**) total score, (**B**) impact score, (**C**) symptoms score, and (**D**) activity score. The center line denotes the median value, the boxes represent the interquartile range (25th to 75th percentiles), and the whiskers mark the minimum and maximum values; values available in Table E3. N is the number of patients with data. Biomarker positivity is defined as history of allergy (restricted to seasonal allergic rhinitis/sinusitis; perennial allergic rhinitis/sinusitis; allergic conjunctivitis; atopic eczema; skin allergy; latex, mold, or animal allergy; or positive test for atopy), blood EOS greater than or equal to 300 cells/μL, and/or FeNO greater than or equal to 25 ppb. Low blood EOS is defined as blood EOS count of less than 300 cells/μL. Triple-negative biomarkers are defined as no history of allergy, blood EOS less than 300 cells/μL, and FeNO less than 25 ppb. *EOS*, Blood eosinophil; *FeNO*, fractional exhaled nitric oxide; *ppb*, parts per billion; *SGRQ*, St George's Respiratory Questionnaire.

control, greater dyspnea, worse health status, more exacerbations, and higher health care resource utilization versus controlled severe asthma, consistent with findings in other studies.[4] Among subgroups of patients with uncontrolled severe asthma, the disease burden was broadly similar, regardless of whether the patients were positive for 2 or more biomarkers, only 1 biomarker, or had low blood EOS count. Patients who were triple-negative for biomarkers were more likely to be female, to be obese, and to have clinically important breathlessness compared with the other uncontrolled subgroups.

Most patients with uncontrolled (85.9%) and controlled (88.6%) severe asthma had 1 or more elevated biomarker, with the most common being a history of allergy. Among patients with uncontrolled severe asthma, 11.7% were positive for all 3 biomarkers, 43.9% had 2 or more biomarkers, and 32.3% had 2 biomarkers. In comparison, a cluster analysis of inflammatory biomarker expression in the International Severe Asthma Registry (ISAR, N = 1175), in which a similar proportion of patients (80%) had uncontrolled asthma,[34] reported high proportions of patients with elevated biomarkers (serum IgE, blood EOS count, and FeNO level): 27% had elevated levels of all 3 markers, 59% had 2 or more elevated biomarkers, and 88% had 1 or more elevated biomarker. Although the thresholds of blood EOS count and FeNO level in ISAR were consistent with our analysis (>300 cells/μL and >25 ppb, respectively), ISAR assessed levels of total IgE (threshold 75 kU/L); the proportion positive for this biomarker (59%) was lower than the proportion with history of allergies in the present study (67.9%). In a small cross-sectional Danish study (N = 166; thresholds: blood EOS count $\geq 0.3 \times 10^9$/L, total serum IgE ≥150 U/mL, and FeNO ≥25 ppb),[35] 15.1% had elevated levels of all biomarkers, 39.2% had 2 or more elevated biomarkers, and

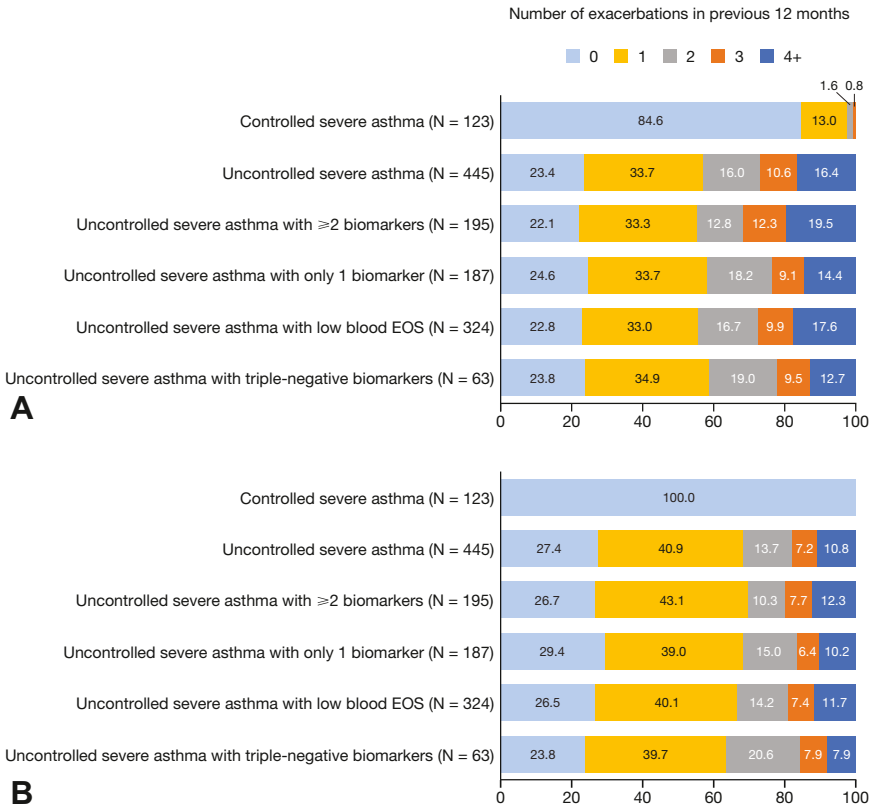

FIGURE 3. Proportion of patients with severe asthma and (**A**) asthma exacerbations (any severity), and (**B**) severe asthma exacerbations in the previous 12 months, by control status and biomarker subgroups. Severe exacerbations required systemic corticosteroids, ER visits, or hospital admission. N is the number of patients with data. Biomarker positivity is defined as history of allergy (restricted to seasonal allergic rhinitis/sinusitis; perennial allergic rhinitis/sinusitis; allergic conjunctivitis; atopic eczema; skin allergy; latex, mold, or animal allergy; or positive test for atopy), blood EOS greater than or equal to 300 cells/μL, and/or FeNO greater than or equal to 25 ppb. Low blood EOS is defined as blood EOS count of less than 300 cells/μL. Triple-negative biomarkers are defined as no history of allergy, blood EOS less than 300 cells/μL, and FeNO less than 25 ppb. *EOS*, Blood eosinophil; *ER*, emergency room; *FeNO*, fractional exhaled nitric oxide; *ppb*, parts per billion.

69.9% of patients with severe asthma had 1 or more elevated biomarker. Although that study did not differentiate between uncontrolled and controlled severe asthma, two-thirds (66.3%) of patients had uncontrolled symptoms, which was similar to our analysis (68.9%). However, 30.1% of their patients were triple-negative for biomarkers, which was much higher than the corresponding proportion in our analysis (14.1%). Of note, the Danish study used a higher threshold for total IgE (150 U/mL) than the ISAR study. In a study aiming to calculate the number of patients with type-2 uncontrolled severe asthma who would be eligible for dupilumab therapy in Italy (n = 19,960),[36] 24.8% had elevated levels of all 3 markers, 64.0% had 2 or more elevated biomarkers, and 90.6% of patients had 1 or more elevated biomarker. Although the proportions of patients were higher than in our analysis, this study used thresholds of total IgE greater than or equal to 30 IU/mL, blood EOS count greater than or equal to 150 cells/μL, and FeNO greater than or equal to 25 ppb, which is likely to have influenced the patient proportions observed.

In common with other studies,[35,37] most patients with uncontrolled severe asthma in our analysis had low blood EOS levels (72.9%), highlighting the importance of this phenotype. In addition, following exclusion of the 11.7% of patients with uncontrolled severe asthma who were treated with anti-IL-5/IL-5R, there was a similar proportion of patients with low blood EOS count (70.3%; Table E13). When excluding the 39.5% of patients with uncontrolled severe asthma who were treated with anti-IgE, anti-IL-5/IL-5R, and/or maintenance OCS, there was a similar proportion of patients with a low blood EOS count (70.5%; Table E15). Characterization of patients with severe asthma in the UK Severe Asthma Registry found that patients with type-2 low severe asthma frequently had prior high blood EOS count, consistent with the known variability of blood EOS[11] or possible suppression by corticosteroid exposure at the time of registry enrollment in a study where 68.9% of patients were treated with type-2 biologic therapy.[12] The Global Initiative for Asthma recommends repeating blood EOS and FeNO measurements up to 3 times when assessing patients for type-2 inflammation.[1] Bronchoalveolar lavage or sputum induction can be used to identify airway eosinophilia; however, because bronchoalveolar lavage is an invasive technique and sputum induction may not be possible for patients with impaired lung function, their use as routine procedures for biomarker assessment is limited.[38] In our analysis, OCS use was higher among patients with uncontrolled severe asthma than in those with controlled asthma and was similar across uncontrolled asthma biomarker subgroups.

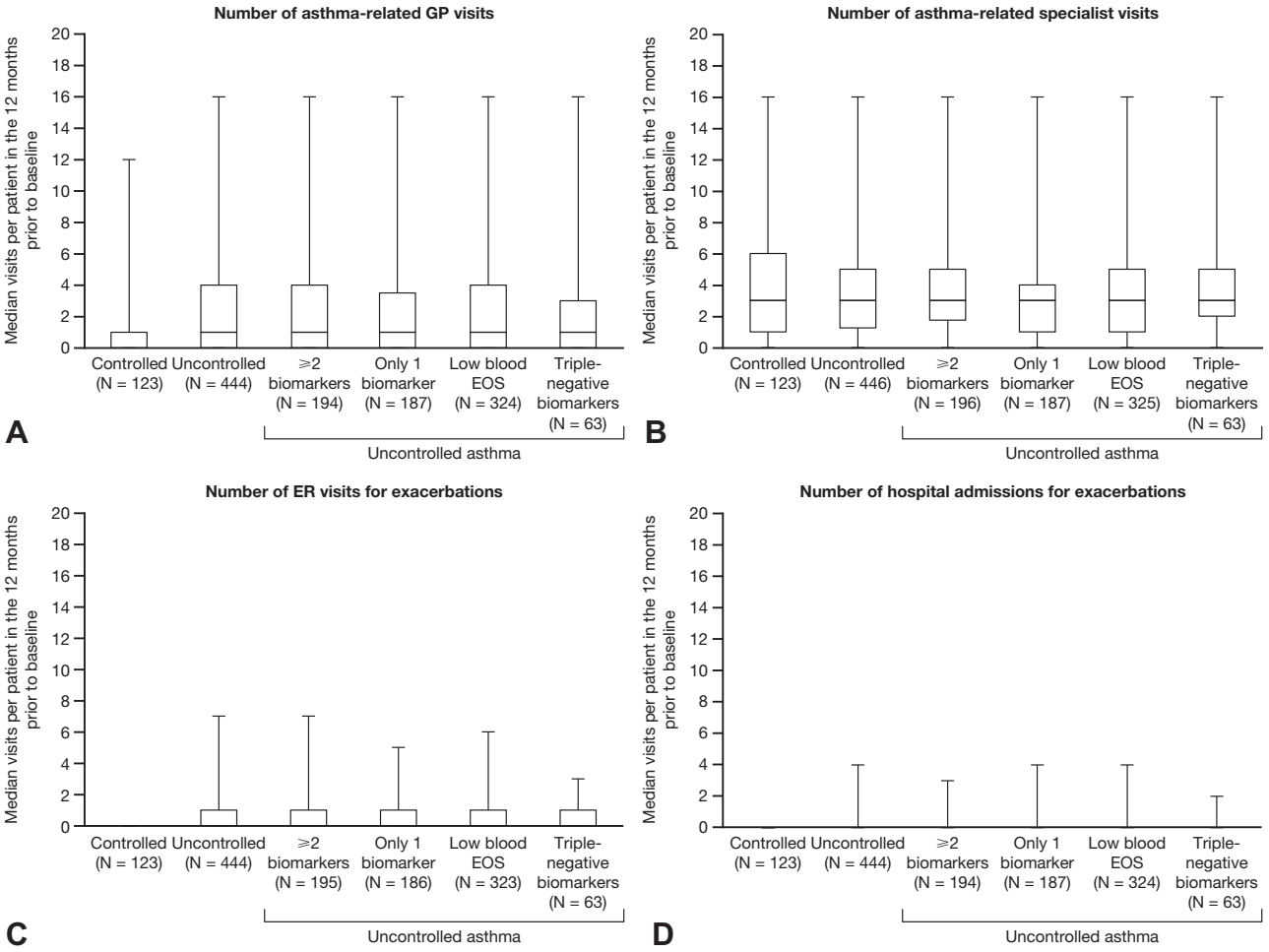

FIGURE 4. Asthma-related health care resource utilization in terms of number of (**A**) GP visits, (**B**) specialist visits, (**C**) ER visits for exacerbations, and (**D**) hospital admissions for exacerbations in the previous 12 months. The center line denotes the median value, the boxes represent the interquartile range (25th to 75th percentiles), and the whiskers mark the minimum and maximum values; values available in Table E4. N is the number of patients with data. Biomarker positivity is defined as history of allergy (restricted to seasonal allergic rhinitis/sinusitis; perennial allergic rhinitis/sinusitis; allergic conjunctivitis; atopic eczema; skin allergy; latex, mold, or animal allergy; or positive test for atopy), blood EOS greater than or equal to 300 cells/μL, and/or FeNO greater than or equal to 25 ppb. Low blood EOS is defined as blood EOS count of less than 300 cells/μL. Triple-negative biomarkers are defined as no history of allergy, blood EOS less than 300 cells/μL, and FeNO less than 25 ppb. *EOS*, Blood eosinophil; *ER*, emergency room; *FeNO*, fractional exhaled nitric oxide; *GP*, general practitioner; *ppb*, parts per billion.

As described previously, the thresholds used to distinguish high/low biomarker levels can vary between studies.[36,39-45] Indeed, it is becoming increasingly apparent that combining markers increases their clinical prediction value versus 1 marker alone.[39,43,44,46] For example, although many payers currently restrict type-2 biologic therapy to patients with a high blood EOS level (≥300 cells/μL), it has been suggested that patients who have blood EOS levels greater than or equal to 150 to less than 300 cells/μL while treated with high-dose ICS/LABA could qualify for biologic add-on therapy in the presence of other specific biomarkers.[36,42] Of note, we found that in patients with positivity for 2 or more biomarkers, exacerbation rate was similar to that in patients with low blood EOS count and in patients who were triple-negative, further highlighting the disease burden in patients who are negative for 3 biomarkers. In addition, patients with 2 or more biomarkers spent fewer nights in hospital due to exacerbations, compared with other subgroups of patients with uncontrolled severe asthma.

The strengths of NOVELTY include the fact that it is a large, global, observational study of patients recruited from clinical practice. To avoid the selection bias observed in regulatory studies,[28,47] NOVELTY enrolled an unselected population of patients with physician-assigned diagnosis and physician-assessed severity without provision of specific criteria, thereby increasing the generalizability of findings to real-world clinical practice.

Limitations have been described previously,[27] including potential variation in criteria used by physicians to diagnose asthma or COPD and in classification of disease severity, including

compared with severe asthma guidelines.[30] Furthermore, patients may not have had their treatment optimized in terms of inhaler technique and adherence, as is required by severe asthma guidelines[30] but is uncommon in clinical practice,[48] and patient recruitment may have been biased toward patients who made more frequent health care visits. Although NOVELTY included patients from 19 high-income and middle-income countries, the findings may not be representative of other countries; for example, the disease burden of patients from low-income countries is likely to be additionally impacted by underdiagnosis and undertreatment as well as poor access to health care.[1] With regard to the biomarkers used, the presence of atopy is typically established for clinical trials through skin prick testing or measurement of total serum IgE levels, rather than patient history of allergy; therefore, data presented do not correspond to the standard eligibility criteria for anti-IgE therapy. In addition, biomarker levels are known to fluctuate over time[11,49] or with OCS treatment.[12]

CONCLUSIONS

This analysis confirms that patients with uncontrolled severe asthma in clinical practice have a higher disease burden compared with patients with controlled severe asthma. In addition, type-2 inflammatory biomarkers did not reliably differentiate disease burden in patients with uncontrolled severe asthma; disease burden was similar in patients with uncontrolled severe asthma with positivity for 2 or more biomarkers, only 1 biomarker, and those with low blood EOS count, with only slight differences observed in patients who were triple-negative for biomarkers. This suggests that improved treatment options may assist in alleviating the burden of uncontrolled severe asthma for all patients, regardless of their biomarker status. Furthermore, patients with type-2 low airway inflammation have limited biologic therapy options and represent a large proportion of patients with uncontrolled severe asthma; 72.9% of patients with uncontrolled severe asthma in our analysis had low blood EOS levels, and 14.1% were triple-negative for biomarkers. Their unmet clinical needs should be further evaluated and addressed. Treatment options for patients with no or low type-2 inflammation are limited. Most current treatments target mediators of type-2 inflammation, and are effective in patients with high type-2 inflammation but may be ineffective in patients with low type-2 inflammation. Among currently available biologic treatments, tezepelumab has demonstrated efficacy irrespective of biomarker status and oral steroid dependence[50]; further treatment options are also being investigated for this population.

Acknowledgments

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