Original Research

Retrospective Study on the Association of Biomarkers With Real-world Outcomes of Omalizumab-treated Patients With Allergic Asthma

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ABSTRACT

Purpose: Biomarkers, including blood eosinophils (EoS) and fractional exhaled nitric oxide (FeNO), may affect omalizumab outcomes in allergic asthma, but evidence in the literature remains mixed. This study assessed omalizumab outcomes in real-world patients with allergic asthma stratified by pretreatment biomarker levels.

Methods: Patients with allergic asthma aged ≥12 years initiated on omalizumab with ≥12 months of data after index were identified in the Allergy Partners electronic medical records (2007–2018). Patients with ≥1 diagnosis of chronic obstructive pulmonary disease in combination with ≥10 pack-years of smoking, cystic fibrosis, Alpha-1 antitrypsin deficiency, bronchiectasis, interstitial lung disease, and sarcoidosis in the 12 months before or after index were excluded. Patients were stratified by pretreatment EoS (≥/<300 cells/μL) and FeNO (≥/<25 parts per billion). Outcomes, including Asthma Control Test (ACT) scores, forced expiratory volume in 1 second (FEV_1), and FEV_1 as a percentage of predicted value (FEV_1% predicted), were compared using generalized estimating equations at 6 and 12 months after versus before index date in stratified patients with outcome measures available at both time periods.

Findings: A total of 77 and 86 patients were stratified into the high and low EoS strata, respectively, and 56 patients into each of the intermediate-high and low FeNO strata. Compared with 6 months before index, mean difference (MD) in ACT scores at 6 months after index reached the minimally important difference of ≥3 points in high (MD = 3.75; 95% CI, 2.05–5.45) and low (MD = 4.56; 95% CI, 2.86–6.26) EoS, as well in the intermediate-high (MD = 3.75; 95% CI, 1.95–5.55) and low (MD = 3.55; 95% CI, 1.53–5.57) FeNO strata. Statistically significant improvements in mean FEV_1 were observed in the high EoS (MD = 0.22 L/s; 95% CI, 0.08–0.35 L/s) and intermediate-high FeNO (MD = 0.13 L/s; 95% CI, 0.03–0.24 L/s) strata but not in the lower strata. In terms of mean FEV_1% predicted, a statistically significant improvement was observed in high EoS stratum (MD = 4.95%; 95% CI, 0.60%–9.30%). Results that compared 12 months after versus before index date were similar.

Implications: Omalizumab was associated with statistically significant improvements in ACT scores largely reaching or exceeding minimally important difference across biomarker levels and with a statistically significant improvement in lung function more evident in high biomarker strata. Although response varied by biomarkers for some outcomes, all strata indicated improvements on ≥1 measure. Real-world patients with allergic asthma could benefit from omalizumab regardless of pretreatment biomarker levels, suggesting that pretreatment biomarker levels might not inform response. (*Clin Ther*. 2019;41:1956–1971)

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INTRODUCTION

In the United States, >25 million people are affected by asthma,[1] with nearly one-half reporting poorly controlled asthma.[2,3] Omalizumab is a biologic indicated for patients ≥6 years of age with moderate-to-severe persistent allergic asthma whose symptoms are inadequately controlled with inhaled corticosteroids (ICSs) and ≥1 other controller medication, such as long-acting β-agonists (LABAs).[4]

Omalizumab has been available for clinical use since 2003, and its efficacy and safety profile has been documented in randomized controlled trials.[5–8] Several observational studies have found omalizumab's effectiveness in a real-world setting.[9–15]

Variations in treatment response to asthma therapy are frequently observed[6,16,17] and are thought to be related to differing asthma phenotypes and endotypes.[18] Biomarkers, such as levels of blood eosinophils (EoS) and fractional exhaled nitric oxide (FeNO), were found to identify patients with a T-helper type 2-high asthma endotype, who are more likely to respond to treatments that target the T-helper type 2 inflammatory cascade.[19] A number of studies have examined the predictive value of EoS and FeNO for omalizumab outcomes among patients with asthma,[20–25] but evidence remains mixed. This study aimed to generate additional evidence on the association of biomarkers with omalizumab outcomes in a real-world setting and potentially facilitate clinicians with the selection of patients most likely to respond to treatment.

PATIENTS AND METHODS

Data Source

Data for this study (January 1, 2007, to June 30, 2018) were retrieved from electronic medical records (EMRs) of Allergy Partners (AP). The AP network consists of >120 providers, spanning >21 US states and 110 total locations of service. The study used no patient-identifiable information and was exempt from an independent review board review by the New England Independent Review Board.

Study Design

This study had a retrospective before–after design, in which patients became their own controls. The first administration of omalizumab defined the index date. The baseline period of ≤12 months before and including the index date was used to capture patient characteristics, with total serum immunoglobulin E (IgE), EoS, and FeNO measured any time before or on the index date and the treatment history before omalizumab observed any time before the index date. Outcomes were measured in the follow-up period, which spanned 12 months after the index date.

Patients included in the study had ≥1 diagnosis for asthma (International Classification of Diseases, Ninth Revision, Clinical Modification 493.xx or International Classification of Diseases, 10th Revision, Clinical Modification J45.xxx) and ≥1 administration of omalizumab in any of the AP clinics on the same date or after the first observed diagnosis for asthma. Omalizumab had to be indicated for asthma and not received before the first visit to AP. Patients were required to be ≥12 years old on the index date and have ≥12 months of data after the index date. Patients with ≥1 diagnosis of chronic obstructive pulmonary disease combined with ≥10 pack-years of smoking and patients with cystic fibrosis, Alpha-1 antitrypsin deficiency, bronchiectasis, interstitial lung disease, and sarcoidosis in either the baseline or follow-up period were excluded.

Patients were classified into 2 strata based on each biomarker level: high (≥300 cells/μL) and low (<300 cells/μL) EoS and intermediate-high (≥25 parts per billion [ppb]) and low (<25 ppb) FeNO.[20,26] For patients with the information on EoS and FeNO and on the total IgE missing in the structured EMR, it was obtained through a chart abstraction.

Outcomes within each EoS and FeNO stratum were assessed at 6 and 12 months of follow-up relative to baseline in patients with information available in both the baseline and follow-up periods. If multiple assessments of an outcome were available during a period, the most recent assessment was used. For outcomes assessed at month 6 of follow-up, baseline values were measured ≤6 months before and including the index date.

Omalizumab Use

Omalizumab use was described during the 12-month follow-up period. Omalizumab discontinuation was

defined as a gap of ≥90 days between consecutive administrations of omalizumab or between the last administration and the end of follow-up; omalizumab discontinuation date was defined as the date of the last administration before the gap plus 14 days. Continuous omalizumab use was measured from the first administration to the first discontinuation date, or, in the absence of discontinuation, until 14 days after the last administration.

Outcome Measures

Asthma control was measured with the Asthma Control Test (ACT), a patient-completed survey with scores that ranged from 5 to 25.[27,28] Well-controlled asthma was defined as ACT ≥20,[29] and the minimally important difference (MID) in the ACT score was defined as 3 points.[29]

Lung function was measured with pulmonary function test results, including forced expiratory volume in 1 second (FEV_1) and FEV_1 as a percentage of predicted value (FEV_1% predicted). A lung function below normal was defined as FEV1% predicted <80%,[30] and the MID in FEV1% was defined as 10%.[31]

The study also assessed patient-reported symptoms of wheezing, shortness of breath, chest tightness, and coughing.

The use of rescue medication was assessed as a new short-term (<30 days) oral corticosteroid (OCS) prescription, and the use of controller medication as a new high-dose ICS prescription, and a change in the number of controller medications (eg, ICS, LABA, leukotriene modifier) used.

Statistical Analyses

Patient baseline characteristics, omalizumab use, and outcome measures were described with frequency counts and proportions for binary variables and with means, SDs, and medians for continuous variables. Outcomes within the EoS and FeNO strata were assessed through statistical comparisons between baseline and observation periods with the use of univariate generalized estimating equations with adjustment for measurements on the same patients. Binary variables were compared, assuming binomial distribution and a logit link. Results were reported as odds ratios (ORs) with 95% CIs. Continuous variables were compared, assuming normal distribution. Results were reported as mean differences (MDs) with 95% CIs. All analyses were conducted with SAS 9.4 or the latest version (SAS Institute, Cary, North Carolina).

RESULTS

Baseline Characteristics

A total of 473 patients met all selection criteria, among whom 34.5% had information on EoS and 23.7% on FeNO. For EoS, 77 and 86 patients were stratified into the high and low EoS subgroups, respectively, and for FeNO, 56 patients were stratified into each of the intermediate-high and low subgroups.

Age varied slightly between the high and low EoS (median = 43 and 47 years, respectively) and intermediate-high and low FeNO (median = 52 and 43 years, respectively) strata (Table I). Most patients in the high and low EoS (62.3%; 62.8%) and intermediate-high and low FeNO (64.3%; 66.1%) strata were women. Patients in all strata were predominantly white, privately insured, and resided in the South. Total IgE was higher in the high biomarker strata. Before omalizumab initiation, most patients had a record of a medium-to-high-dose ICS and LABA prescription (75.0%−87.0%), and at least 1 course of short-term OCS (55.4%−63.6%).

Omalizumab Use

The median number of omalizumab administrations was 12 among patients in both EoS strata, 13 in the intermediate-high, and 12 in the low FeNO strata. Initial median dose of omalizumab was 300 mg in all strata. Among >90% of patients with ≥2 administrations of omalizumab, the initial frequency of administration was almost evenly split between every 2- or 4-week intervals in both the high and low EoS strata; 2-week intervals were more common in the intermediate-high FeNO stratum (59.3%), whereas 4-week intervals were more common in the low FeNO stratum (57.1%). Median continuous treatment duration was 360 days in all strata. In the high and low EoS strata, respectively, 30 patients (39.0%) and 26 patients (30.2%) discontinued treatment. In the intermediate-high and low FeNO strata, respectively, 18 patients (32.1%) and 17 patients (30.4%) discontinued treatment.

Treatment Response

Across ACT score and FEV_1 values, baseline measurements were taken and at a mean of 1 to 2

Table I. Baseline characteristics*.

Variable	EoS†		FeNO†	
	High (≥300 cells/μL) (N = 77)	Low (<300 cells/μL) (N = 86)	Intermediate-high (≥25 ppb) (N = 56)	Low (<25 ppb) (N = 56)
Demographic characteristic				
Age‡	39.66 ± 18.96 [43]	46.87 ± 14.23 [47]	46.11 ± 20.63 [52]	41.77 ± 16.79 [43]
12–17 y	17 (22.1)	4 (4.7)	11 (19.6)	8 (14.3)
≥18 y	60 (77.9)	82 (95.3)	45 (80.4)	48 (85.7)
Female	48 (62.3)	54 (62.8)	36 (64.3)	37 (66.1)
Race				
White	56 (72.7)	68 (79.1)	39 (69.6)	45 (80.4)
Black/African American	18 (23.4)	13 (15.1)	15 (26.8)	8 (14.3)
Other	1 (1.3)	3 (3.5)	1 (1.8)	1 (1.8)
Unknown	2 (2.6)	2 (2.3)	1 (1.8)	2 (3.6)
Region				
South	57 (74.0)	57 (66.3)	31 (55.4)	38 (67.9)
West	14 (18.2)	23 (26.7)	17 (30.4)	15 (26.8)
Midwest	4 (5.2)	4 (4.7)	8 (14.3)	2 (3.6)
Northeast	2 (2.6)	2 (2.3)	0 (0.0)	1 (1.8)
Healthcare insurance type				
Private	58 (75.3)	69 (80.2)	42 (75.0)	42 (75.0)
Medicare	8 (10.4)	15 (17.4)	12 (21.4)	9 (16.1)
Medicaid	8 (10.4)	0 (0.0)	1 (1.8)	2 (3.6)
Self-pay	3 (3.9)	2 (2.3)	1 (1.8)	3 (5.4)
Year of index date				
2011	10 (13.0)	9 (10.5)	3 (5.4)	1 (1.8)
2012	3 (3.9)	4 (4.7)	1 (1.8)	2 (3.6)
2013	3 (3.9)	5 (5.8)	4 (7.1)	8 (14.3)
2014	12 (15.6)	9 (10.5)	11 (19.6)	7 (12.5)
2015	17 (22.1)	13 (15.1)	18 (32.1)	13 (23.2)
2016	26 (33.8)	37 (43.0)	15 (26.8)	21 (37.5)
2017	6 (7.8)	9 (10.5)	4 (7.1)	4 (7.1)

(*continued on next page*)

Table I. (*Continued*)

Variable	EoS[†]		FeNO[†]	
	High (≥300 cells/μL) (N = 77)	Low (<300 cells/μL) (N = 86)	Intermediate-high (≥25 ppb) (N = 56)	Low (<25 ppb) (N = 56)
Clinical characteristic				
Time to omalizumab from first observed asthma diagnosis, d	402.58 ± 485.57 [252]	433.10 ± 518.78 [226]	410.93 ± 399.52 [249]	444.63 ± 580.69 [199]
BMI available[§]	76 (98.7)	80 (93.0)	55 (98.2)	55 (98.2)
BMI	29.95 ± 7.64 [30]	32.88 ± 8.00 [31]	29.10 ± 7.77 [29]	31.47 ± 8.46 [31]
Underweight (BMI < 18.5)	1 (1.3)	1 (1.3)	1 (1.8)	1 (1.8)
Normal (18.5 ≤ BMI < 25)	20 (26.3)	11 (13.8)	18 (32.7)	14 (25.5)
Overweight (25 ≤ BMI < 30)	17 (22.4)	24 (30.0)	13 (23.6)	12 (21.8)
Obese (BMI ≥ 30)	38 (50.0)	44 (55.0)	23 (41.8)	28 (50.9)
Total IgE,[†] IU/mL	754.06 ± 1333.62 [315]	376.39 ± 887.69 [177]	526.34 ± 857.16 [181]	323.42 ± 678.26 [156]
Top-3 asthma-related conditions[‖]				
Allergic rhinitis	73 (94.8)	82 (95.3)	50 (89.3)	54 (96.4)
Gastroesophageal reflux disease	18 (23.4)	30 (34.9)	21 (37.5)	17 (30.4)
Chronic sinusitis	18 (23.4)	21 (24.4)	11 (19.6)	15 (26.8)
Asthma medication use[¶]				
SABA	72 (93.5)	78 (90.7)	52 (92.9)	52 (92.9)
Medium-to-high-dose ICS+LABA	67 (87.0)	69 (80.2)	48 (85.7)	42 (75.0)
LTM	64 (83.1)	65 (75.6)	46 (82.1)	44 (78.6)
OCS				
Short-term (<30 d)	49 (63.6)	48 (55.8)	34 (60.7)	31 (55.4)
Long-term (≥30 d) or undefined	36 (46.8)	24 (27.9)	19 (33.9)	17 (30.4)
Smoking status				
Never smoked	53 (68.8)	56 (65.1)	33 (58.9)	36 (64.3)
Former smoker	16 (20.8)	26 (30.2)	15 (26.8)	14 (25.0)

Table I. (*Continued*)

Variable	EoS†		FeNO†	
	High (≥300 cells/μL) (N = 77)	Low (<300 cells/μL) (N = 86)	Intermediate-high (≥25 ppb) (N = 56)	Low (<25 ppb) (N = 56)
Current smoker	2 (2.6)	2 (2.3)	1 (1.8)	3 (5.4)
Unknown	6 (7.8)	2 (2.3)	7 (12.5)	3 (5.4)

BMI = body mass index; EoS = eosinophil; FeNO = fractional exhaled nitric oxide; ICS = inhaled corticosteroid; IgE, immunoglobulin E; LABA = long-acting β agonist; LTM = leukotriene modifier; OCS = oral corticosteroid; ppb, parts per billion; SABA = short-acting β agonist.
* Data are expressed as mean±SD [median], or n (%).
† Measured any time before and including the index date; the value closest to the index date was selected.
‡ Measured at the index date.
§ Measured up to 12 months before the index date or on the index date; the value closest to the index date was selected.
‖ Conditions were active on the patient problem list as of the index date, identified with The International Classification of Diseases, Ninth Revision, Clinical Modification and with The International Classification of Diseases, 10th Revision, Clinical Modification codes.
¶ Treatments on the patient medication list any time before the index date.

months before the index date; follow-up measurements were taken at a mean of 3.5 to 4 months after the index date for the 6-month follow-up evaluation and at a mean of 8 to 9 months after the index date for the 12-month follow-up evaluation (Table II).

Asthma Control

A statistically significant improvement in mean ACT score exceeding MID was observed across all EoS and FeNO strata at 6 months versus baseline (MD = 3.75 [95% CI, 2.05−5.45] in high EoS; 4.56 [95% CI, 2.86−6.26] in low EoS; 3.75 [95% CI, 1.95−5.55] in intermediate-high FeNO; and 3.55 [95% CI, 1.53−5.57] in low FeNO). At 12 months versus baseline, mean change in ACT score that reached MID was sustained in all EoS strata and the intermediate-high FeNO stratum (MD = 2.88 [95% CI, 0.81−4.96] in high EoS; 4.18 [95% CI, 2.26−6.11] in low EoS; and 3.60 [95% CI, 1.55−5.64] in intermediate-high FeNO). Although at 12 months versus baseline the improvement in mean ACT score in the low FeNO stratum did not reach MID, it was statistically significant (MD = 2.37 [95% CI, 0.37−4.37]; Figure 1).

Odds of well-controlled asthma (ACT ≥ 20) were significantly higher in all strata at month 6 and 12 versus baseline (Table II). More than one-half of patients achieved MID of ≥3 points in ACT score in the high and low EoS strata and the low FeNO strata at 6 months and in all strata at 12 months.

Lung Function

At 6 months versus baseline, patients with high EoS had a statistically significant improvement of 0.22 L/s in mean FEV_1 (MD = 0.22 L/s; 95% CI, 0.08−0.35 L/s) and of 4.95 percentage points in mean FEV_1% predicted (MD = 4.95%; 95% CI, 0.60%−9.30%), but patients with low EoS had no improvements in either measure (FEV_1, MD = −0.03 L/s [95% CI, −0.14 to 0.08L/s]; FEV_1% predicted, MD = −1.63% [95% CI, −5.28% to 2.02%]; Figures 2 and 3). Patients with intermediate-high FeNO had a statistically significant improvement of 0.13 L/s in mean FEV_1 (MD = 0.13 L/s; 95% CI, 0.03−0.24 L/s) and a borderline significant improvement of 3.53 percentage points in mean FEV_1% predicted (MD = 3.53%; 95% CI, −0.04% to 7.10%), but patients with low FeNO had no improvements in

Table II. Biomarkers and reaching asthma control and lung function thresholds*

Variable	Descriptive Statistics		Comparative Statistics†		Descriptive Statistics		Comparative Statistics†	
	6-Month Baseline	Month 6	OR/MD (95% CI)	*P*	12-Month Baseline	Month 12	OR/MD (95% CI)	*P*
EoS‡								
High (≥300 cells/μL)	77				77			
≥1 ACT	44 (57.1)			51 (66.2)				
Well-controlled, n (%)	12 (27.3)	22 (50.0)	2.67 (1.21–5.90)	0.015§	14 (27.5)	26 (51.0)	2.75 (1.24–6.07)	0.012§
MID	23 (52.3)				27 (52.9)			
Days between measurement date and index date	41.57 ± 44.72 [28]	123.95 ± 46.62 [139]	–	–	42.82 ± 43.40 [32]	277.37 ± 72.64 [293]	–	–
≥1 FEV_1% predicted	41 (53.2)				54 (70.1)			
Below normal	23 (56.1)	20 (48.8)	0.75 (0.45–1.23)	0.251	31 (57.4)	24 (44.4)	0.59 (0.36–0.99)	0.047§
MID	13 (31.7)				21 (38.9)			
Days between measurement date and index date	36.54 ± 40.09 [27]	121.76 ± 43.30 [137]	–	–	63.39 ± 86.33 [34]	231.28 ± 101.54 [263]	–	–
Low (<300 cells/μL)	86				86			
≥1 ACT	41 (47.7)				49 (57.0)			
Well-controlled	10 (24.4)	24 (58.5)	4.38 (1.81–10.57)	0.001§	14 (28.6)	30 (61.2)	3.95 (1.80–8.68)	<0.001§
MID	26 (63.4)				32 (65.3)			
Days between measurement date and index date	34.20 ± 28.33 [34]	113.29 ± 44.86 [110]	–	–	47.78 ± 59.82 [35]	267.57 ± 92.80 [298]	–	–
≥1 FEV_1% predicted	46 (53.5)				60 (69.8)			
Below normal	23 (50.0)	23 (50.0)	1.00 (0.66–1.52)	1.000	32 (53.3)	31 (51.7)	0.94 (0.63–1.39)	0.739
MID	6 (13.0)				13 (21.7)			
Days between measurement date and index date	40.24 ± 36.52 [35]	116.91 ± 46.21 [119]	–	–	50.85 ± 52.75 [38]	259.13 ± 87.23 [277]	–	–
FeNO†								
Intermediate-high (≥25 ppb)	56				56			
≥1 ACT	32 (57.1)			42 (75.0)				
Well-controlled	11 (34.4)	22 (68.8)	4.20 (1.80–9.77)	<0.001§	16 (38.1)	30 (71.4)	4.06 (1.77–9.34)	<0.001§
MID	15 (46.9)				22 (52.4)			

Table II. (*Continued*)

Variable	Descriptive Statistics		Comparative Statistics[†]		Descriptive Statistics		Comparative Statistics[†]	
	6-Month Baseline	Month 6	OR/MD (95% CI)	*P*	12-Month Baseline	Month 12	OR/MD (95% CI)	*P*
Days between measurement date and index date	29.44 ± 34.39 [27]	121.88 ± 41.95 [132]	—	—	60.64 ± 85.53 [28]	240.69 ± 98.46 [267]	—	—
≥1 FEV_1% predicted	34 (60.7)				45 (80.4)			
Below normal	20 (58.8)	17 (50.0)	0.70 (0.42–1.17)	0.170	26 (57.8)	22 (48.9)	0.70 (0.36–1.34)	0.281
MID	9 (26.5)				17 (37.8)			
Days between measurement date and index date	30.21 ± 35.29 [16]	111.59 ± 53.52 [127]	—	—	55.22 ± 90.68 [27]	235.18 ± 103.70 [270]	—	—
Low (<25 ppb)	56				56			
≥1 ACT	38 (67.9)				43 (76.8)			
Well-controlled	8 (21.1)	23 (60.5)	5.75 (2.43–13.61)	<0.001[§]	11 (25.6)	20 (46.5)	2.53 (1.18–5.40)	0.016[§]
MID	20 (52.6)				22 (51.2)			
Days between measurement date and index date	43.18 ± 33.60 [39]	115.76 ± 46.98 [118]	—	—	41.23 ± 32.07 [35]	271.56 ± 76.48 [294]	—	—
≥1 FEV_1% predicted	33 (58.9)				41 (73.2)			
Below normal	18 (54.5)	15 (45.5)	0.69 (0.41–1.17)	0.170	21 (51.2)	19 (46.3)	0.82 (0.48–1.41)	0.478
MID	8 (24.2)				11 (26.8)			
Days between measurement date and index date	47.70 ± 35.44 [38]	114.21 ± 47.64 [120]	—	—	62.61 ± 55.57 [45]	269.41 ± 67.90 [271]	—	—

ACT = Asthma Control Test; EoS = eosinophil; FeNO = fractional exhaled nitric oxide; FEV1% predicted = forced expiratory volume in 1 second as percentage of predicted value; MD = mean difference; MID = minimally important difference; OR = odds ratio; ppb = parts per billion.

* Data are expressed as mean±SD [median], n, or n (%).

† Compared with univariate generalized estimating equations with adjustment for repeated measurements, binominal distribution, and a logit link.

‡ Measured any time before and including the index date; the value closest to the index date was selected.

§ Statistically significant.

either measure (FEV_1, MD = 0.04 L/s [95% CI, −0.08 to 0.15 L/s]; FEV_1% predicted, MD = 1.61% [95% CI, −2.01% to 5.23%]).

At 12 months versus baseline, patients in the high biomarker strata had sustained statistically significant improvements in mean FEV_1 (MD = 0.16 L/s [95% CI, 0.04−0.29 L/s] in high EoS; 0.14 L/s [95% CI, 0.04−0.25 L/s] in intermediate-high FeNO), and in mean FEV_1% predicted (MD = 5.22% [95% CI, 1.72%−8.73%] in high EoS, 4.51% [95% CI, 0.90%−8.12%] in intermediate-high FeNO). Patients in the low biomarker strata had no improvements in either measure (FEV_1, MD = 0.06 L/s [95% CI, −0.05 to 0.17 L/s] in low EoS, 0.08 L/s [95% CI, −0.04 to 0.20 L/s] in low FeNO; FEV_1% predicted, MD = 2.48% [95% CI, −1.61% to 6.58%] in low EoS; and 3.76% [95% CI, −0.91% to 8.42%] in low FeNO).

No significant change was found in the odds of having lung function below normal (FEV_1 < 80%) in all strata at both time points, except for the high EoS stratum at 12 months versus baseline (Table II). At month 6, proportions of patients achieving MID of at least 10% in FEV_1% predicted were generally low, but higher in the high biomarker strata. At 12 months, this trend was sustained.

Asthma-related Symptoms

At 6 months versus baseline, odds of wheezing, shortness of breath, chest tightness, and coughing were significantly lower in all biomarker strata (Figure 4). Odds of wheezing, shortness of breath, and coughing decreased by ~60% to 70% across the EoS strata, whereas patients with high EoS appeared to have reported a larger decrease in odds of chest tightness (71%) relative to patients with low EoS (54%). Results were more mixed across FeNO strata, with a larger decrease in odds of wheezing (84%; 61%) and smaller decreases in odds of shortness of breath (64%; 82%), chest tightness (62%; 74%), and coughing (50%; 53%) in patients with intermediate-high FeNO versus low FeNO.

At 12 months versus baseline, odds of all asthma-related symptoms were still significantly lower in both EoS strata, and odds of all symptoms, except for coughing, were significantly lower in both FeNO strata (Figure 5).

Medication Use

At 6 months versus baseline, patients with low EoS had lower odds of using short-term OCS (OR = 0.29; 95% CI, 0.15−0.54]), but no statistically significant change was observed for patients with high EoS. Patients with high EoS (OR= 0.29; 95% CI, 0.14−0.59) and low EoS (OR = 0.15; 95% CI, 0.07−0.35]) were less likely to use high-dose ICSs. Patients with intermediate-high and low FeNO had lower odds of using both short-term OCSs (OR = 0.50 [95% CI, 0.26−0.99] and 0.34 [95% CI, 0.16−0.73]) and high-dose ICSs (OR = 0.46 [95% CI, 0.23−0.93] and 0.24 [95% CI, 0.09−0.61]), respectively. No statistically significant difference was found in the number of controller medications used in all strata. Results at 12 months compared with baseline were largely similar.

DISCUSSION

In this real-world study, omalizumab was associated with a significant improvement in asthma control across pretreatment EoS and FeNO levels. The mean increase in ACT score at 6 months exceeded the MID of 3 points in all strata and was observed at 12 months in both the EoS and the intermediate-high FeNO strata. Mild benefits for lung function manifested in high biomarker strata, and in all strata patients experienced fewer asthma-related symptoms. A trend for decreased medication use was observed in all strata, but these results were not statistically significant.

Recent evidence on the association of biomarkers with omalizumab treatment outcomes includes that of PROSPERO (the Prospective Observational Study to Evaluate Predictors of Clinical Effectiveness in Response to Omalizumab).[25] In PROSPERO, a significant increase in mean ACT scores achieving MID over a 12-month period was observed regardless of biomarker status. Although the mean increase in ACT scores was greater in patients with high versus low EoS (≥300 and <300 cells/μL; 5.2 versus 4.1; $P = 0.003$), it was similar between FeNO strata (≥25 and <25 ppb; 4.7 versus 4.3; $P = 0.26$). For before bronchodilator FEV_1, mean improvement was significantly greater in the high versus low EoS (0.08 versus −0.01; $P = 0.011$) and the high versus low FeNO (0.08 versus −0.02; $P = 0.002$) strata, although the magnitude of change was modest.

Similar to PROSPERO, in our study, the MID in ACT was largely achieved or exceeded across biomarker strata, and lung function improvement was more evident in the high biomarker strata. Although response varied by biomarkers for some outcomes, all strata indicated improvements on ≥1 measure. Because asthma symptoms are heterogeneous and patients present with various unmet needs, it is possible that benefits patients receive from omalizumab also differ. Overall, because patients across biomarker strata achieve improvements after omalizumab initiation, the relevance of biomarkers in treatment decision making remains unclear.

Randomized clinical trials and observational studies appear to provide contradicting evidence about the association of biomarkers with omalizumab treatment outcomes. Trials have linked high baseline levels of biomarkers to better response to omalizumab.[23,32–34] However, as pointed out in PROSPERO, the differential response to omalizumab in patients with high and low baseline EoS and FeNO levels observed in

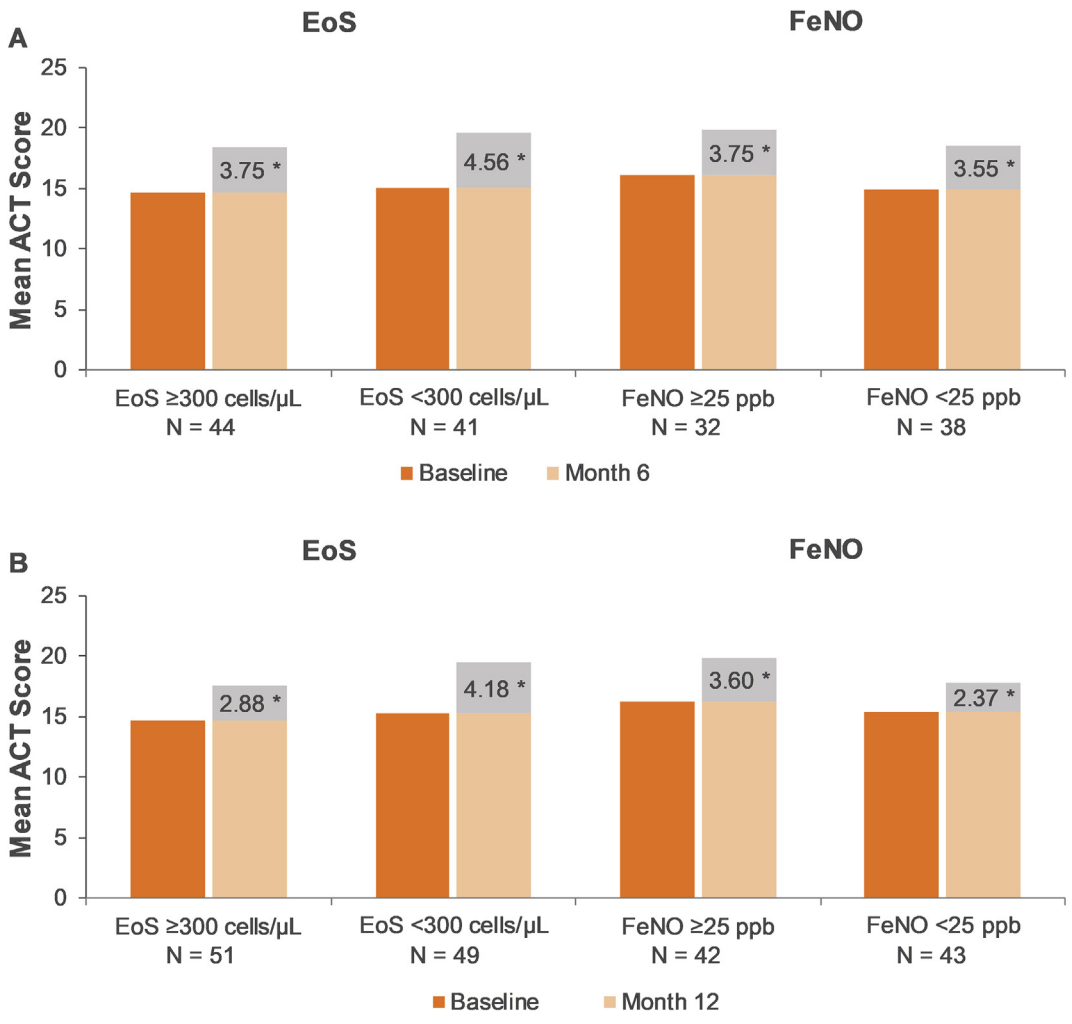

Figure 1. Biomarkers and mean change in Asthma Control Test (ACT) score. Biomarkers were measured any time before and including the index date; the value closest to the index date was selected. ACT score was compared with baseline with the use of univariate generalized estimating equations with adjustment for repeated measurements, normal distribution, and an identity link. EoS = eosinophil; FeNO = fractional exhaled nitric oxide. *Statistically significant at 5%.

trials may be attributed to the high exacerbation rate in the untreated/placebo arms.[25] For instance, when data from patients only treated with omalizumab were considered in the Study of Omalizumab (Xolair) in Subjects with Moderate to Severe Persistent Asthma (EXTRA), no substantial difference in exacerbation frequency between the high and low EoS and FeNO subgroups were observed, suggesting that all patients can benefit from omalizumab treatment irrespective of biomarker status.[25]

Literature has reported that other biomarkers, such as IgE,[35–37] periostin,[38] C-X-C motif chemokine 10,[39] and interleukin-12,[39] may also be of importance for patients treated with omalizumab.

This study had several limitations. With the exception of omalizumab, EMR data contained information on prescriptions ordered, not dispensed, and matched pharmacy claims were not available. Because a prescription order does not guarantee that medication was dispensed, the use of medications

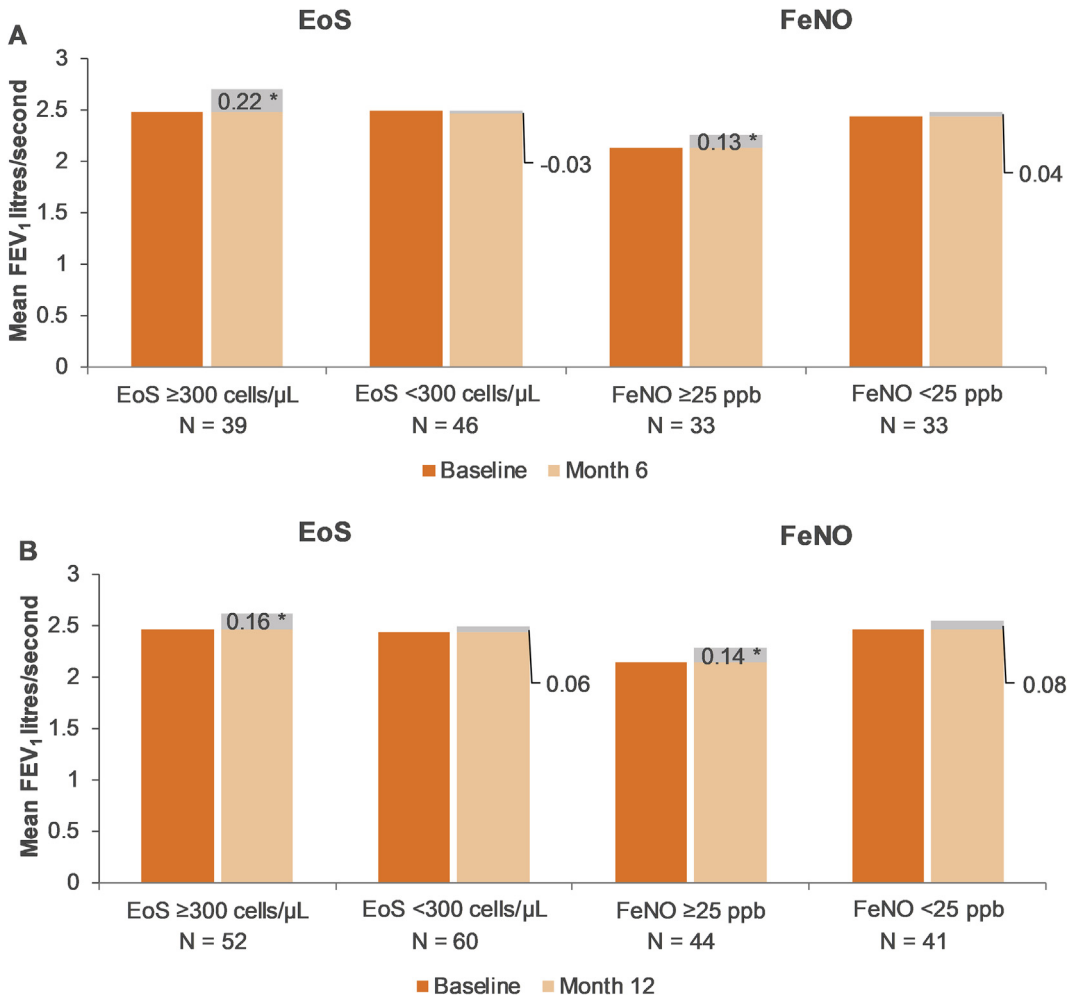

Figure 2. Biomarkers and mean change in forced expiratory volume in 1 second (FEV_1). Biomarkers were measured any time before and including the index date; the value closest to the index date was selected. FEV_1 was compared with baseline with the use of univariate generalized estimating equations with adjustment for repeated measurements, normal distribution, and an identity link. EoS = eosinophil; FeNO = fractional exhaled nitric oxide. *Statistically significant at 5%.

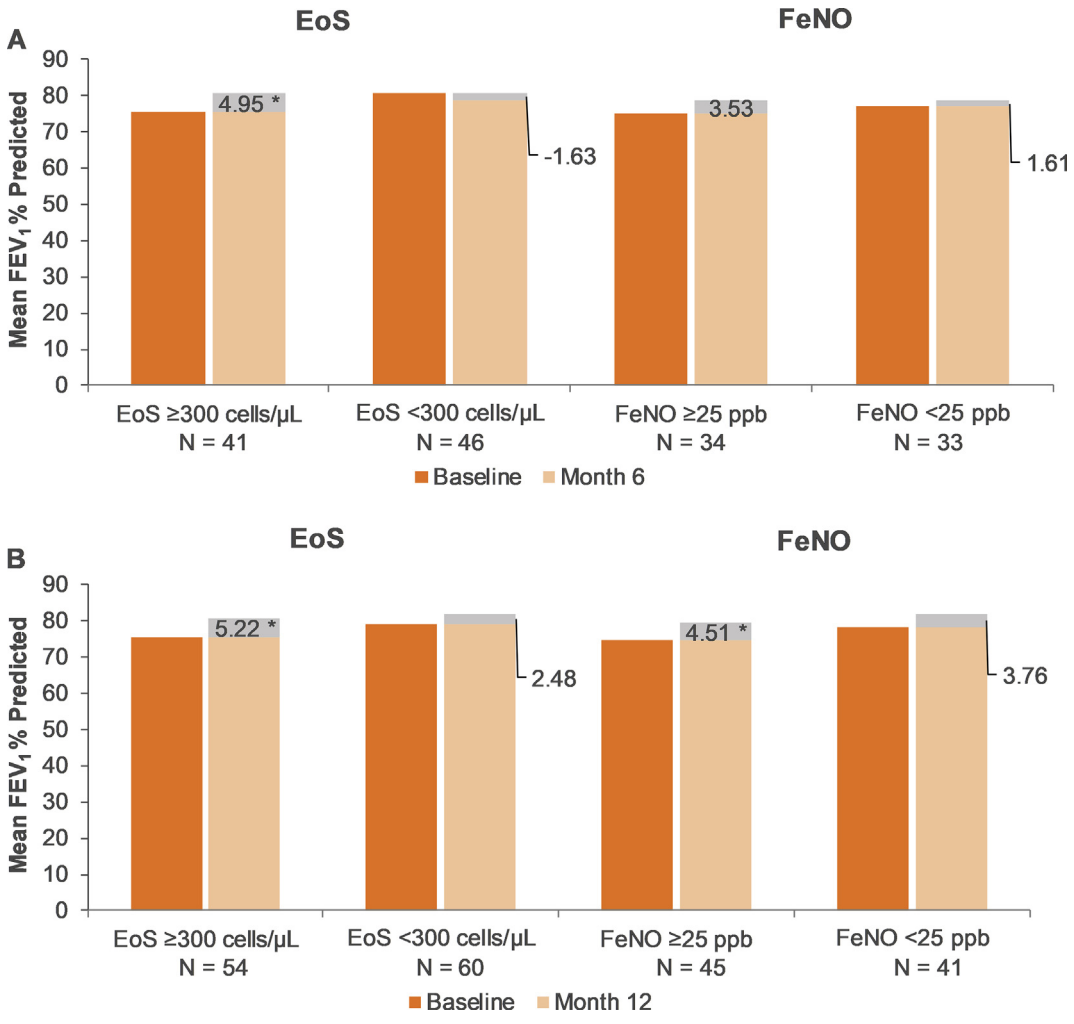

Figure 3. Biomarkers and mean change in forced expiratory volume in 1 second as percentage of predicted value (FEV_1% predicted). Biomarkers were measured any time before and including the index date; the value closest to the index date was selected. FEV_1% predicted was compared with baseline with the use of univariate generalized estimating equations with adjustment for repeated measurements, normal distribution, and an identity link. EoS = eosinophil; FeNO = fractional exhaled nitric oxide. *Statistically significant at 5%.

other than omalizumab may have been overestimated. However, information on care, including prescriptions received outside of the AP network, was unavailable, which could have led to an underestimation of the use of medications other than omalizumab. Moreover, results for short-term OCS use might have been underestimated because of missing information in some records on the number of pills administered and the duration of prescriptions, as well as inconclusive medication use instructions. The study had no control arm because of the challenges of retrospectively identifying patients eligible for omalizumab but not receiving it. Finally, because most AP clinics are located in the South, more than one-half of patients were from this region. If important differences exist between patients with

asthma by region, results might not be generalizable to patients outside of the South.

CONCLUSIONS

In this large real-world study of US patients with allergic asthma omalizumab initiation was associated with an improvement in asthma control, lung function, and asthma-related symptoms. Across biomarker strata, improvements in ACT score largely reached or exceeded MID, and patients were less likely to experience asthma-related symptoms, whereas lung function benefits were observed in the high biomarker strata. Although response varied by biomarkers for some outcomes, all strata indicated improvements on ≥1 measure. This study suggests that omalizumab could be beneficial in patients with allergic asthma regardless of pretreatment biomarker levels, and pretreatment biomarker levels might not inform response.

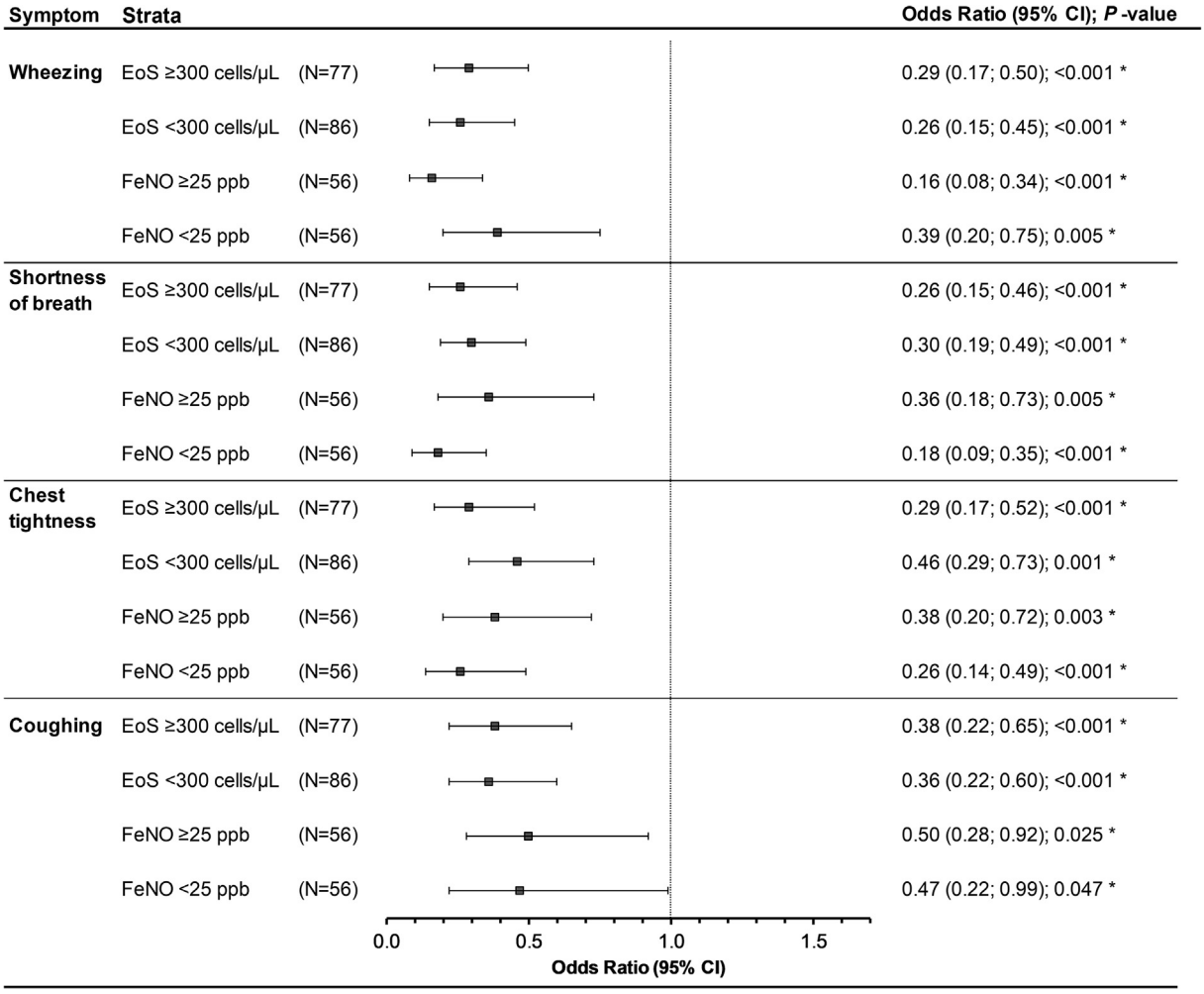

Figure 4. Biomarkers and patient reported symptoms at 6 months versus at baseline. Biomarkers were measured any time before and including the index date; the value closest to the index date was selected. Strata with baseline were conducted with the use of univariate generalized estimating equations with adjustment for repeated measurements, binominal distribution, and a logit link. EoS = eosinophil; FeNO = fractional exhaled nitric oxide. *Statistically significant at 5%.

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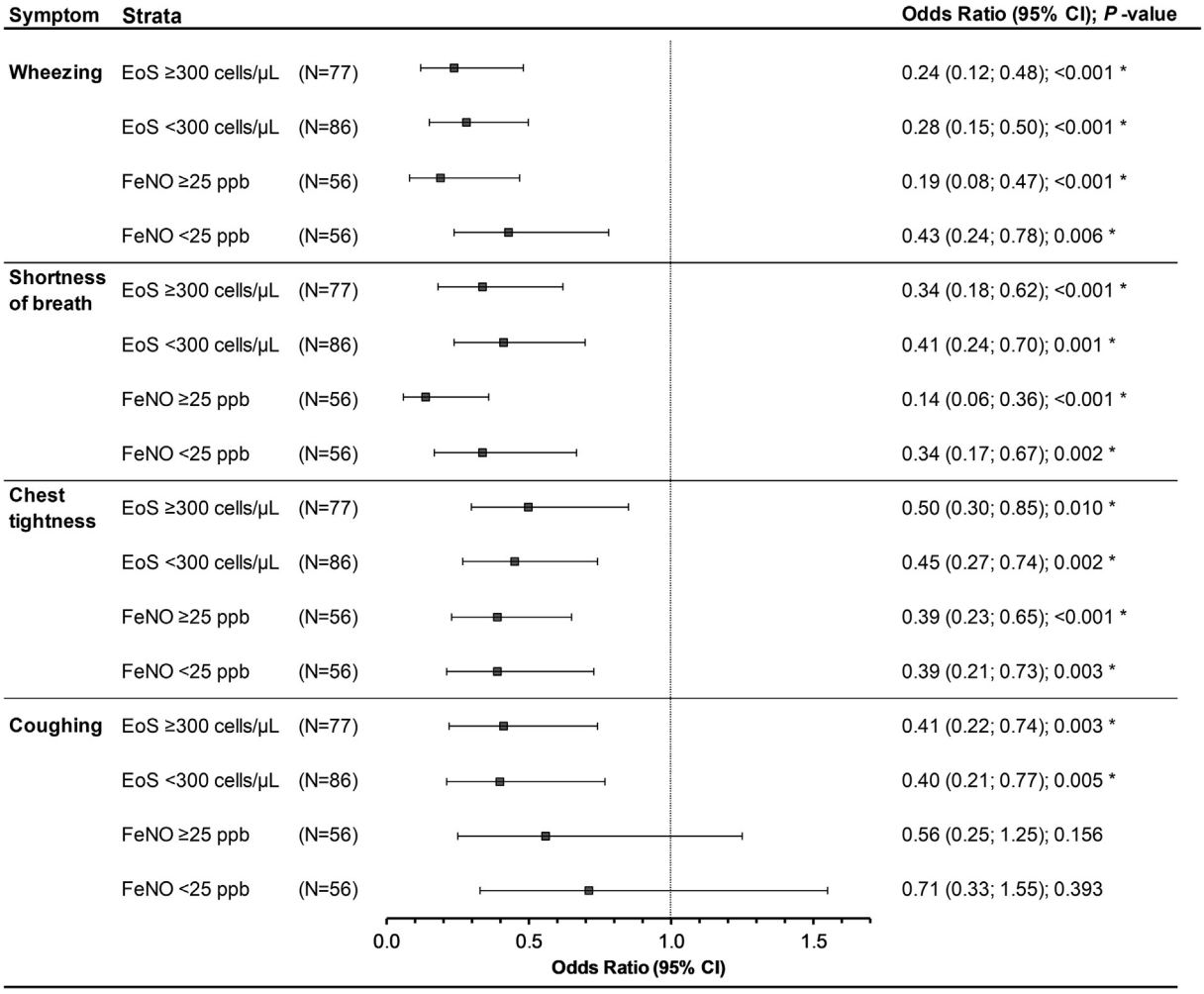

Figure 5. Biomarkers and patient-reported symptoms at 12 months versus at baseline. Biomarkers were measured any time before and including the index date; the value closest to the index date was selected. Strata with baseline were conducted with the use of univariate generalized estimating equations with adjustment for repeated measurements, binominal distribution, and a logit link. EoS = eosinophil; FeNO = fractional exhaled nitric oxide. *Statistically significant at 5%.

project administration; supervision; validation; and writing, editing, and review. Harriet Ho provided conceptualization, formal analysis, investigation, methodology, validation, visualization, and writing of the original draft. Patrick Lefebvre provided conceptualization; investigation; methodology; project administration; supervision; validation; and writing, review, and editing. Brian Stone provided conceptualization; data curation; investigation; methodology; validation; and writing, review, and editing.

DISCLOSURES

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