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Effect of clinically significant thresholds of eosinophil elevation on health care resource use in asthma

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ABSTRACT

Background: Blood eosinophil counts correlate with exacerbations, but there is a lack of consensus on a clinically relevant definition of eosinophil count elevation.

Objective: To analyze health care resource use among patients with elevated blood eosinophil counts defined at 150 cells/μL or greater and 300 cells/μL or greater.

Methods: Data on patients who received a diagnosis of asthma between 2007 and 2016 were extracted from EMRClaims + database. Patients were defined as having elevated eosinophil counts if any test result during 3 months before follow-up found blood eosinophil count of 150 cells/μL or more or 300 cells/μL or more. Hospitalizations, emergency department visits, outpatient visits, and associated costs were compared. With logistic regression, likelihood of hospitalization was assessed in the presence of eosinophil elevation.

Results: Among 3687 patients who met the study criteria, 1152 received a test within 3 months before the follow-up period, of whom 644 (56%) had elevated eosinophil counts of 150 cells/μL or greater and 322 (29%) had eosinophil counts of 300 cells/μL or greater. Overall, the mean (SD) number of hospitalizations for patients with elevated eosinophil counts vs the comparator was significantly greater (0.29 [0.92] vs 0.17 [0.57], $P < .001$ at $\geq$150 cells/μL and 0.30 [0.95] vs 0.18 [0.61] at $\geq$300 cells/μL, $P = .001$). The total mean cost was significantly greater for patients with elevated eosinophil counts (at $\geq$150 cells/μL: $10,262 vs $7149, $P < .001$ and at $\geq$300 cells/μL: $9966 vs $7468, $P = .003$).

Conclusion: Patients with asthma incurred greater health care resource use when their blood eosinophil counts were elevated at 150 cells/μL or greater and 300 cells/μL or greater as measured within 3 months of follow-up.

Introduction

Treatment of asthma and its complications results in a significant burden to the health care system. In 2015, approximately 25 million Americans were reported to have asthma.[1] In 2014, in the United States, asthma was associated with 3651 deaths, 439,000 hospitalizations, 2.1 million emergency department (ED) visits, and more than 11 million outpatient or office visits.[1] Studies report a wide range of patients with uncontrolled asthma (17%-34%)[2–4] and severe asthma (5%-20%).[4-6] The small percentage of patients with uncontrolled and severe asthma drives disproportionately higher health care expenditure and cost based on exacerbations, health care utilization, and total expenditure.[6,7] Significant unmet medical needs for these patients remain evident,[8] and it is hoped that recently approved biologics and those in development will mitigate these needs. The association of inflammatory factors, such as elevated eosinophil counts, has been repeatedly reported to correlate with asthma exacerbations and severity.[4,9-11] The use of biomarkers, such as blood and sputum eosinophil counts and

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immunoglobulin E concentrations, has more recently emerged to help advance the treatment of specific asthma phenotypes based on the availability of newer biologic treatment options for the patients with the most severe conditions. These biomarkers can help identify patients appropriate for biologic treatment based on predictive models of severity or the risk of exacerbations.[12-15] Because exacerbation is often defined by medical resource measures, such as hospitalizations and ED visits, we anticipate that elevation of eosinophil counts would be a good predictor of medical resource use.[16,17]

Although the notion of elevated peripheral blood eosinophil counts is an accepted manifestation of inflammatory response in some phenotypes of asthma, consensus on what constitutes a clinically significant elevation is less evident. In the case of eosinophilia, recent clinical trials on treatments with newer monoclonal antibodies have been designed with different eosinophil thresholds, such as 140 cells/μL, 150 cells/μL, 300 cells/μL, or 400 cells/μL.[9-11,18-23] The literature offers little agreement on a meaningful, evidence-based definition of abnormal elevation, neither by a defined specific cutoff (ie, cells per microliter) or based on the progression, persistence, and recency of this key inflammatory response biomarker.

With this study, we aim to better correlate elevation in peripheral blood eosinophil counts with resource use, cost, and lung function among patients with asthma in a real-world health care system. This information may help provide more actionable treatment pathways based on specific eosinophil counts.

The objective of this study was to assess the clinical and economic effect of recent eosinophil count elevation for patients with asthma with blood eosinophil counts of 150 cells/μL or greater and 300 cells/μL or greater.

Methods

Data Source

Data on patients with asthma diagnosis were extracted between January 2007 and December 2014 from the EMRClaims + database, specifically the Midwest component, including national commercial insurance claims, Medicare claims, and regional electronic medical record data linked with claims. The administrative insurance claims across approximately 690,000 lives are linked to an overlapping health care practitioner database of electronic medical records data, including laboratory values and practitioner billing files. The database tracks patient encounters through longitudinal claims data, including pharmacy data (all filled prescriptions), and medical claims for insured members who have medical encounters within the electronic medical record—reporting hospitals and outpatient facilities.

Study Design

Adult patients ($\geq$18 years) were included in this retrospective, observational study if they had at least 1 primary asthma diagnosis (*International Classification of Diseases, Ninth Revision, Clinical Modification* code 493.xx or *International Classification of Diseases, Tenth Revision* codes J45-J45.999) in the inpatient setting or at least 2 separate instances of asthma diagnosis recorded in the outpatient or ED setting. The first date of recorded asthma diagnosis was defined as the index date. Patients were required to have continuous enrollment for 24 months after the index date; the 12-month period after the index date was defined as the assessment period and the next 12 months as the follow-up period. Patients were required to have at least 1 eosinophil test result during the assessment period. Patients were excluded if there were any diagnoses of confounding disease states known to increase eosinophil counts, such as chronic obstructive pulmonary disease, eosinophilic granulomatosis with polyangiitis, cystic or pulmonary fibrosis, allergic bronchopulmonary aspergillosis, lung cancer, and malignant leukemia or lymphoma, during the assessment period.

Study Measures

Patient demographics were recorded as of the index date, and comorbidities included in the Charlson Comorbidity Index (CCI) were identified during the assessment period. Patients were classified as having an elevated eosinophil count if at least 1 eosinophil test result within 3 months before the follow-up period revealed counts of 150 cells/μL or greater. A similar definition was used to separately identify patients with elevated eosinophil counts using a threshold of 300 cells/μL or greater. The comparison group consisted of patients without a test within 3 months before follow-up or patients whose counts were measured as not elevated in the same period. Patients' asthma control status was defined according to the European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines.[24] Specifically, patients were classified as having uncontrolled asthma in the presence of any of the following factors during the assessment period: (1) frequent severe exacerbations defined as 2 or more bursts of systemic corticosteroids (>3 days each), defined as 2 or more prescription claims with more than 3 days of supply; (2) serious exacerbations based on the presence of at least 1 hospitalization with a primary diagnosis of asthma as the primary discharge diagnosis, intensive care unit stay, or mechanical ventilatory support required; or (3) airflow limitation, based on forced expiratory volume in 1 second of 80% or less predicted after appropriate bronchodilator withholding (in the face of reduced forced expiratory volume in 1 second/forced vital capacity ratio defined as less than the lower limit of normal). Patients were also classified by asthma severity status, and severe asthma was defined as any prescription for a high dosage of inhaled corticosteroids based on the Global Initiative for Asthma (GINA) 2017 report.[25]

Outcome measures were resource use and cost during follow-up. Resource use was defined as all-cause hospitalizations, ED visits, or outpatient visits. Cost for each of these events was estimated using paid insurance claims. In cases in which encounters were recorded for members of integrated delivery networks where the practitioner and payer are the same organization, actual paid medical claims were not available because under these relationships claims are not required to be paid. In such cases, practitioner-billed amounts (charges) in the absence of third-party claims were converted to cost based on a method previously published.[4]

Statistical Analysis

All measures were compared separately between the group with elevated eosinophil counts and the comparison groups at the 150 cells/μL or greater and 300 cells/μL or greater thresholds. Demographics and comorbidities were reported. Percentages of patients with resource use during follow-up were also compared between the eosinophil groups and mean resource and cost. Comparisons were conducted for the overall study sample and the uncontrolled, controlled, and severe asthma subgroups. All categorical comparisons were made using χ^2 tests, and mean values were compared using nonparametric tests. Logistic regression analysis was conducted to identify factors that influence likelihood of hospitalization during follow-up. Eosinophil elevation was the key independent predictor. Covariates included were resource use during assessment period and demographics, such as age, race, sex, and the CCI score, during the assessment period.

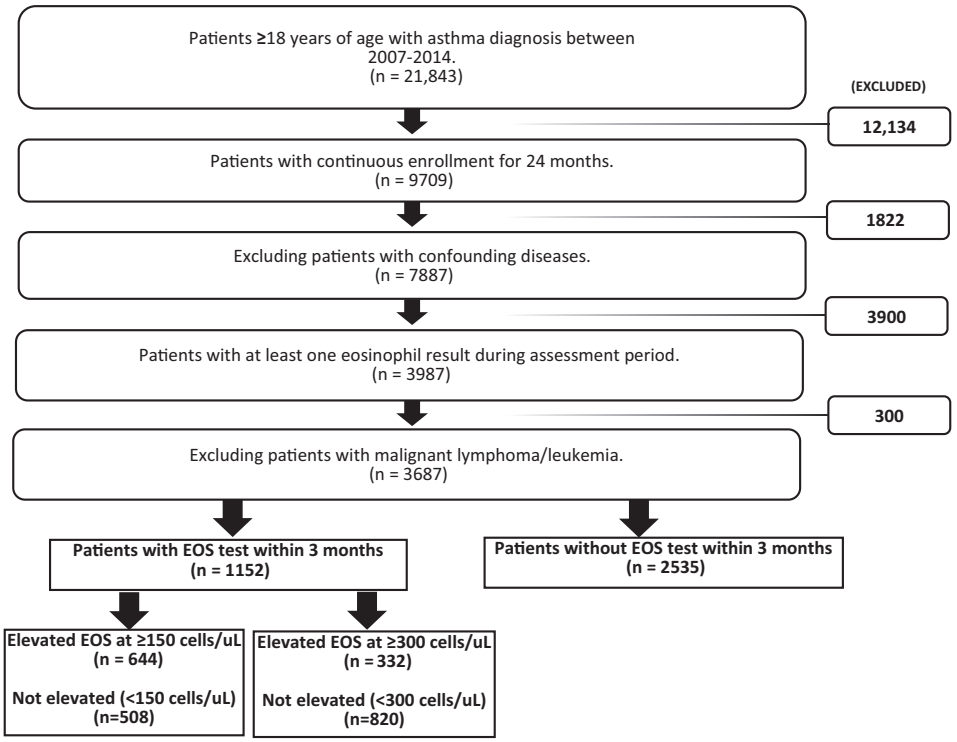

Figure 1. Sample attrition. EOS, eosinophil.

As part of sensitivity analyses, to account for changes in practice patterns, introduction of new medications, and patient lifestyle and other factor changes throughout the years, we conducted resource use and cost comparisons between the elevated and nonelevated eosinophil groups, restricting the data to the most recent 5-year period (2012-2016).

Results

A total of 3687 patients were included in the study. Fifteen percent were classified as patients with uncontrolled asthma by ERS/ATS guidelines, and 14% were classified as having severe asthma by GINA guidelines (Fig 1). Within the 3-month period before follow-up, 1152 patients had an eosinophil test conducted, of whom 644 (56%) had blood eosinophil counts of 150 cells/μL or greater and 332 (29%) had eosinophil counts of 300 cells/μL or greater. The comparison group for the 150 cells/μL or greater threshold included 3043 patients, consisting of those who did not have an elevation (n = 508) and those who did not receive a test (n = 2535) within the 3 months before follow-up. The comparison group for the 300 cells/μL or greater threshold consisted of 3355 patients, including those who did not have an elevation (n = 820) and those who did not get tested (n = 2535) within 3 months before follow-up.

Table 1 provides the demographic comparisons between the elevated eosinophil and comparison groups. Overall, there was a greater percentage of women in the study sample, but the distribution of women between the elevated eosinophil count and comparison groups were similar. The elevated eosinophil count group had a greater mean CCI score at baseline for both eosinophil thresholds. In addition, the group with eosinophil counts elevated at 150 cells/μL or greater had a larger percentages of patients with diabetes, renal disease, and congestive heart failure. The group with eosinophil counts of 300 cells/μL or greater had larger percentages of patients with diabetes and renal disease.

In the overall study sample, a greater percentage of patients with elevated eosinophil counts at the 150 cells/μL or greater threshold incurred hospitalizations (18% vs 12%, $P < .001$), ED visits (32% vs 27%, $P = .03$), and outpatient visits (62% vs 54%, $P < .001$) in the follow-up period (Fig 2). Although a numerically greater proportion of patients with elevated eosinophil counts in the uncontrolled asthma and severe asthma subgroups incurred hospitalizations vs the comparison group, these differences were not statistically significant in these patient subgroups (uncontrolled asthma: 19% vs 16%, $P = .34$; severe asthma: 17% vs 14%, $P = .40$). In the subgroup of patients with controlled asthma, a significantly greater percentage of patients with elevated eosinophil counts incurred hospitalizations, ED visits, and outpatient visits. With the use of the greater cutoff (≥300 cells/μL) to define eosinophil count elevation, the percentage of patients with elevated eosinophil counts who incurred all-cause hospitalizations reached statistical significance for the overall study sample and the subgroup of patients with controlled asthma (19% vs 13%, $P = .002$ for the overall asthma subgroup and 19% vs 12%, $P = .004$ for the controlled asthma subgroup).

The mean number of hospitalizations, ED visits, and outpatient visits were significantly greater for patients with eosinophil count elevation at the threshold of 150 cells/μL or greater for the overall study sample and the subset of patients with controlled asthma (Table 2). The total mean cost for the elevated eosinophil group in the overall study sample was significantly greater than that for the comparison group at both eosinophil count thresholds (at ≥150 cells/μL: $10,262 vs $7149, $P < .001$; at ≥300 cells/μL: $9966 vs $7468, $P = .003$; Table 2).

Logistic regression models (Fig 3) estimated that patients with elevated eosinophil counts (≥150 cells/μL) within 3 months before follow-up were 1.3 times more likely to be hospitalized during the follow-up period (odds ratio [OR], 1.335; 95% CI, 1.050-1.698), after adjusting for sex, age, race, CCI score, and other clinical factors. Similar results were found at the greater threshold of 300 cells/μL

Table 1
Demographics and Comorbidity Distribution at Baseline

Variable	Eosinophil threshold ≥150 cells/μL			Eosinophil threshold ≥300 cells/μL		
	Elevated eosinophil count (n = 644)	Comparison group (n = 3043)	*P* value	Elevated eosinophil count (n = 332)	Comparison group (n = 3355)	*P* value
Sex						
Female	474 (74)	2258 (74)	.75	236 (71)	2496 (74)	.19
Male	170 (26)	785 (26)		96 (29)	859 (26)	
Age, y						
18-35	90 (14)	501 (16)	.04	46 (14)	545 (16)	.03
36-45	84 (13)	515 (17)		36 (11)	563 (17)	
46-55	164 (25)	693 (23)		86 (26)	771 (23)	
56-64	144 (22)	632 (21)		75 (23)	701 (21)	
≥65	162 (25)	702 (23)		89 (27)	775 (23)	
Race						
White	331 (51)	1327 (44)	.002	173 (52)	1485 (44)	.02
AAF	246 (38)	1343 (44)		122 (37)	1467 (44)	
Other	67 (10)	373 (12)		37 (11)	403 (12)	
Comorbidities						
Diabetes	167 (26)	675 (22)	.04	87 (26)	755 (23)	.12
Renal disease	56 (9)	189 (6)	.02	33 (10)	212 (6)	.01
CHF	72 (11)	229 (8)	.002	44 (13)	257 (8)	<.001
Cerebrovascular disease	36 (6)	145 (5)	.38	19 (6)	162 (5)	.47
CCI score						
0	370 (57)	1960 (64)	<.001	189 (57)	2141 (64)	<.001
1	142 (22)	604 (20)		73 (22)	673 (20)	
2-3	66 (10)	323 (11)		31 (9)	358 (11)	
≥4	66 (10)	156 (5)		39 (12)	183 (5)	
Mean CCI score	1.01	0.72	<.001	1.07	0.74	.001

Abbreviations: AAF, African American; CCI, Charlson Comorbidity Index; CHF, congestive heart failure.
NOTE. Data are presented as number (percentage) of patients unless otherwise indicated.

or greater (OR, 1.40; 95% CI, 1.030-1.903). Within the uncontrolled and severe asthma subgroups, eosinophil count elevation was not a significant predictor. In the controlled asthma subgroup, eosinophil count elevation was associated with a 38% (≥150 cells/μL: OR, 1.379; 95% CI, 1.051-1.809) and 43% (≥300 cells/μL: OR, 1.432; 95% CI, 1.006-2.037) increase in likelihood of hospitalization during follow-up.

Sensitivity Analysis

Uncontrolled asthma was identified in 319 patients (15%), and 282 (13%) were classified as having severe asthma. Within the overall study sample, a significantly greater percentage of patients with recent eosinophil count elevation had hospitalizations at both eosinophil count thresholds (16% vs 10% at ≥150 cells/μL [$P < .001$] and 17% vs 11% at ≥300 cells/μL [$P = .01$]) and significantly greater ED (38% vs 29%, $P < .001$) and outpatient visits (64% vs 52%, $P < .001$) at the threshold of 150 cells/μL or greater. Similar observations were noted in the controlled asthma subgroup (≥150 cells/μL: 16% vs 10%, $P = .003$; ≥300 cells/μL: 15% vs 10%, $P = .046$) and the severe asthma subgroups (≥150 cells/μL: 28% vs 12%, $P = .003$; ≥300 cells/μL: 31% vs 14%, $P = .01$). The total mean (SD) cost was significantly greater in patients with elevated eosinophil counts in the overall study sample (≥150 cells/μL: $9791 [$14,072] vs $6814 [$11,563], $P < .001$; ≥300 cells/μL: $10,472 [$16,132] vs $7042 [$11,558], $P = .001$). For the threshold of 150 cells/μL or greater, logistic regression results showed similar trends to the main results with eosinophil elevation associated with increased likelihood of follow-up hospitalization (OR, 1.52; 95% CI, 1.108-2.082).

Discussion

The association of elevated eosinophil counts with asthma exacerbations and severity has received increasing focus during the past few years. With the introduction of new guidelines for asthma and novel biologic medicines, the potential of biomarkers to predict risk of exacerbations or guide treatment selection for individual patients has gained attention.[4,12,24] In their review article, Pavord et al[26] emphasized the need to identify reliable biomarkers and their practical clinical application. Researchers studying 3 available biologic treatments that lower eosinophil counts have selected different criteria to classify clinically significant eosinophil count elevation in pivotal studies.[9–11,18–23] A recent study by Shrimanker et al[27] found an increased risk of severe exacerbations in the high eosinophil count (≥150 cells/μL) group, with a significant risk reduction observed in the arm that was treated with the biologic (compared with placebo-treated arm). Castro et al[28] found that exacerbation rates in the biologic-treated group were significantly (65%) lower than those in the placebo group.

Our study assessed 2 different thresholds of eosinophil elevation to better understand the risk relationship between recent (within 3 months) absolute blood eosinophil counts and patient outcomes (health care resource use and cost) using a large, real-world database of patients diagnosed with asthma. Although controlled trials are essential to understand the relationship between different clinical measures and outcomes, real-world retrospective database studies help establish the relevance of those relationships in actual practice. In addition, applying the associative findings of eosinophil count elevation and resource use can help clinicians identify patients in need of better management earlier in their treatment. Our study incorporates an important inclusion criterion with respect to the timing of test observations using the most recent eosinophil test before the follow-up period. We recently reported data showing the influence of eosinophil elevations based on a range of test timing criteria (3 months, 6 months, and at any point during the 12-month assessment period and based on the mean count of all test results during the assessment period).[29] We found that significant differences in resource use and cost were in fact only noted when elevation was defined based on test results within a recent 3- to 6-month period before the resource-use assessment period.[29] Ironically, regardless of our applied standard, in this real-world study only 53% of patients had even a single complete blood cell count test with

Note: * indicates significance of p<0.05 comparing elevated versus not-elevated EOS counts.

Figure 2. Percentages of patients with asthma with health care resource use. Asterisks indicate significance of $P < .05$ comparing elevated and nonelevated eosinophil counts. ED, emergency department; OP, outpatient.

differential within 12 months after their asthma diagnosis (2007-2014), highlighting an immediate area for improvement. These findings suggest that patients with asthma may benefit from eosinophil testing, and additional studies might be warranted to determine optimal frequency and timing of testing.

In the overall sample, we found that at both thresholds, elevated eosinophil counts increased the likelihood of and percentage of patients admitted to the hospital. These differences, although numerically greater, were not statistically significant in the subgroup with uncontrolled asthma or the subgroup with severe asthma, perhaps indicating that in a subgroup of patients already at high risk of exacerbations and health care utilization, eosinophils do not significantly add to the already existing burden. Perhaps these patients whose asthma is not well controlled are more aggressively treated (possibly with prednisone). Steroid treatment may mitigate further increases in resource consumption in the short term vs patients whose asthma is well controlled and who are less likely to receive prednisone. However, across both eosinophil thresholds, within the subgroup that had controlled asthma at baseline and eosinophil count elevation, there was a significantly greater percentage of patients hospitalized, a significantly greater mean number of hospitalizations, and significantly greater cost related to hospitalizations as well as total medical- and prescription-related cost in the 1-year follow-up period compared with patients with controlled asthma and no eosinophil count elevation at baseline. This finding suggests that the patients who are considered to have controlled asthma at baseline, according to standard guidelines, but have elevated eosinophil counts are at

Table 2
Mean Health Care Resource Use and Cost During Follow-up Period

Variable	Eosinophil threshold of ≥150 cells/μL			Eosinophil threshold of ≥300 cells/μL		
	Elevated eosinophil count	Comparison group	*P* value	Elevated eosinophil count	Comparison group	*P* value
Mean (SD) resource use						
Overall						
All-cause hospitalizations	0.29 (0.92)	0.17 (0.57)	<.001	0.30 (0.95)	0.18 (0.61)	.001
All-cause ED visits	0.66 (1.48)	0.51 (1.21)	.01	0.64 (1.62)	0.53 (1.22)	.35
All-cause OP visits	12.28 (15.61)	8.90 (13.20)	<.001	11.70 (14.73)	9.27 (13.59)	.003
Uncontrolled						
All-cause hospitalizations	0.34 (1.17)	0.24 (0.67)	.36	0.42 (1.49)	0.23 (0.65)	.34
All-cause ED visits	0.80 (2.14)	0.73 (1.96)	.90	0.96 (2.71)	0.72 (1.87)	.86
All-cause OP visits	13.61 (15.99)	12.21 (15.91)	.26	14.04 (16.46)	12.32 (15.84)	.40
Controlled						
All-cause hospitalizations	0.28 (0.85)	0.16 (0.55)	<.001	0.26 (0.71)	0.17 (0.60)	.004
All-cause ED visits	0.62 (1.24)	0.47 (1.03)	.008	0.55 (1.07)	0.49 (1.07)	.33
All-cause OP visits	11.91 (15.50)	8.35 (12.62)	<.001	10.98 (14.11)	8.74 (13.09)	.009
Severe						
All-cause hospitalizations	0.33 (1.23)	0.18 (0.49)	.37	0.45 (1.61)	0.18 (0.50)	.18
All-cause ED visits	0.64 (1.61)	0.58 (1.47)	.94	0.73 (2.01)	0.57 (1.41)	.89
All-cause OP visits	15.42 (19.48)	10.44 (13.71)	.03	16.34 (19.31)	10.92 (14.62)	.053
Mean (SD) cost, $						
Overall						
All-cause hospitalizations	2543 (10,702)	1469 (7857)	<.001	2142 (7795)	1609 (8492)	.03
All-cause ED visits	499 (1686)	313 (991)	<.001	409 (1159)	339 (1144)	.20
All-cause OP visits	2230 (4842)	1353 (3269)	<.001	2150 (4997)	1442 (3435)	.02
Total all-cause medical	5272 (13,575)	3135 (9563)	<.001	4700 (11,178)	3390 (10,320)	.01
Prescriptions	4990 (20,916)	4014 (34,382)	<.001	5266 (24,655)	4078 (33,106)	.02
Total	10,262 (26,023)	7149 (35,874)	<.001	9966 (28,563)	7468 (34,893)	.003
Uncontrolled						
All-cause hospitalizations	2318 (8669)	2263 (13,594)	.53	3028 (10,957)	2157 (12,797)	.55
All-cause ED visits	444 (1282)	435 (1454)	.64	532 (1593)	422 (1383)	.88
All-cause OP visits	2682 (6609)	1835 (4644)	.15	2561 (6528)	1961 (4964)	.59
Total all-cause medical	5444 (12,645)	4532 (14,986)	.22	6121 (15,037)	4540 (14,347)	.64
Prescriptions	5981 (7690)	4814 (7099)	.03	5677 (6923)	5010 (7314)	.18
Total	11,425 (16,913)	9346 (16,894)	.054	11,798 (19,678)	9550 (16,426)	.37
Controlled						
All-cause hospitalizations	2606 (11,208)	1339 (6440)	.001	1870 (6531)	1515 (7509)	.04
All-cause ED visits	515 (1783)	293 (892)	<.001	371 (989)	325 (1098)	.19
All-cause OP visits	2104 (4222)	1274 (2977)	<.001	2023 (4430)	1354 (3090)	.03
Total all-cause medical	5224 (13,833)	2905 (8325)	<.001	4264 (9687)	3193 (9448)	.02
Prescriptions	4715 (23,292)	3883 (36,984)	.06	5139 (27,940)	3918 (35,702)	.20
Total	9939 (28,038)	6789 (38,086)	<.001	9403 (30,793)	7111 (37,138)	.04
Severe						
All-cause hospitalizations	1874 (7987)	1606 (6408)	.63	3009 (10,713)	1484 (6,059)	.36
All-cause ED visits	337 (999)	266 (881)	.71	355 (1140)	272 (873)	.85
All-cause OP visits	2894 (6969)	1237 (2465)	.07	3253 (7531)	1389 (3206)	.14
Total all-cause medical	5105 (12,324)	3108 (7606)	.14	6618 (15,600)	3144 (7506)	.18
Prescriptions	8534 (24,633)	9926 (88,299)	.04	6638 (7296)	10,015 (83,644)	.08
Total	13,638 (29,422)	$13,034 (88,456)	.046	13,256 (20,678)	13,159 (83,891)	.12

Abbreviations: ED, emergency department; OP, outpatient.

greater risk of losing symptom control. Although the patients with uncontrolled asthma require greater therapy management to control exacerbations, those with controlled asthma cannot be assumed to have better or more favorable outcomes. The sensitivity of patient outcomes to even modest elevation is highlighted by the observed difference in resource use at the 150 cells/μL or greater threshold compared with the 300 cells/μL or greater threshold. The relative increase in the mean number of hospitalizations at 150 cells/μL or greater is 75% greater than in the comparison group (0.28 vs 0.16); at 300 cells/μL or greater, this difference is 53% (0.26 vs 0.17). Routine measurement of blood eosinophil counts incorporated as a standard of care for all patients with asthma may offer benefit in identifying those likely to benefit from further intervention regardless of control status.

The findings of this study should be viewed in light of a few limitations. This was a retrospective analysis, so patients were not managed by any protocol with respect to blood testing or follow-up with their health care practitioner. Certain patient characteristics, such as smoking status, are missing in the database and may influence clinical outcomes. Despite a large patient population within the claims database, the sample sizes for patients with severe asthma and uncontrolled asthma who met the entry criteria were relatively low and may have limited our ability to detect some significant findings. Asthma was identified through diagnosis recorded in claims, and missed or erroneous diagnosis is always a possibility in these cases. However, erroneous diagnosis instances were mitigated by the requirement of at least 2 asthma claims for the ED and outpatient visit encounters. The findings of this study can only be applied to patients who sought care within this network of health care systems and may not be applied to patients without insurance. All measures included in the ERS/ATS or GINA guidelines were identified by recorded diagnosis, test values in patient medical records, or recorded prescription claims. Patients may choose not to undergo lung function testing or to fill their prescriptions; hence, these data were considered missing in this study. Our comparison group consisted of patients with test results below the eosinophil elevation threshold, as well as patients who did not get tested during the 3 months before follow-up. With this method of classification, some patients who did not get tested in the comparison group may potentially have had elevated eosinophil counts within 3 months of follow-up. This potential misclassification would bias the result toward a null finding by adding

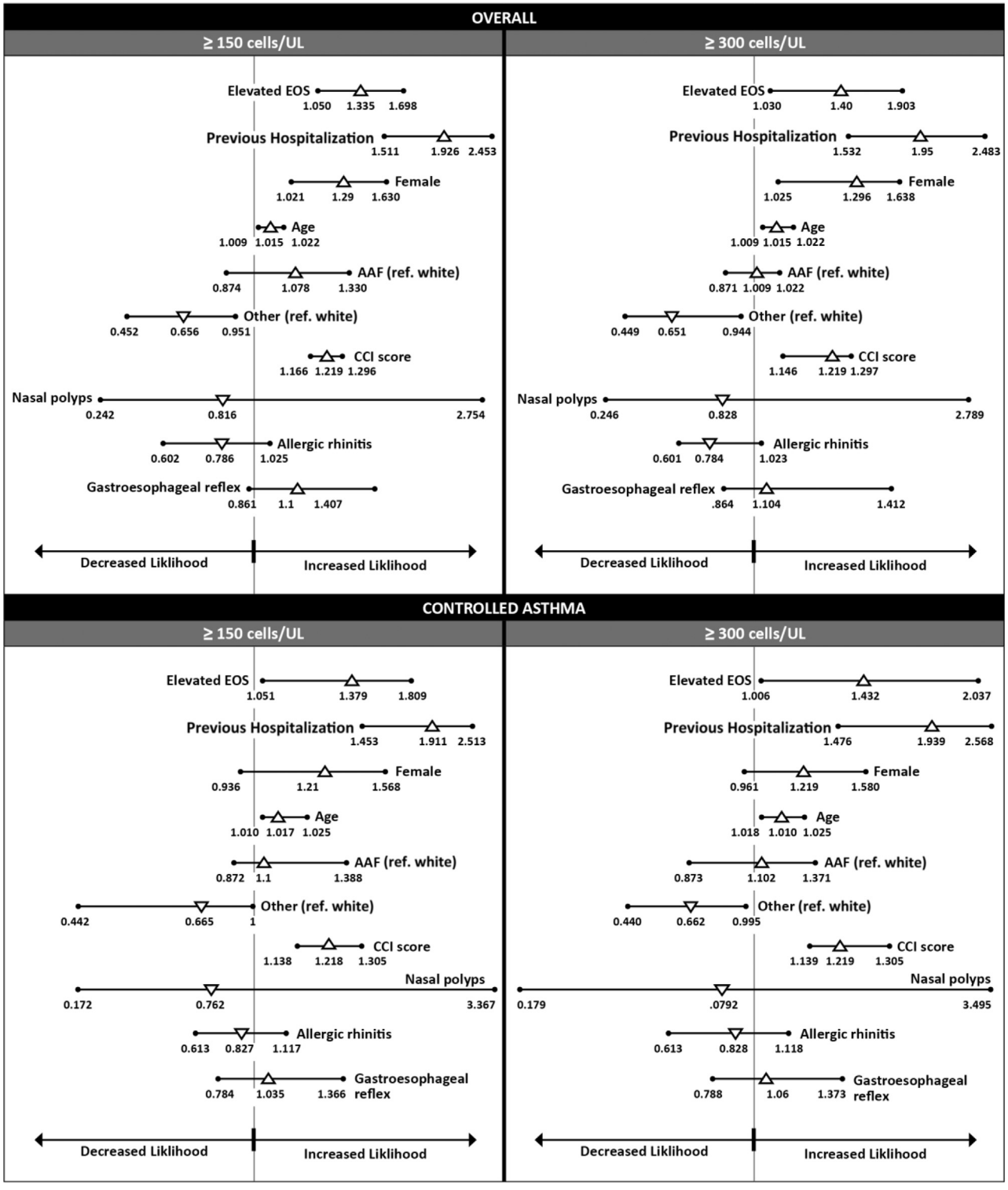

Figure 3. Likelihood of incurring hospitalizations during follow-up. AAF, African American; CCI, Charlson Comorbidity Index; EOS, eosinophil.

incremental resource use and cost of patients with elevated eosinophil counts to the comparison group. Despite this potential misclassification, we observed significantly greater resource use and cost in the group with elevated eosinophil counts. Of the 3043 patients in the comparison group for the threshold of 150 cells/μL or greater, 83% did not receive a test during the 3-month period before the follow-up. Of these patients, 39% had normal eosinophil counts and 61% had elevated eosinophil counts during the rest of the assessment period (9 months before the 3-month window). These results further emphasize the fact that in addition to elevated eosinophil counts, recency of those counts in relation to when we measure follow-up is an important factor in predicting resource use and cost.

Our data indicate that patients with asthma are more likely to incur health care resource use and related costs if their peripheral eosinophil counts are elevated at 150 cells/μL or greater, specifically

within a recent time frame. The most notable difference in health care use was in the subset of patients with controlled asthma with an elevated eosinophil count of 150 cells/μL or greater. All patients with asthma could benefit from frequent peripheral blood eosinophil count screening to potentially identify the subgroup that may benefit from a step-up in asthma therapy. Additional research with larger samples of uncontrolled and severe uncontrolled asthma is warranted to understand the subgroups that would have the greatest potential to prevent subsequent health care resource use and associated costs. Furthermore, interventional studies with step-up of care for elevated eosinophil counts will be needed to determine whether the increased health care resource use can be mitigated.

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