

Clinical and Economic Burden of Uncontrolled Severe Noneosinophilic Asthma

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The CDC estimated that 24.7 million Americans were living with asthma in 2018.¹ When uncontrolled, this chronic inflammatory disorder of the airways can result in hospitalization, disability, and death.² The majority of the economic and humanistic burden of asthma can be attributed to the 5% to 10% of patients with severe disease.³⁻⁷

Clinically, asthma is characterized by shortness of breath, wheezing, coughing, chest tightness, and variable airflow limitation.^{8,9} In patients with mild or moderate disease, these symptoms can be controlled through the use of a low-dose inhaled corticosteroid (ICS) in combination with a short-acting or long-acting β_2 -agonist (SABA or LABA, respectively). However, patients with severe uncontrolled asthma have exacerbations or persistent symptoms despite treatment with medium-dose to high-dose ICS with additional controllers, such as LABA.³⁻⁵

Despite significant heterogeneity, severe asthma can be generally segmented into 2 subtypes based on the presence of elevated eosinophil counts.^{10,11} Severe eosinophilic asthma, defined by a blood eosinophil count (BEC) of at least 300 cells/mcL,^{10,12,13} has been well characterized in recent years due to the availability of novel biologic therapies and the association with a greater exacerbation burden.¹⁴ Biologics approved for severe asthma, including omalizumab, which is approved for those with allergic disease, have all demonstrated a greater response among patients with eosinophilic asthma and limited and/or inconsistent efficacy among those with noneosinophilic asthma, defined as a BEC less than 260 to 300 cells/mcL.¹⁵⁻¹⁹ As a result, there is a significant unmet need among the approximately 50% to 60% of patients with severe uncontrolled asthma whose disease is noneosinophilic.^{11,20,21}

Due in part to the lack of effective therapies for the non-eosinophilic severe uncontrolled asthma population, limited data exist on the cost of noneosinophilic asthma in a US population, and prior studies have not provided a detailed analysis of cost contributors.^{22,23} This descriptive study assessed asthma exacerbations, levels of asthma control based on health care utilization, and all-cause/asthma-related health care utilization and costs within a commercially insured (including private Medicare) population in

ABSTRACT

OBJECTIVES: To quantify the clinical and economic burden of patients with severe asthma with low blood eosinophil counts (BECs) untreated with biologics.

STUDY DESIGN: Retrospective cohort study in IBM MarketScan claims database.

METHODS: Patients 12 years and older with severe asthma with BEC data were selected between January 1, 2013, and June 30, 2018 (date of the most recent BEC was used as the index date). Inclusion criteria were (1) presence of BEC laboratory test result, (2) continuous enrollment for 12 months preceding and following the index date, (3) meeting the Healthcare Effectiveness Data and Information Set definition of persistent asthma, (4) meeting the Global Initiative for Asthma definition of severe asthma, and (5) an absence of biologic treatment, other respiratory diagnoses, and malignancies 12 months preceding and following the index date. Asthma exacerbations, levels of disease control, and all-cause and asthma-related health care costs were reported during the 12-month postindex period for patients with a BEC less than 300 cells/mcL.

RESULTS: The sample included 8073 patients with severe asthma; 78% (n = 6260) presented with a BEC less than 300 cells/mcL. Mean (SD) age of the sample was 54.8 (14.2) years; 64% were female. Eighteen percent of patients had an asthma exacerbation; 19% had either uncontrolled or suboptimally controlled asthma based on the frequency of asthma-related hospital admissions, emergency department visits, or corticosteroid prescription fills. One-year all-cause and asthma-related total health care costs were \$25,845 and \$2802, respectively. Patients with suboptimally controlled and uncontrolled asthma spent \$1471 and \$3872 more, respectively, on asthma-related claims compared with patients with controlled asthma.

CONCLUSIONS: Among patients with severe asthma with low eosinophils untreated with biologics, there is a high burden of disease among those who have suboptimal disease control, highlighting an unmet need in severe asthma treatment.

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the United States in the 12 months following a BEC of less than 300 cells/mcL. Outcomes were examined by level of disease control and BEC at baseline.

METHODS

Study Design and Data Source

This was an observational, retrospective cohort study of deidentified US health care claims data spanning January 1, 2012, through June 30, 2019, from IBM MarketScan databases: the Commercial Claims and Encounters Database, Medicare Supplemental and Coordination of Benefits Database, and Lab Results Database.

Patient Selection

Patients with at least 1 laboratory result for a BEC between January 1, 2013, and June 30, 2018, were identified. Laboratory results that occurred within 30 days after systemic corticosteroid or myelosuppressive chemotherapy treatment were excluded, as these treatments can depress BECs.²⁴ The date of the most recent qualifying laboratory result was defined as the index date.

Patients were required to have at least 12 months of continuous enrollment with medical and pharmacy benefits before (preindex period) and after (postindex period) the index date. Additional inclusion criteria included meeting the definition of persistent asthma as defined by the Healthcare Effectiveness Data and Information Set (HEDIS),²⁵ meeting the definition of severe asthma outlined in the Global Initiative for Asthma (GINA) guidelines,²⁶ and being at least 12 years old on the index date. HEDIS and GINA criteria are described in detail in the [eAppendix Text](#) (Appendix available at [ajmc.com](#)). Patients with evidence of biologic treatment for asthma, diagnosis of other respiratory conditions (except for chronic obstructive pulmonary disease), or diagnosis of malignancies (except for nonmelanoma skin cancer) during the preindex or postindex periods were excluded from the analysis.

The primary focus of the analyses was among patients with noneosinophilic asthma with a low BEC of less than 300 cells/mcL. Results for eosinophilic patients with a high BEC of at least 300 cells/mcL were exploratory and are included in the [eAppendix material](#). Levels of asthma control were established using health care utilization claims during the postindex period. Patients were categorized hierarchically as having uncontrolled, suboptimally controlled, or controlled asthma using the following definitions, consistent with American Thoracic Society/European Respiratory Society guidelines.²⁷

Components of asthma control are described in [eAppendix Table 1](#). A burst of systemic corticosteroids was defined as 1 dose of injectable corticosteroids or a prescription for oral corticosteroids with a days' supply of at least 3 days. Maintenance use of systemic corticosteroids was also assessed and was defined as having a days' supply of at least 180 days during the postindex period. When a

TAKEAWAY POINTS

Among patients with severe asthma with low eosinophils untreated with biologics, there is a high burden of disease among those who have suboptimal disease control, highlighting an unmet need in severe asthma treatment.

- ▶ The majority of patients with severe asthma identified in this study presented with a low blood eosinophil count (BEC) of less than 300 cells/mcL, representing an understudied population.
- ▶ In a 1-year period, one-fifth of patients with a low BEC had disease that was not optimally controlled, which was associated with higher asthma-related health care costs.
- ▶ Overall, patients with a low BEC accounted for two-thirds of the total uncontrolled disease burden and three-fourths of all asthma-related health care costs.

patient was on maintenance use of systemic corticosteroids, it was not possible to classify claims representing a burst use of systemic corticosteroids. To avoid potentially miscategorizing patients, patients with maintenance systemic corticosteroid use were excluded from the analysis of level of asthma control.²⁸

Outcomes

Patient characteristics. Patient age, sex, geographic region of residence, and index year were measured on the index date. The Deyo-Charlson Comorbidity Index (DCI) score²⁹ and number and percentage of patients with claims for comorbid conditions, listed in [eAppendix Table 2](#), were measured during the postindex period. The use of nonbiologic asthma medications in the postindex period was reported by class as listed in [Table 1](#). Asthma exacerbations were captured during the postindex period via an asthma diagnosis code on either a mechanical ventilation claim, an inpatient admission, or an outpatient visit with burst systemic corticosteroids use within 7 days.

Health care resource utilization and costs. All-cause and asthma-related health care resource utilization and costs were assessed during the postindex period. Asthma-related utilization and costs were based on inpatient admissions with a primary diagnosis for asthma, outpatient medical claims with a diagnosis for asthma, and outpatient pharmacy claims for all treatments indicated for treating asthma. Health care costs were calculated based on paid amounts of adjudicated claims, including insurer and health plan payments, as well as patient cost sharing. All costs were adjusted for inflation using the medical care component of the Consumer Price Index obtained from the US Bureau of Labor Statistics and standardized to 2019 US\$.³⁰

Statistical Analysis

Patient characteristics, disease exacerbation data, and health care service use and costs were reported for all eligible patients with asthma with a low BEC (< 300 cells/mcL), stratified by BEC subgroup (< 150 cells/mcL and 150-299 cells/mcL) and by the level of asthma control based on health care utilization. Mean and SD were reported for continuous variables. Frequencies and percentages were reported for categorical variables. All data analyses were conducted using WPS version 4.1 (World Programming).

TABLE 1. Patient Characteristics

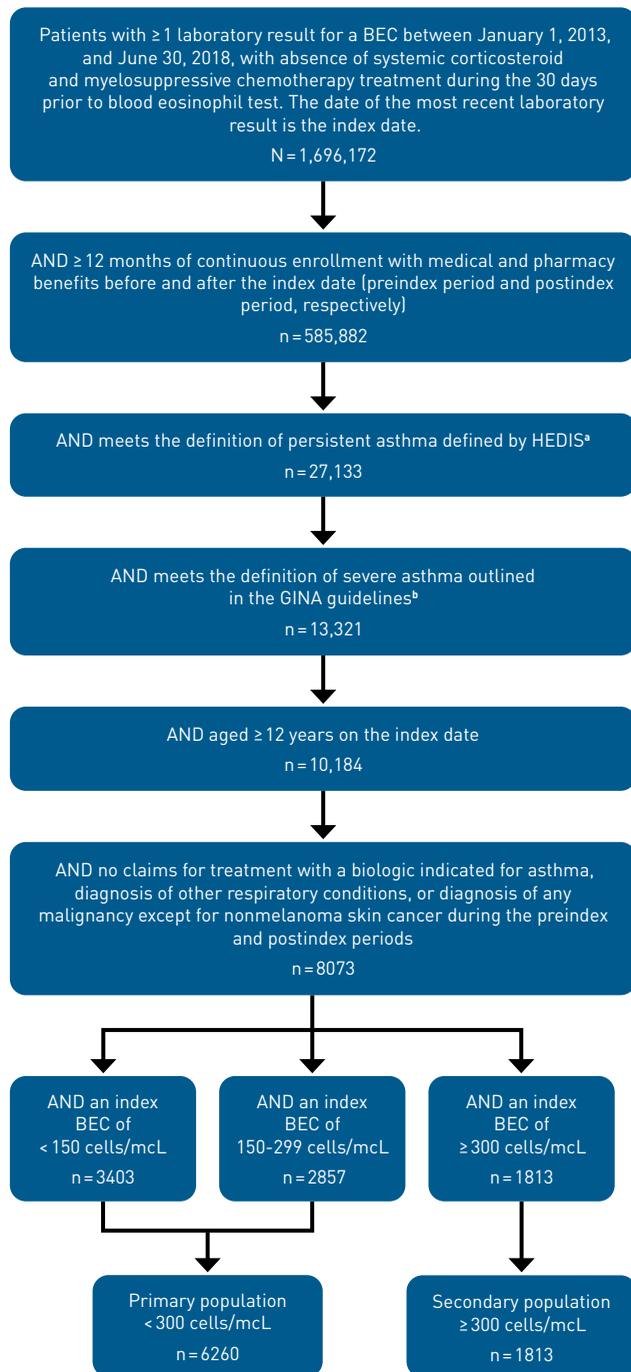
Characteristics	Primary population	Primary population by BEC			Primary population by level of disease control ^a		
	<300 cells/mcL	<150 cells/mcL	150-299 cells/mcL	Uncontrolled	Suboptimally controlled	Controlled	
	N = 6260	n = 3403	n = 2857	n = 286	n = 896	n = 4955	
Age in years, mean (SD)	54.8 (14.2)	54.1 (14.7)	55.6 (13.4)	50.5 (14.3)	53.1 (15.2)	55.3 (13.9)	
Age category in years, n (%)							
12-17	125 (2.0%)	77 (2.3%)	48 (1.7%)	8 (2.8%)	32 (3.6%)	84 (1.7%)	
18-34	406 (6.5%)	263 (7.7%)	143 (5.0%)	29 (10.1%)	62 (6.9%)	305 (6.2%)	
35-44	683 (10.9%)	389 (11.4%)	294 (10.3%)	51 (17.8%)	106 (11.8%)	511 (10.3%)	
45-54	1379 (22.0%)	753 (22.1%)	626 (21.9%)	63 (22.0%)	225 (25.1%)	1068 (21.6%)	
55-64	2602 (41.6%)	1336 (39.3%)	1266 (44.3%)	100 (35.0%)	349 (39.0%)	2109 (42.6%)	
65-74	649 (10.4%)	360 (10.6%)	289 (10.1%)	26 (9.1%)	60 (6.7%)	550 (11.1%)	
≥75	416 (6.6%)	225 (6.6%)	191 (6.7%)	9 (3.1%)	62 (6.9%)	328 (6.6%)	
Female, n (%)	3982 (63.6%)	2284 (67.1%)	1698 (59.4%)	214 (74.8%)	608 (67.9%)	3067 (61.9%)	
Geographic region, n (%)							
Northeast	1970 (31.5%)	1080 (31.7%)	890 (31.2%)	98 (34.3%)	304 (33.9%)	1535 (31.0%)	
North Central	1819 (29.1%)	957 (28.1%)	862 (30.2%)	65 (22.7%)	248 (27.7%)	1462 (29.5%)	
South	2133 (34.1%)	1186 (34.9%)	947 (33.1%)	114 (39.9%)	310 (34.6%)	1664 (33.6%)	
West	333 (5.3%)	178 (5.2%)	155 (5.4%)	9 (3.1%)	34 (3.8%)	289 (5.8%)	
Unknown	5 (0.1%)	2 (0.1%)	3 (0.1%)	0 (0.0%)	0 (0.0%)	5 (0.1%)	
Index year, n (%)							
2013	744 (11.9%)	481 (14.1%)	263 (9.2%)	28 (9.8%)	96 (10.7%)	610 (12.3%)	
2014	1031 (16.5%)	559 (16.4%)	472 (16.5%)	43 (15.0%)	132 (14.7%)	838 (16.9%)	
2015	830 (13.3%)	428 (12.6%)	402 (14.1%)	38 (13.3%)	121 (13.5%)	651 (13.1%)	
2016	1234 (19.7%)	669 (19.7%)	565 (19.8%)	54 (18.9%)	183 (20.4%)	966 (19.5%)	
2017	1277 (20.4%)	642 (18.9%)	635 (22.2%)	74 (25.9%)	201 (22.4%)	973 (19.6%)	
2018	1144 (18.3%)	624 (18.3%)	520 (18.2%)	49 (17.1%)	163 (18.2%)	917 (18.5%)	
Asthma-related medications, ^b n (%)							
SCS ^c	4320 (69.0%)	2409 (70.8%)	1911 (66.9%)	284 (99.3%)	849 (94.8%)	3064 (61.8%)	
≥180 days' supply of SCS	1377 (22.0%)	917 (26.9%)	460 (16.1%)				
ICS/LABA	3993 (63.8%)	1973 (58.0%)	2020 (70.7%)	234 (81.8%)	708 (79.0%)	2992 (60.4%)	
Leukotriene receptor antagonists	2185 (34.9%)	1170 (34.4%)	1015 (35.5%)	183 (64.0%)	448 (50.0%)	1499 (30.3%)	
Short-acting β ₂ -agonists	1338 (21.4%)	654 (19.2%)	684 (23.9%)	167 (58.4%)	468 (52.2%)	661 (13.3%)	
Tiotropium	691 (11.0%)	366 (10.8%)	325 (11.4%)	41 (14.3%)	123 (13.7%)	511 (10.3%)	
Inhaled corticosteroids	645 (10.3%)	368 (10.8%)	277 (9.7%)	64 (22.4%)	137 (15.3%)	425 (8.6%)	
Short-acting muscarinic antagonists	97 (1.5%)	41 (1.2%)	56 (2.0%)	9 (3.1%)	36 (4.0%)	50 (1.0%)	
Theophylline and other methylxanthines	95 (1.5%)	47 (1.4%)	48 (1.7%)	6 (2.1%)	16 (1.8%)	69 (1.4%)	
Asthma exacerbation, n (%)							
≥1 asthma diagnosis on mechanical ventilation claim	7 (0.1%)	4 (0.1%)	3 (0.1%)				
≥1 asthma diagnosis as primary discharge on inpatient admission	28 (0.4%)	15 (0.4%)	13 (0.5%)				
≥1 asthma diagnosis on outpatient visit with burst SCS within 7 days	1148 (18.3%)	581 (17.1%)	567 (19.8%)				
Number of asthma exacerbations, mean (SD)	0.26 (0.63)	0.25 (0.63)	0.27 (0.63)				

BEC, blood eosinophil count; ICS/LABA, inhaled corticosteroid/long-acting β₂-agonist; SCS, systemic corticosteroids.

^aOutcomes by level of disease control were reported among patients with a BEC less than 300 cells/mcL; 98 patients were excluded from level of disease control analysis because burst use of SCS for exacerbation treatment could not be distinguished from SCS used in daily control.

^bLong-acting muscarinic antagonist/LABA combinations and mast cell stabilizers were used by less than 1% of patients and are not reported in the table.

^cIncludes both injectable and oral corticosteroids.

FIGURE 1. Patient Selection

BEC, blood eosinophil count; ED, emergency department; GINA, Global Initiative for Asthma; HEDIS, Healthcare Effectiveness Data and Information Set.

*At least 1 of the following during both the preindex and postindex periods: [1] ≥ 1 inpatient admission or ED visit with a principal diagnosis of asthma; [2] ≥ 4 asthma medication dispensing events; or [3] ≥ 4 non-rule-out claims on different days with an asthma diagnosis in any position and ≥ 2 asthma medication dispensing events.

^bAt least 1 of the following during the preindex period: [1] ≥ 2 claims for medium- to high-dose inhaled corticosteroid/long-acting β_2 -agonist combination; [2] ≥ 2 claims for medium- to high-dose inhaled corticosteroid with additional controllers; or [3] ≥ 180 cumulative days' supply of oral corticosteroids.

RESULTS

Patient Characteristics

We identified 8073 commercially insured patients with severe persistent asthma, no evidence of biologic therapy, and at least 1 available BEC (Figure 1). Of these, 3403 (42%) had a BEC less than 150 cells/mcL and 2857 (35%) had a BEC of 150 to 299 cells/mcL. This resulted in a primary study population of 6260 patients (78%) with severe persistent asthma and a low BEC of less than 300 cells/mcL.

The mean (SD) age was 54.8 (14.2) years, and 63.6% were female (Table 1). Mean age was similar between BEC subgroups; however, patients with a BEC less than 150 cells/mcL were more likely to be female than patients with a BEC of 150 to 299 cells/mcL (67.1% vs 59.4%). The mean (SD) DCI score was 1.5 (1.5), and the incidence of select comorbid conditions can be found in eAppendix Table 2.

During the postindex period, the most widely used asthma-related medications were systemic corticosteroids (69.0%), ICS/LABAs (63.8%), and leukotriene receptor antagonists (34.9%) (Table 1). There were 1377 (22.0%) patients who had evidence consistent with maintenance use of systemic corticosteroids. Treatment characteristics varied by BEC. Patients with a BEC less than 150 cells/mcL had higher maintenance use of systemic corticosteroids (26.9% vs 16.1%) but lower use of ICS/LABAs (58.0% vs 70.7%) and SABAs (19.2% vs 23.9%) compared with patients with a BEC of 150 to 299 cells/mcL.

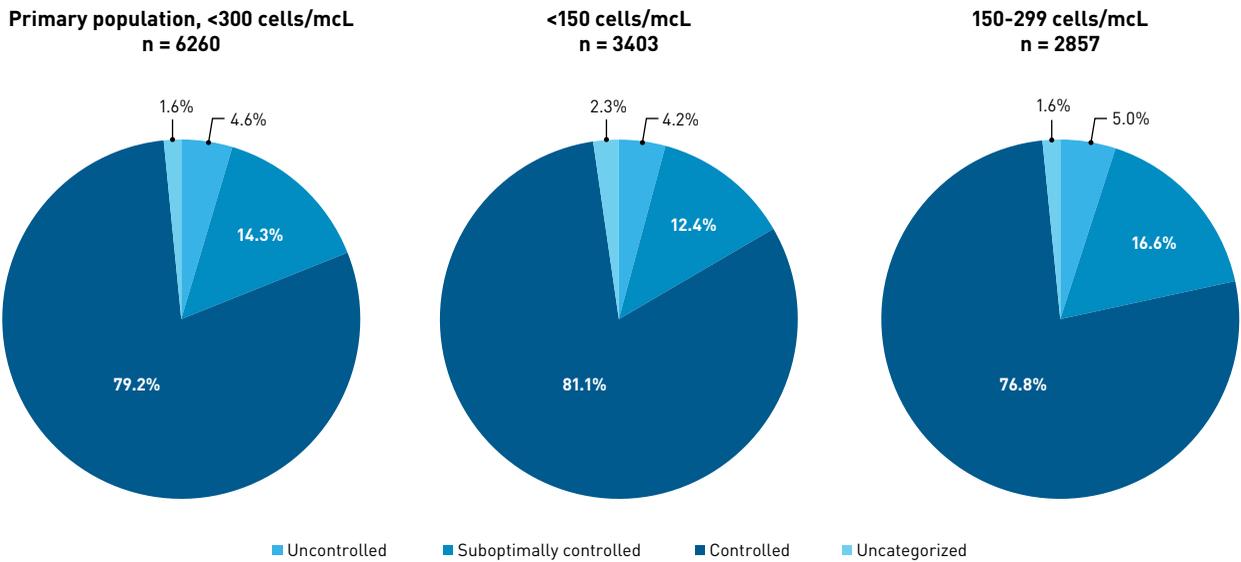
During the postindex period, 18.4% of patients had evidence of at least 1 asthma exacerbation (Table 1). The mean (SD) number of exacerbations was 0.26 (0.63), with similar numbers for the subgroups with BEC less than 150 cells/mcL and 150 to 299 cells/mcL. Based on health care claims in the postindex period, 4.6% of patients were classified as having uncontrolled asthma, 14.3% were classified as having suboptimally controlled asthma, 79.2% were classified as having controlled asthma, and 1.6% could not be categorized (Figure 2). The percentage of patients with uncontrolled or suboptimally controlled asthma was slightly lower among patients with a BEC less than 150 cells/mcL compared with patients with a BEC of 150 to 299 cells/mcL (16.7% vs 21.5%).

Patients with uncontrolled asthma were more likely to be younger (aged 50.5 vs 55.3 years), be female (74.8% vs 61.9%), and have greater use of nonbiologic asthma control medications than patients classified as having controlled asthma (Table 1). Overall, 99.3% of patients with uncontrolled asthma and 94.8% of patients with suboptimally controlled asthma had at least 1 outpatient claim for systemic corticosteroids compared with 61.8% of patients with controlled asthma. Comorbidities varied by level of asthma control (eAppendix Table 2).

Health Care Resource Utilization and Costs

During the postindex period, 15.4% of patients had an all-cause inpatient admission; however, only 28 patients (0.4%) had an asthma-related inpatient admission (Table 2). One-third of patients (33.9%) had an all-cause emergency department (ED) visit, and 6.5%

FIGURE 2. Level of Asthma Control Classification^a for Primary Population by Blood Eosinophil Count at Index



SCS, systemic corticosteroid.

^aLevel of control was assigned hierarchically into mutually exclusive categories: uncontrolled (≥ 1 inpatient admission with an asthma diagnosis with or without mechanical ventilation or ≥ 2 outpatient visits with an asthma diagnosis treated with SCS within 7 days), suboptimally controlled (exactly 1 outpatient visit with an asthma diagnosis treated SCS within 7 days or ≥ 4 claims for short-acting β_2 -agonist), and controlled (none of the above). Outpatient visits were inclusive of emergency department visit, urgent care visit, or other outpatient visits, and burst SCS use was defined as 1 dose of injectable corticosteroids or oral corticosteroids for ≥ 3 days. Patients were uncategorized when SCS burst for exacerbation treatment could not be distinguished from SCS used in daily control.

had an asthma-related ED visit. Health care utilization by BEC at index is presented in [eAppendix Table 3](#). Patients with uncontrolled asthma had greater health care utilization than patients with suboptimally controlled or controlled asthma (Table 2). Among patients with uncontrolled asthma, 9.8% had an asthma-related inpatient admission. The mean (SD) number of asthma-related ED visits (0.0 [0.3] vs 0.2 [0.6] vs 0.5 [1.0]), outpatient office visits (0.7 [1.3] vs 2.3 [2.1] vs 4.4 [2.8]), and prescription fills (7.3 [5.4] vs 11.2 [7.5] vs 14.1 [8.6]) each increased as the level of asthma control decreased, from controlled to suboptimally controlled to uncontrolled, respectively.

Mean (SD) 1-year all-cause and asthma-related total health care costs for patients were \$25,845 (\$43,896) and \$2802 (\$3965), respectively ([Figure 3](#) and [eAppendix Table 4](#)). All-cause health care costs were higher for patients with a BEC less than 150 cells/mcL compared with patients with a BEC of 150 to 299 cells/mcL (\$27,876 [\$46,581] vs \$23,423 [\$40,339]), but asthma-related costs were similar (\$2659 [\$4101] vs \$2973 [\$3791]) ([eAppendix Table 4](#)).

All-cause costs were similar across levels of disease control, but the percentage that was asthma related was 25.5% (\$6258 of \$24,518) for patients with uncontrolled asthma, 15.9% (\$3857 of \$24,258) for patients with suboptimally controlled asthma, and 9.3% (\$2386 of \$25,527) for patients with controlled asthma. Patients with suboptimally controlled and uncontrolled asthma spent \$1471 and \$3872 more, respectively, on asthma-related claims compared with patients with controlled asthma.

Exploratory Results

Eosinophilic patients with a high BEC of at least 300 cells/mcL were more likely than patients with a low BEC of less than 300 cells/mcL to have exacerbations (25.6% vs 18.4%) and uncontrolled disease (7.9% vs 4.6%) ([eAppendix Table 5](#)). But among all patients with uncontrolled asthma, 67% had a BEC less than 300 cells/mcL and 34% had a BEC less than 150 cells/mcL. Patients with a high BEC had lower all-cause costs but higher asthma-related costs (\$21,293 [\$38,142] and \$3229 [\$3244], respectively) compared with patients with a low BEC (\$25,845 [\$43,896] and \$2802 [\$3965], respectively) ([eAppendix Table 4](#)). Still, among all costs captured within this population with low and high BEC and severe asthma not treated with biologics, 81% of all-cause and 75% of asthma-related costs were attributable to patients with BEC less than 300 cells/mcL.

DISCUSSION

In this descriptive study of commercially insured patients with severe asthma and a low BEC who were untreated with biologics, 1-year all-cause costs were \$25,845 per person per year, and 18.9% of patients were identified as having uncontrolled or suboptimally controlled asthma based on health care utilization alone. Although all-cause costs did not differ by level of disease control, in part attributable to the older age and higher rates of several comorbidities among patients with controlled asthma, 1-year

TABLE 2. All-Cause and Asthma-Related Health Care Utilization During the 12-Month Postindex Period

Utilization	Primary population	Primary population by level of disease control ^a		
	< 300 cells/mcL N = 6260	Uncontrolled n = 286	Suboptimally controlled n = 896	Controlled n = 4955
All-cause health care utilization				
Patients with an admission, n (%)	966 (15.4%)	56 (19.6%)	152 (17.0%)	710 (14.3%)
Number of inpatient admissions, mean (SD)	0.2 (0.6)	0.3 (0.7)	0.2 (0.6)	0.2 (0.6)
Number of inpatient admissions among patients with admission, mean (SD)	1.4 (1.0)	1.4 (0.8)	1.4 (0.9)	1.4 (1.0)
Length of stay per admission in days, mean (SD)	5.5 (4.2)	5.4 (3.4)	5.2 (2.9)	5.5 (4.5)
Patients with an outpatient service, n (%)	6246 (99.8%)	286 (100.0%)	896 (100.0%)	4941 (99.7%)
Patients with an ED visit, n (%)	2121 (33.9%)	142 (49.7%)	398 (44.4%)	1514 (30.6%)
Number of ED visits, mean (SD)	0.7 (1.7)	1.3 (2.5)	0.9 (1.6)	0.6 (1.5)
Number of ED visits among patients with visit, mean (SD)	2.1 (2.4)	2.6 (3.0)	2.1 (1.9)	1.9 (2.2)
Patients with an office visit, n (%)	6204 (99.1%)	286 (100.0%)	891 (99.4%)	4904 (99.0%)
Number of office visits, mean (SD)	11.0 (8.3)	14.8 (9.8)	11.7 (8.3)	10.5 (7.8)
Number of office visits among patients with visit, mean (SD)	11.1 (8.3)	14.8 (9.8)	11.7 (8.3)	10.6 (7.8)
Patients with another outpatient service, ^b n (%)	6222 (99.4%)	286 (100.0%)	893 (99.7%)	4921 (99.3%)
Patients with an outpatient prescription, n (%)	6251 (99.9%)	286 (100.0%)	896 (100.0%)	4946 (99.8%)
Number of prescriptions, mean (SD)	47.0 (35.0)	56.4 (40.0)	50.9 (36.0)	45.1 (33.9)
Number of prescriptions among patients with prescription, mean (SD)	47.1 (35.0)	56.4 (40.0)	50.9 (36.0)	45.2 (33.9)
Asthma-related health care utilization				
Patients with an admission, n (%)	28 (0.4%)	28 (9.8%)	0 (0.0%)	0 (0.0%)
Number of inpatient admissions, mean (SD)	0.0 (0.1)	0.1 (0.3)		
Number of inpatient admissions among patients with admission, mean (SD)	1.1 (0.3)	1.1 (0.3)		
Length of stay per admission in days, mean (SD)	4.8 (1.9)	4.8 (1.9)		
Patients with an outpatient service, n (%)	3133 (50.0%)	284 (99.3%)	796 (88.8%)	1933 (39.0%)
Patients with an ED visit, n (%)	410 (6.5%)	80 (28.0%)	147 (16.4%)	165 (3.3%)
Number of ED visits, mean (SD)	0.1 (0.5)	0.5 (1.0)	0.2 (0.6)	0.0 (0.3)
Number of ED visits among patients with visit, mean (SD)	1.5 (1.4)	1.8 (1.3)	1.3 (0.8)	1.3 (1.1)
Patients with an office visit, n (%)	2822 (45.1%)	282 (98.6%)	733 (81.8%)	1699 (34.3%)
Number of office visits, mean (SD)	1.1 (1.8)	4.4 (2.8)	2.3 (2.1)	0.7 (1.3)
Number of office visits among patients with visit, mean (SD)	2.5 (2.0)	4.4 (2.7)	2.8 (1.9)	2.0 (1.4)
Patients with another outpatient service, ^b n (%)	2388 (38.1%)	255 (89.2%)	649 (72.4%)	1378 (27.8%)
Patients with an outpatient prescription, n (%)	6075 (97.0%)	285 (99.7%)	891 (99.4%)	4781 (96.5%)
Number of prescriptions, mean (SD)	8.3 (6.3)	14.1 (8.6)	11.2 (7.5)	7.3 (5.4)
Number of prescriptions among patients with prescription, mean (SD)	8.5 (6.2)	14.1 (8.6)	11.2 (7.5)	7.6 (5.3)

ED, emergency department.

^aOutcomes by level of disease control were reported among patients with a blood eosinophil count less than 300 cells/mcL; 98 patients were excluded from level of disease control analysis because burst use of systemic corticosteroids for exacerbation treatment could not be distinguished from systemic corticosteroids used for daily control.

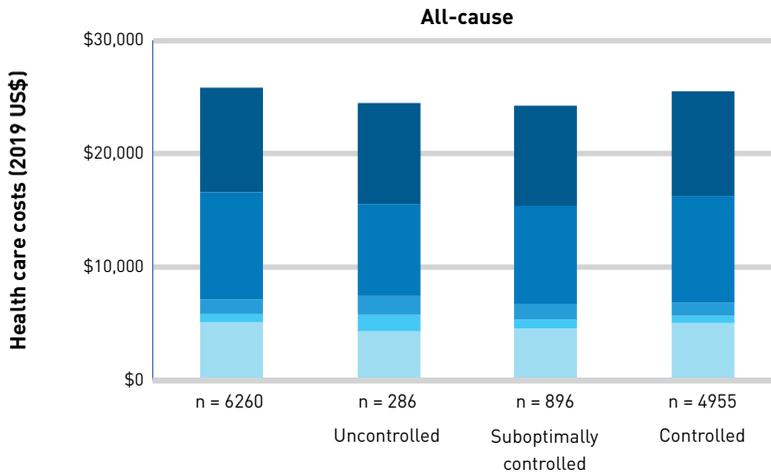
^bOffice-administered medications are captured as other outpatient services.

asthma-related costs increased as the level of control decreased, from \$2386 among those with controlled asthma to \$6258 among those with uncontrolled disease. The higher asthma-related costs among patients with uncontrolled asthma were due predominantly to nonpharmacy services such as inpatient admissions, ED visits, and other outpatient services.

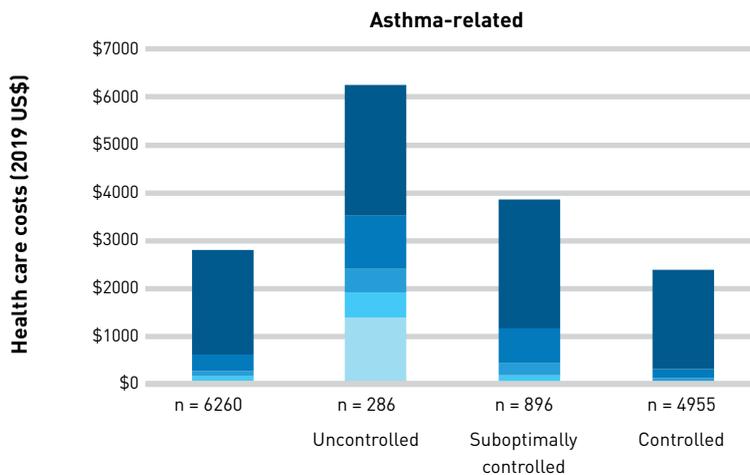
In a prior analysis of commercially insured patients living in 7 Midwestern states, 1-year costs among patients with severe asthma

and a BEC below 400 cells/mcL were \$13,168 (2015 US\$).²² These costs were estimated from billed charges from a single managed care plan using a 0.33 cost-to-charge ratio. Costs were higher among patients with elevated eosinophils, but the authors did not provide a detailed analysis to see if this was due to hospitalizations, medication use, or other utilization. Despite the increased per-patient burden of asthma outcomes among those with eosinophilic asthma, the majority of patients with severe asthma untreated with

FIGURE 3. All-Cause and Asthma-Related Health Care Costs During the 12-Month Postindex Period



	All primary	Primary by level of disease control		
Total	\$25,845	\$24,518	\$24,258	\$25,527
OP pharmacy	\$9215	\$8935	\$8803	\$9244
Other OP services	\$9494	\$8150	\$8733	\$9364
OP office visits	\$1272	\$1672	\$1294	\$1212
ED visits	\$680	\$1392	\$809	\$594
Inpatient	\$5185	\$4369	\$4619	\$5113



	All primary	Primary by level of disease control		
Total	\$2802	\$6258	\$3857	\$2386
OP pharmacy	\$2181	\$2744	\$2692	\$2067
Other OP services	\$339	\$1099	\$714	\$201
OP office visits	\$130	\$493	\$262	\$80
ED visits	\$88	\$530	\$189	\$38
Inpatient	\$64	\$1392	\$0	\$0

biologics in the current study were identified as having noneosinophilic asthma (78%) and accounted for a greater proportion of both the overall uncontrolled disease burden (67%) and asthma-related health care costs (75%). Further, the proportion of asthma-related costs attributable to outpatient pharmacy was 44% among patients with low BEC and uncontrolled asthma, compared with 76% among patients with high BEC. Taken together, these results underscore the unmet and often overlooked need for additional treatments for patients with noneosinophilic asthma within the broader severe asthma population.

Current therapy options for severe asthma, including ICS and biologics, have limited effectiveness among patients with low eosinophil counts.^{15-19,31} As a result, many patients often rely on systemic corticosteroids to maintain disease control. In this study, maintenance systemic corticosteroid was observed in 22% of patients with a BEC of less than 300 cells/mcL and 27% of patients with a BEC of less than 150 cells/mcL. This percentage is high, but within the range reported in a systematic review of the literature. Bleecker et al reported that estimates of the rate of long-term systemic corticosteroid use ranged from 0.5% to 26.8% depending on patient population and definition of long-term use.³² Although systemic corticosteroids are potentially effective at reducing exacerbations, maintenance use of these agents is associated with costly acute and chronic complications, including severe infections, osteoporosis, hypertension, and diabetes.³³⁻³⁸ In a prior MarketScan analysis of costs among patients with persistent asthma, adjusted 3-year all-cause costs were \$22,310 (2018 US\$) more for patients with at least 4 claims for systemic corticosteroids in a 12-month period compared with patients who had not used systemic corticosteroids.³⁷ The high use of systemic corticosteroids in patients with noneosinophilic asthma further underscores the need for more effective asthma treatments in this population.

Limitations

This study is subject to the limitations inherent in any retrospective database analysis. First, this study was limited to individuals with commercial health coverage, including private Medicare supplemental coverage, and the results of this

ED, emergency department; OP, outpatient.

analysis may not be generalizable to patients with other insurance or without health insurance coverage. Second, the claims data are subject to coding limitations and data entry errors, which introduce the potential for misclassification of disease status, covariates, and study outcomes. Third, the level of asthma control assignment was based on health care utilization alone and could not capture patient-reported symptoms; therefore, some patients classified as having controlled asthma may have had uncontrolled asthma.

Fourth, the patient selection algorithm used the most recent BEC result, and some patients may have been inappropriately included in or excluded from the study. Other options for assigning a BEC were considered, such as taking the highest count or the mean of all counts, but the small number of patients with multiple counts from different BEC categories was insufficient to affect the study results. Fifth, the study excluded patients who were taking biologics because these medications can lower BEC. The exclusion of patients with any use of biologics may have skewed the study sample toward patients with noneosinophilic asthma, given that current biologics are indicated for and/or perform better in those with eosinophilic asthma. Additionally, some patients classed as having noneosinophilic asthma may have a suppressed BEC due to maintenance systemic corticosteroid use, despite our exclusion of BEC results within 30 days after a corticosteroid prescription. The percentage of patients with noneosinophilic asthma with maintenance systemic corticosteroid use was higher in this study compared with published data.³⁹ This discrepancy could be because of the fact that we did not exclude patients with autoimmune conditions and other diseases commonly treated by steroids, our capture of both oral and injectable systemic corticosteroids, and the inability in claims to confirm when medications were prescribed for maintenance use vs repeat, intermittent use. Finally, there may have been systematic differences among the study cohorts that contribute to the differences found in health care costs and utilization (eg, race and ethnicity, which are not available in the databases used in this study). Future analyses may consider using other data sets or applying matching and multivariable methods to control for measurable differences among groups.

CONCLUSIONS

There is a significant unmet need among patients with severe uncontrolled asthma and low eosinophils. In a 1-year period, 1 in 5 commercially insured patients with a low BEC of less than 300 cells/mcL had asthma that was not optimally controlled, which was associated with higher asthma-related health care costs. Overall, patients with a low BEC accounted for two-thirds of the total uncontrolled disease burden and three-fourths of all asthma-related health care costs. ■

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Clinical and Economic Burden of Uncontrolled Severe Non-Eosinophilic Asthma

Supplementary Information

eAppendix Text. HEDIS and GINA criteria description

To meet the HEDIS criteria for persistent asthma, patients were required to meet at least one of the following criteria during the pre-index and post-index periods: A) at least one inpatient admission or emergency department (ED) visit with a principal diagnosis of asthma; B) at least four asthma medication dispensing events; or C) at least four non rule-out claims on different days with an asthma diagnosis in any position and at least two asthma medication dispensing events.¹ To meet the GINA criteria for severe asthma, patients were required to meet at least one of the following criteria during the pre-index period: A) at least two claims for medium to high dose ICS/LABA combination; B) at least two claims for medium to high dose ICS with separate claims for additional controllers; or C) at least 180 cumulative days' supply of oral corticosteroids.²

1. National Committee for Quality Assurance. Healthcare Effectiveness Data and Information Set (HEDIS) measures. Available at:<https://www.ncqa.org/hedis/measures/>. Accessed October 15, 2020.
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eAppendix Table 1. Level of asthma control components

Level of Asthma Control	Components
Uncontrolled	≥1 inpatient admission with a primary discharge diagnosis of asthma (with or without and a corresponding claim for mechanical ventilation during the stay)
	≥2 outpatient visits (emergency room visits, urgent care visits, or other outpatient visit) with an asthma diagnosis and receipt of burst systemic corticosteroids ^a within 7 days of each visit
Suboptimally controlled	=1 outpatient visits (emergency room visits, urgent care visits, or other outpatient visit) with an asthma diagnosis and receipt of burst systemic corticosteroids ^a within 7 days of each visit
	≥4 claims for SABAs
Controlled	Not meeting the definition of uncontrolled or suboptimally controlled
Uncategorized	Patients with maintenance systemic corticosteroid use ^b were excluded from the level of control analysis

^a burst of systemic corticosteroids was defined as one dose of injectable corticosteroids or a prescription for oral corticosteroids with a days' supply of at least three days.

^b Maintenance use of systemic corticosteroids was defined as having a days' supply of at least 180 days during the follow-up period.

eAppendix Table 2. Comorbid conditions

	Primary Population		Primary Population by BEC				Exploratory Population		Primary Population by Level of Disease Control ^a						
	<300 cells/ μ L		<150 cells/ μ L		150-299 cells/ μ L		\geq 300 cells/ μ L		Uncontrolled		Suboptimally Controlled		Controlled		
	N = 6,260		N = 3,403		N = 2,857		N = 1,813		N = 286		N = 896		N = 4,955		
DCI (Mean, SD)	1.5	1.5	1.5	1.5	1.5	1.4	1.4	1.4	1.4	1.9	1.5	1.6	1.4	1.4	1.5
Clinical conditions (N, %)															
Hypertension	3,614	57.7%	1,927	56.6%	1,687	59.0%	968	53.4%	145	50.7%	501	55.9%	2,879	58.1%	
Dyslipidemia	3,094	49.4%	1,595	46.9%	1,499	52.5%	897	49.5%	128	44.8%	410	45.8%	2,488	50.2%	
COPD	1,734	27.7%	883	25.9%	851	29.8%	503	27.7%	60	21.0%	277	30.9%	1,355	27.3%	
Allergic rhinitis	1,649	26.3%	905	26.6%	744	26.0%	569	31.4%	155	54.2%	331	36.9%	1,112	22.4%	
Gastroesophageal reflux disease	1,511	24.1%	837	24.6%	674	23.6%	347	19.1%	103	36.0%	245	27.3%	1,116	22.5%	
Diabetes	1,456	23.3%	757	22.2%	699	24.5%	422	23.3%	60	21.0%	197	22.0%	1,166	23.5%	
Tobacco dependence	1,304	20.8%	678	19.9%	626	21.9%	355	19.6%	57	19.9%	214	23.9%	1,007	20.3%	
Depression	1,147	18.3%	631	18.5%	516	18.1%	271	14.9%	56	19.6%	183	20.4%	870	17.6%	
Anxiety	1,130	18.1%	641	18.8%	489	17.1%	322	17.8%	69	24.1%	183	20.4%	837	16.9%	
Sleep apnea	1,034	16.5%	515	15.1%	519	18.2%	281	15.5%	58	20.3%	175	19.5%	770	15.5%	
Ischemic heart disease	876	14.0%	464	13.6%	412	14.4%	237	13.1%	24	8.4%	102	11.4%	723	14.6%	
Chronic sinusitis	609	9.7%	344	10.1%	265	9.3%	231	12.7%	74	25.9%	127	14.2%	377	7.6%	
Insomnia	426	6.8%	245	7.2%	181	6.3%	113	6.2%	27	9.4%	61	6.8%	322	6.5%	
Atopic dermatitis	111	1.8%	57	1.7%	54	1.9%	46	2.5%	14	4.9%	17	1.9%	78	1.6%	
Chronic urticaria	108	1.7%	65	1.9%	43	1.5%	27	1.5%	10	3.5%	20	2.2%	73	1.5%	
Vocal cord dysfunction	88	1.4%	51	1.5%	37	1.3%	12	0.7%	6	2.1%	13	1.5%	62	1.3%	
Nasal polyps with or without chronic rhinosinusitis	45	0.7%	19	0.6%	26	0.9%	90	5.0%	4	1.4%	15	1.7%	25	0.5%	
Eosinophilic esophagitis	16	0.3%	8	0.2%	8	0.3%	10	0.6%	0	0.0%	2	0.2%	14	0.3%	

BEC, blood eosinophil count; DCI, Deyo-Charlson Comorbidity Index; SD, standard deviation

^a Outcomes by level of disease control were reported among patients with eosinophil count <300 cells/ μ L; 98 patients were excluded from level of disease control analysis because burst use of systemic corticosteroids for exacerbation treatment could not be distinguished from systemic corticosteroids used in daily control

eAppendix Table 3. All-cause and asthma-related healthcare utilization during the 12-month post-index period by blood eosinophil count at index

	Primary Population by BEC				Exploratory Population	
	<150 cells/ μ L N = 3,403		150-299 cells/ μ L N = 2,857		\geq 300 cells/ μ L N = 1,813	
All-Cause Healthcare Utilization						
Patients with an admission (N, %)	553	16.3%	413	14.5%	246	13.6%
Number of inpatient admissions (Mean, SD)	0.2	0.7	0.2	0.6	0.2	0.6
Number of inpatient admissions among patients with admission (Mean, SD)	1.4	1.0	1.4	1.0	1.4	0.9
Length of stay per admission (Mean, SD)	5.7	4.5	5.1	3.7	5.4	4.4
Patients with an outpatient service (N, %)	3,395	99.8%	2,851	99.8%	1,804	99.5%
Patients with an ED visit (N, %)	1,214	35.7%	907	31.7%	571	31.5%
Number of ED visits (Mean, SD)	0.7	1.8	0.7	1.5	0.6	1.2
Number of ED visits among patients with visit (Mean, SD)	2.1	2.6	2.1	2.0	1.9	1.4
Patients with an office visit (N, %)	3,373	99.1%	2,831	99.1%	1,787	98.6%
Number of office visits (Mean, SD)	11.6	8.6	10.4	7.9	9.5	7.3
Number of office visits among patients with visit (Mean, SD)	11.7	8.6	10.5	7.8	9.6	7.2
Patients with an other outpatient service ^a (N, %)	3,377	99.2%	2,845	99.6%	1,795	99.0%
Patients with an outpatient prescription (N, %)	3,398	99.9%	2,853	99.9%	1,813	100.0%
Number of prescriptions (Mean, SD)	47.5	34.6	46.3	35.6	41.3	30.4
Number of prescriptions among patients with prescription (Mean, SD)	47.6	34.6	46.4	35.5	41.3	30.4
Asthma-Related Healthcare Utilization						
Patients with an admission (N, %)	15	0.4%	13	0.5%	8	0.4%
Number of inpatient admissions (Mean, SD)	0.0	0.1	0.0	0.1	0.0	0.1
Number of inpatient admissions among patients with admission (Mean, SD)	1.1	0.3	1.1	0.3	1.4	0.7
Length of stay per admission (Mean, SD)	4.9	1.9	4.6	2.0	3.6	1.7

Patients with an outpatient service (N, %)	1,592	46.8%	1,541	53.9%	1,094	60.3%
Patients with an ED visit (N, %)	226	6.6%	184	6.4%	164	9.0%
Number of ED visits (Mean, SD)	0.1	0.6	0.1	0.4	0.1	0.5
Number of ED visits among patients with visit (Mean, SD)	1.6	1.7	1.3	0.8	1.4	0.9
Patients with an office visit (N, %)	1,427	41.9%	1,395	48.8%	1,004	55.4%
Number of office visits (Mean, SD)	1.1	1.9	1.2	1.7	1.5	2.1
Number of office visits among patients with visit (Mean, SD)	2.6	2.2	2.4	1.8	2.7	2.2
Patients with an other outpatient service ^a (N, %)	1,226	36.0%	1,162	40.7%	837	46.2%
Patients with an outpatient prescription (N, %)	3,284	96.5%	2,791	97.7%	1,791	98.8%
Number of prescriptions (Mean, SD)	8.2	6.3	8.4	6.2	8.8	6.3
Number of prescriptions among patients with prescription (Mean, SD)	8.5	6.2	8.6	6.2	8.9	6.3

BEC, blood eosinophil count; ED, emergency department; SD, standard deviation

^a Office-administered medications are captured as other outpatient services

eAppendix Table 4. Expanded, all-cause and asthma-related healthcare costs during the 12-month post-index period

	Primary Population		Primary Population by BEC				Exploratory Population		Primary Population by Level of Disease Control ¹					
	<300 cells/ μ L		<150 cells/ μ L		150-299 cells/ μ L		\geq 300 cells/ μ L		Uncontrolled		Suboptimally Controlled		Controlled	
	N = 6,260		N = 3,403		N = 2,857		N = 1,813		N = 286		N = 896		N = 4,955	
Healthcare Costs	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
<u>All-Cause</u>														
Inpatient	\$5,185	\$22,590	\$5,524	\$20,284	\$4,782	\$25,059	\$5,072	\$24,449	\$4,369	\$11,260	\$4,619	\$18,028	\$5,113	\$23,444
OP	\$11,445	\$28,412	\$12,763	\$33,127	\$9,875	\$21,385	\$8,566	\$18,230	\$11,214	\$14,164	\$10,837	\$30,675	\$11,170	\$28,229
ED visit	\$680	\$3,247	\$745	\$3,956	\$601	\$2,110	\$584	\$2,161	\$1,392	\$3,260	\$809	\$2,404	\$594	\$3,358
OP office visit	\$1,272	\$1,054	\$1,342	\$1,105	\$1,188	\$983	\$1,078	\$857	\$1,672	\$1,170	\$1,294	\$957	\$1,212	\$1,011
Other OP services	\$9,494	\$27,685	\$10,676	\$32,370	\$8,086	\$20,687	\$6,904	\$17,474	\$8,150	\$12,098	\$8,733	\$30,160	\$9,364	\$27,548
OP pharmacy	\$9,215	\$16,309	\$9,593	\$16,920	\$8,765	\$15,542	\$7,655	\$12,383	\$8,935	\$16,687	\$8,803	\$15,286	\$9,244	\$16,517
Total	\$25,845	\$43,896	\$27,879	\$46,581	\$23,423	\$40,339	\$21,293	\$38,142	\$24,518	\$29,422	\$24,258	\$41,799	\$25,527	\$44,141
<u>Asthma-Related</u>														
Inpatient	\$64	\$1,134	\$51	\$803	\$78	\$1,432	\$68	\$1,242	\$1,392	\$5,139	\$0	\$0	\$0	\$0
OP	\$557	\$2,195	\$530	\$1,845	\$590	\$2,550	\$701	\$2,109	\$2,122	\$3,209	\$1,165	\$3,143	\$319	\$1,610
ED visit	\$88	\$601	\$90	\$546	\$85	\$660	\$131	\$719	\$530	\$1,396	\$189	\$880	\$38	\$360
OP office visit	\$130	\$223	\$127	\$233	\$135	\$211	\$169	\$243	\$493	\$354	\$262	\$262	\$80	\$153
Other OP services	\$339	\$1,981	\$312	\$1,605	\$370	\$2,351	\$401	\$1,813	\$1,099	\$2,681	\$714	\$2,887	\$201	\$1,499
OP pharmacy	\$2,181	\$2,992	\$2,078	\$3,493	\$2,305	\$2,249	\$2,461	\$2,083	\$2,744	\$2,357	\$2,692	\$2,814	\$2,067	\$3,057
Total	\$2,802	\$3,965	\$2,659	\$4,101	\$2,973	\$3,791	\$3,229	\$3,244	\$6,258	\$6,833	\$3,857	\$4,184	\$2,386	\$3,472

BEC, blood eosinophil count; ED, emergency department; OP, outpatient

^a Outcomes by level of disease control were reported among patients with eosinophil count <300 cells/ μ L; 98 patients were excluded from level of disease control analysis because burst use of systemic corticosteroids for exacerbation treatment could not be distinguished from systemic corticosteroids used in daily control

eAppendix Table 5. Patient characteristics for exploratory population

	Exploratory Population ≥300 cells/μL N = 1,813	
Age (Mean, SD)	54.6	14.5
Age category (N, %)		
12-17	38	2.1%
18-34	132	7.3%
35-44	194	10.7%
45-54	409	22.6%
55-64	732	40.4%
65-74	183	10.1%
75+	125	6.9%
Female (N, %)	1,008	55.6%
Geographic region (N, %)		
Northeast	639	35.2%
North Central	500	27.6%
South	587	32.4%
West	87	4.8%
Unknown	0	0.0%
Index year (N, %)		
2013	174	9.6%
2014	300	16.5%
2015	297	16.4%
2016	354	19.5%
2017	379	20.9%
2018	309	17.0%
Asthma-related medications^a (N, %)		
Systemic corticosteroids (SCS) ^b	1,135	62.6%
≥ 180 days' supply of SCS	176	9.7%
ICS/LABA	1,416	78.1%
Leukotriene receptor antagonists	729	40.2%
Short-acting beta2-agonists	456	25.2%
Tiotropium	195	10.8%
Inhaled corticosteroids	221	12.2%
Short-acting muscarinic antagonist	25	1.4%
Theophylline and other methylxanthines	27	1.5%
Asthma exacerbation (N, %)	465	25.6%
≥ 1 asthma diagnosis on mechanical ventilation claim	2	0.1%
≥ 1 asthma diagnosis as primary discharge on inpatient admission	8	0.4%

≥ 1 asthma diagnosis on outpatient visit with burst systemic corticosteroids within 7 days	463	25.5%
Number of asthma exacerbations (Mean, SD)	0.4	0.9
Level of asthma control^c (N, %)		
Uncontrolled	143	7.9%
Suboptimally controlled	356	19.6%
Controlled	1,288	71.0%
Uncategorized	26	1.4%

ICS/LABA, inhaled corticosteroid/long-acting beta2-agonist; SD, standard deviation

^a Long-acting muscarinic antagonist /long-acting beta2-agonist and mast cell stabilizers were used by less than 1% of patients and are not reported in the table

^b Includes both injectable and oral corticosteroids

^c Level of control was assigned hierarchically into mutually exclusive categories: uncontrolled (≥1 inpatient admission with an asthma diagnosis with or without mechanical ventilation OR ≥2 outpatient visit with an asthma diagnosis treated with systemic corticosteroid [SCS] within 7 days), sub-optimally controlled (exactly 1 outpatient visit with an asthma diagnosis treated SCS within 7 days OR ≥4 claims for short-acting beta agonist), and controlled (none of the above). Outpatient visits were inclusive of emergency room visit, urgent care visit, or other outpatient visits and burst SCS use was defined as 1 dose of injectable corticosteroids or oral corticosteroids for ≥3 days. Patients were uncategorized when SCS burst for exacerbation treatment could not be distinguished from SCS used in daily control.