

Original Article
Immunology, Allergic
Disorders & Rheumatology



Association Between Clinical Burden and Blood Eosinophil Counts in Asthma: Findings From a Korean Adult Asthma Cohort

Mi-Yeong Kim ,¹ Eun-Jung Jo ,² Sujeong Kim ,³ Min-Hye Kim ,⁴ Jae-Woo Jung ,⁵ Joo-Hee Kim ,⁶ Ji-Yong Moon ,⁷ Jae-Woo Kwon ,⁸ Jae-Hyun Lee ,⁹ Chan Sun Park ,¹⁰ Hyun Jung Jin ,¹¹ Yoo Seob Shin ,¹² Sae-Hoon Kim ,¹³ Young-Joo Cho ,⁴ Jung-Won Park ,⁹ Sang-Heon Cho ,¹⁴ Tae-Bum Kim ,¹⁵ and Hye-Kyung Park ²

OPEN ACCESS

Received: Aug 10, 2021

Accepted: Jan 17, 2022

Published online: Feb 8, 2022

Address for Correspondence:

Hye-Kyung Park, MD, PhD

Department of Internal Medicine, Pusan National University Hospital, Pusan National University College of Medicine, 179, Gudeok-ro, Seo-gu, Busan 49241, Republic of Korea.
Email: parkhk@pusan.ac.kr

Tae-Bum Kim, MD, PhD

Department of Allergy and Clinical Immunology, Asan Medical Center, University of Ulsan College of Medicine, 88, Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Republic of Korea.
Email: tbkim@amc.seoul.kr

© 2022 The Korean Academy of Medical Sciences.

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<https://creativecommons.org/licenses/by-nc/4.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ORCID iDs

Mi-Yeong Kim
<https://orcid.org/0000-0002-2640-6258>
Eun-Jung Jo
<https://orcid.org/0000-0003-3712-6216>
Sujeong Kim
<https://orcid.org/0000-0002-2494-9216>
Min-Hye Kim
<https://orcid.org/0000-0002-1775-3733>
Jae-Woo Jung
<https://orcid.org/0000-0002-3411-735X>

¹Department of Internal Medicine, Inje University Busan Paik Hospital, Inje University College of Medicine, Busan, Korea

²Department of Internal Medicine, Pusan National University Hospital, Pusan National University College of Medicine, Busan, Korea

³Department of Internal Medicine, School of Medicine, Kyungpook National University, Daegu, Korea

⁴Department of Internal Medicine, College of Medicine, Ewha Womans University, Seoul, Korea

⁵Department of Internal Medicine, Chung-Ang University College of Medicine, Seoul, Korea

⁶Department of Internal Medicine, Hallym University Sacred Heart Hospital, Hallym University College of Medicine, Anyang, Korea

⁷Department of Internal Medicine, Hanyang University Guri Hospital, Hanyang University College of Medicine, Guri, Korea

⁸Department of Internal Medicine, Kangwon National University School of Medicine, Chuncheon, Korea

⁹Division of Allergy and Immunology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea

¹⁰Department of Internal Medicine, Inje University Haeundae Paik Hospital, Inje University College of Medicine, Busan, Korea

¹¹Department of Internal Medicine, Yeungnam University College of Medicine, Daegu, Korea

¹²Department of Allergy and Clinical Immunology, Ajou University School of Medicine, Suwon, Korea

¹³Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, Korea

¹⁴Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Korea

¹⁵Department of Allergy and Clinical Immunology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

ABSTRACT

Background: Some reports have suggested that the clinical and economic burdens of asthma are associated with blood eosinophil levels. The association between clinical burden and blood eosinophil counts were evaluated in a Korean adult asthma cohort.

Methods: Clinical information including blood eosinophil counts that were not affected by systemic corticosteroids were extracted from the Cohort for Reality and Evolution of Adult Asthma in Korea database. Clinical burden was defined as 1) asthma control status, 2) medication demand and 3) acute exacerbation (AE) events during 1 consecutive year after enrollment. All patients were divided into atopic and non-atopic asthmatics. The associations between asthma outcomes and the blood eosinophil count were evaluated.

Results: In total, 302 patients (124 atopic and 178 non-atopic asthmatics) were enrolled. In all asthmatics, the risk of severe AE was higher in patients with blood eosinophil levels < 100 cells/μL than in patients with levels ≥ 100 cells/μL (odds ratio [OR], 5.406; 95% confidence interval [CI], 1.266–23.078; adjusted *P* = 0.023). Among atopic asthmatics, the risk of moderate AE was higher in patients with blood eosinophil levels ≥ 300 cells/μL than

Joo-Hee Kim 
<https://orcid.org/0000-0002-1572-5149>
 Ji-Yong Moon 
<https://orcid.org/0000-0003-2459-3448>
 Jae-Woo Kwon 
<https://orcid.org/0000-0003-1639-3606>
 Jae-Hyun Lee 
<https://orcid.org/0000-0002-0760-0071>
 Chan Sun Park 
<https://orcid.org/0000-0003-0113-8354>
 Hyun Jung Jin 
<https://orcid.org/0000-0003-2888-420X>
 Yoo Seob Shin 
<https://orcid.org/0000-0002-9855-3185>
 Sae-Hoon Kim 
<https://orcid.org/0000-0002-2572-5302>
 Young-Joo Cho 
<https://orcid.org/0000-0002-9414-5934>
 Jung-Won Park 
<https://orcid.org/0000-0003-0249-8749>
 Sang-Heon Cho 
<https://orcid.org/0000-0002-7644-6469>
 Tae-Bum Kim 
<https://orcid.org/0000-0001-5663-0640>
 Hye-Kyung Park 
<https://orcid.org/0000-0003-4065-2962>

Funding

This research was supported by the Bio & Medical Technology Development Program of the National Research Foundation (NRF) funded by the Korean government (MSIT) (2019M3E5D3073365).

Disclosure

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Kim MY, Park HK. Data curation: Kim MY, Jo EJ, Kim S, Kim MH, Jung JW, Kim JH, Moon JY, Kwon JW, Lee JH, Park CS, Jin HJ, Shin YS, Kim SH, Cho YJ, Park JW, Cho SH, Kim TB, Park HK. Formal analysis: Kim MY. Funding acquisition: Kim TB. Investigation: Kim MY, Park HK, Kim TB. Validation: Kim MY. Visualization: Kim MY. Writing - original draft: Kim MY. Writing - review & editing: Kim MY, Jo EJ, Kim S, Kim MH, Jung JW, Kim JH, Moon JY, Kwon JW, Lee JH, Park CS, Jin HJ, Shin YS, Kim SH, Cho YJ, Park JW, Cho SH, Kim TB, Park HK.

in patients with levels < 300 cells/ μ L (OR, 3.558; 95% CI, 1.083–11.686; adjusted P = 0.036). Among non-atopic asthmatics, the risk of medication of Global Initiative for Asthma (GINA) steps 4 or 5 was higher in patients with high blood eosinophil levels than in patients with low blood eosinophil levels at cutoffs of 100, 200, 300, 400, and 500 cells/ μ L.

Conclusion: The baseline blood eosinophil count may predict the future clinical burden of asthma.

Keywords: Asthma; Blood Eosinophils; Clinical Burden

INTRODUCTION

Asthma is defined as chronic airway inflammation and reversible airway limitation.¹ The traditional concept of asthma inflammation involves an acute hypersensitivity reaction to specific IgE and a type 2 (T_H2) cell response.² However, with the increasing understanding of the relevant inflammatory mechanisms, there has been recognition that eosinophils, neutrophils, and microgranulocytes are all involved in asthma-mediated airway inflammation and other clinical manifestations. Recently, the terms “T2 high” and “T2 low” have been used to describe asthma inflammation.² Type 2 inflammatory biomarkers comprise the fraction of exhaled nitric oxide, the serum IgE level, blood and/or sputum eosinophil levels, and serum periostin levels.² Given the increasing interest in the roles played by these biomarkers, some authors have investigated whether they might predict future asthma exacerbations. Blood eosinophil count is the most widely used indicator for eosinophilic asthmatics to initiate biologics such as IL-5 monoclonal antibody.^{3,4} The blood eosinophil count is associated with the extent of asthma control and acute exacerbations (AEs).⁵⁻⁸ A high eosinophil count has been associated with a future risk of AEs in patients with both general and severe asthma.^{6,7} A 2014 study from the USA reported an association between the baseline blood eosinophil count and asthma exacerbation within the next year, according to findings from the National Health and Nutrition Examination Survey database. The risk of asthma exacerbation increased in adults with eosinophil counts \geq 300 cells/ μ L, compared to < 300 cells/ μ L. A 2016 study from the UK used cohort data to calculate the relative risks of exacerbation in the years before and after blood eosinophil measurements. Patients with blood eosinophil counts \geq 400 cells/ μ L experienced more severe exacerbations.⁷ These studies employed surveys or medical records with diagnostic codes and key signs of AE such as the use of a systemic corticosteroid or antibiotics. Furthermore, systemic steroid exposure was not considered, and atopic and non-atopic statuses (one of the “T2 high” axes) were neither distinguished nor adjusted. Therefore, we examined the association between the clinical burden of asthma and blood eosinophil count in a Korean adult asthma cohort with consideration of the factors mentioned above.

METHODS

Study population

Clinical information was extracted retrospectively from the database of the Cohort for Reality and Evolution of Adult Asthma in Korea (COREA).⁹ Asthmatics in this cohort were recruited by allergists and pulmonologists beginning in 2005.^{10,11} In 2018, 21 centers were participating in the cohort study.^{10,11} The data extraction period was July 2005 to February 2018. At enrollment in the COREA cohort, laboratory results within 3 months and medication history within 1 month were collected. The inclusion criteria were as follows: 1)

blood eosinophil count collected within 1 month and no exposure to systemic corticosteroids within 1 month or blood eosinophil count collected within 3 months and no treatment; 2) age ≥ 18 years; 3) 1 consecutive year of follow-up; 4) positive result in inhalant allergen skin prick test; and 5) $\geq 50\%$ drug compliance. Patients with chronic obstructive lung disease were excluded. We divided all patients into atopic and non-atopic asthmatics, then assessed the impact of the blood eosinophil count on the outcomes of either group.

Data collection

Data were collected using the Clinical Record Form (CRF) completed at enrollment, as well as four consecutive 3-month follow-up CRFs recorded in the COREA cohort database. Asthma was diagnosed if airway reversibility or hypersensitivity was demonstrated in a patient with asthma-related symptoms (cough, dyspnea or wheezing). Airway reversibility was defined as an increase of $\geq 12\%$ and ≥ 200 mL in the forced expiratory volume in 1 second (FEV₁) after the inhalation of a bronchodilator or after treatment. Airway hypersensitivity was defined by the bronchoprovocation test using methacholine or mannitol; the diagnostic values were PC₂₀ ≤ 25 mg/mL and PD₁₅ ≤ 635 mg. "PC₂₀" refers to the provocative concentration of methacholine causing a 20% reduction in the FEV₁; PD₁₅ refers to the provocative dose of mannitol causing a 15% reduction in the FEV₁. Asthma control state, asthma medication, drug compliance, and history of AEs were checked at 3-month intervals. Age, sex, body mass index (BMI), serum total IgE level, sputum eosinophil percentage, presence of rhinosinusitis, smoking status, and the results of the inhalant allergen skin prick test, pulmonary function test, bronchial provocation test and asthma control test (ACT) were reviewed. The baseline blood eosinophil counts were collected from the enrollment data, as were the percentages of eosinophils in the total white blood cell count/ μ L. Atopy was defined as a positive result for more than one allergen in the inhalant allergen skin prick test.¹² A skin prick test result was considered positive if the mean wheal size for any allergen was greater than or equal to the mean wheal size for histamine (allergen/histamine ratio ≥ 1).¹³ Drug compliance was scored from 0 to 100 points depending on the amount of drug remaining at each visit. Asthma AEs were directly assessed by the cohort researchers: the type of visit (total visits, outpatient department [OPD], emergency department [ED], admission to a ward and admission to the intensive care unit [ICU]), and number of visits were collected.⁹ An OPD visit because of an asthma AE was defined as a moderate exacerbation; and an ED visit or hospitalization because of an asthma AE was defined as a severe exacerbation.

Definition of the clinical burden

Clinical burden was defined as 1) asthma control status, 2) medication demand and 3) exacerbation events during 1 consecutive year after enrollment. Asthma control status included the control state assigned by the clinician at the end of the year (well vs. partially/uncontrolled); a change in asthma control state (from well-controlled to partially/uncontrolled vs. from partially/uncontrolled to well-controlled); and the mean ACT score during the year (mean value ≥ 20 vs. < 19).¹⁴ Medication demand included the Global Initiative for Asthma (GINA) step (2019 GINA report) (steps 1–3 vs. steps 4, 5); a change in GINA medication (from steps 4, 5 to steps 1–3 vs. from steps 1–3 to steps 4, 5) and the inhaled corticosteroid (ICS) dose (low dose vs. medium-to-high dose) at the end of the year.¹⁵

Statistical analysis

Statistical analysis was performed using SPSS version 25 (IBM Co., Armonk, NY, USA). Means and percentages were compared by independent samples *t*-test, Pearson's χ^2 test, or Fisher's exact test. Binominal logistic regression were conducted to adjust for age, sex, BMI, smoking

status, baseline FEV₁, baseline GINA medication step, and mean drug compliance when comparing clinical asthma burden. Two-sided *P* values < 0.05 were considered indicative of statistical significance. Missing data were excluded from the analysis.

Ethics statement

This study was approved by the Institutional Review Board (IRB) of Inje University Busan Paik Hospital (IRB No. 18-0008). Informed consent was waived because of the retrospective nature of the study.

RESULTS

Baseline clinical characteristics and clinical burden of asthma

A flow diagram of the eligible patients is shown in **Fig. 1**. In total, 302 asthmatics were enrolled, including 124 with atopic and 178 with non-atopic asthma. Their clinical characteristics are shown in **Table 1**. Atopic asthmatics, compared with non-atopic asthmatics, were younger (42.7 ± 13.6 vs. 54.8 ± 13.1 years, $P < 0.001$), had a greater proportion of men (56.5% vs. 36.5%, $P = 0.001$), had a higher mean serum total IgE level (555.9 ± 692.3 vs. 272.5 ± 417.8 IU/mL, $P < 0.001$), and had a greater proportion of current smokers. The mean BMI values, blood eosinophil counts, FEV₁ predicted values, asthma control statuses, and GINA medication statuses were similar between atopic and non-atopic asthmatics. Although the data were limited, the mean PC₂₀ and PD₁₅ values were also similar between atopic and non-atopic asthmatics. The mean ACT score was slightly higher in non-atopic asthmatics, but the scores were > 20 in both groups (22.2 ± 3.0 vs. 21.4 ± 3.5 , $P = 0.046$). No asthmatic patients visited the hospital with an asthma AE during the year before enrollment. The clinical burden during the year is shown in **Table 2**; this burden did not differ between atopic and non-atopic asthmatics.

Clinical burden according to the blood eosinophil count in all asthmatics

The associations between clinical burden of asthma and blood eosinophil levels in all asthmatics (adjusted for age, sex, BMI, smoking status, the baseline FEV₁, the baseline GINA medication step, and mean drug compliance) are shown in **Table 3**. The asthma control state, any change in that state, and the mean ACT score were similar in the low and high eosinophil groups at all eosinophil cut-off values. Furthermore, asthma medication demand (in terms of the GINA step), any change in the GINA step, and the ICS dose were also similar. Of all patients, 16.6% experienced AEs (OPD visit, 13.6%; ED visit, 2.0%; admission to a ward, 1.7%). No patient was admitted to an ICU. The percentages of patients who experienced AEs were similar between the high and low eosinophil groups at all blood eosinophil cut-off values. The percentage of patients who experienced moderate AEs were also similar. Comparisons of groups divided according to blood eosinophil counts of 100 cells/ μ L indicated that the percentage of patients who experienced severe asthma AEs was higher in the low eosinophil group (5/51, 9.8%) than in the high eosinophil group (6/212, 2.8%) (odds ratio [OR], 5.406; 95% confidence interval [CI], 1.266–23.078; adjusted $P = 0.023$).

Clinical burden according to the blood eosinophil count in atopic asthmatics

Associations between clinical burden of asthma and blood eosinophil levels in all atopic asthmatics (adjusted for age, sex, BMI, smoking status, baseline FEV₁, baseline GINA medication step, and mean drug compliance) are shown in **Table 4**. The risk of partially/uncontrolled asthma was higher in the low eosinophil group than in the high eosinophil

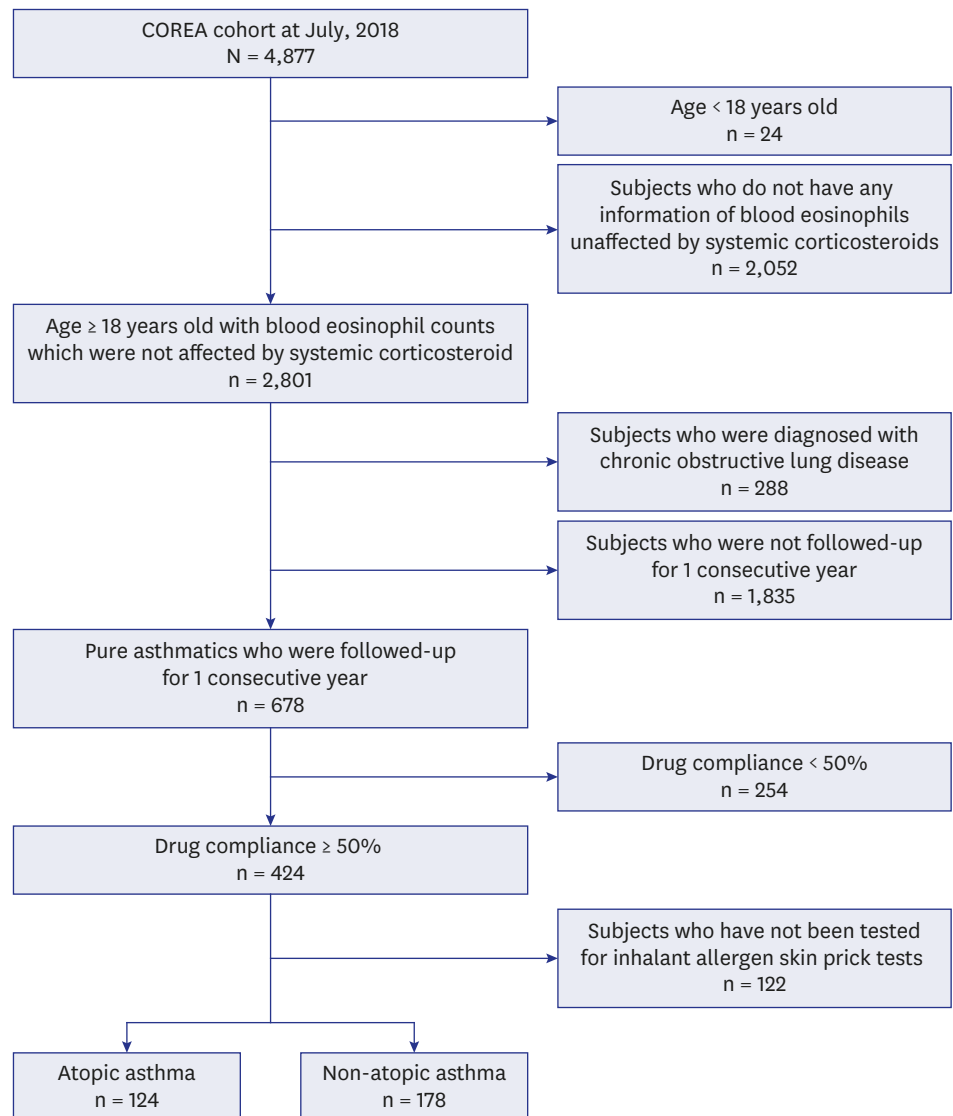


Fig. 1. A flow diagram of eligible subjects from the COREA database. COREA = Cohort for Reality and Evolution of Adult Asthma in Korea.

group (< 300 vs. \geq 300, OR, 3.478; 95% CI, 1.009–11.986; adjusted $P=0.048$; < 400 vs. \geq 400, OR, 4.120; 95% CI, 1.077–15.759; adjusted $P=0.039$; < 500 vs. \geq 500, OR, 7.560; 95% CI, 1.398–40.881; adjusted $P=0.019$). Changes in asthma control state and the mean ACT score during the year were similar in the low and high eosinophil groups at all blood eosinophil cut-off values. Furthermore, asthma medication demand (in terms of the GINA step), any change in the GINA step, and the ICS dose were also similar. Of all patients, 19.4% experienced AEs (OPD visit, 15.3%; ED visit, 3.2%; and admission to a ward, 1.6%). No patient was admitted to an ICU. The percentages of patients who experienced AEs were similar between the high and low eosinophil groups at all blood eosinophil cut-off values. Comparisons of groups divided according to a blood eosinophil count of 300 cells/ μ L showed that the percentage of patients who experienced moderate asthmatic AEs was higher in the high eosinophil group (14/63, 22.2%) than in the low eosinophil group (5/56, 8.9%) (OR, 3.558; 95% CI, 1.083–11.686; adjusted $P=0.036$). However, no differences were evident at blood eosinophil cutoffs of 100,

Table 1. Baseline clinical characteristics of study population

Clinical factors	All asthmatics (302 subjects)	Atopic asthmatics (124 subjects)	Non-atopic asthmatics (178 subjects)	Atopic vs. non-atopic P value
Age, yr	49.5 ± 14.5	42.7 ± 13.6	54.8 ± 13.1	< 0.001
Male	135 (44.7)	70 (56.5)	65 (35.5)	0.001
BMI, kg/m ²	24.2 ± 3.4	23.8 ± 3.7	24.5 ± 3.2	0.081
Serum total IgE, IU/mL	381.0 ± 555.2	555.9 ± 692.3 (n = 67)	272.5 ± 417.8 (n = 108)	< 0.001
Blood eosinophil, cells/μL	388.1 ± 397.2	424.4 ± 364.7	362.8 ± 417.6	0.185
Sputum eosinophil ≥ 3%	32/42	10/16	22/26	1.000
FEV ₁ of predicted value, %		81.3 ± 18.0	79.9 ± 24.1	0.567
PC ₂₀ , mg/mL	5.3 ± 5.8	4.8 ± 5.5 (n = 60)	5.7 ± 5.9 (n = 92)	0.382
PD ₁₅ , mg	185.5 ± 114.6	154.3 ± 130.1 (n = 5)	201.0 ± 110.1 (n = 10)	0.478
Rhinosinusitis history	17/53	5/23	12/30	0.158
Smoking history				< 0.001
Never smoker	153 (50.7)	54 (43.6)	99 (55.6)	
Ex-smoker	112 (37.1)	44 (35.4)	68 (38.2)	
Current smoker	36 (12.0)	26 (21.0)	10 (5.6)	
Asthma control state				0.803
Well-controlled	140	60	80	
Partly/Uncontrolled	36	15	21	
ACT score	21.9 ± 3.2	21.4 ± 3.5	22.2 ± 3.0	0.046
GINA medication step				0.950
Steps 1–3	126 (41.7)	52 (42.0)	74 (41.6)	
Steps 4, 5	176 (58.3)	72 (58.1)	104 (58.4)	
ICS dose				0.415
Low dose	59 (19.5)	21 (16.9)	38 (21.4)	
Medium-to-high dose	151 (50.0)	63 (50.8)	88 (49.4)	

Data are presented as mean ± SD (total number collected), number (%) or number/total number collected. The total number collected is described when the number of collections is insufficient. There were limited data about asthma control status at first regular visit during one consecutive year (49 patients in atopic asthmatics and 71 patients in non-atopic asthmatics were not evaluated).

BMI = body mass index, FEV₁ = forced expiratory volume in 1 second, PC₂₀ = provocative concentration causing a 20% fall in forced expiratory volume in 1 second, PD₁₅ = provocative dose causing a 15% fall in forced expiratory volume in 1 second, ACT = asthma control test, GINA = Global Initiative for Asthma, ICS = inhaled corticosteroid.

200, 400 and 500 cells/μL. The percentages of patients who experienced severe asthmatic AEs were similar in all comparisons of groups divided according to the blood eosinophil counts.

Clinical burden according to blood eosinophil count in non-atopic asthmatics

Associations between clinical burden of asthma and blood eosinophil levels in non-atopic asthmatics (adjusted for age, sex, BMI, smoking status, the baseline FEV₁, the baseline GINA medication step, and mean drug compliance) are shown in **Table 5**. Asthma control state, any change in such state, and the mean ACT score were similar between the low and high eosinophil groups at all blood eosinophil cut-off values. The percentage of patients on GINA medications of steps 4 or 5 was higher in the high eosinophil group than in the low eosinophil group at all blood eosinophil cut-off values (100 [87/139, 62.6% vs. 17/38, 44.7%], 200 [69/106, 65.1% vs. 35/71, 49.3%], 300 [54/80, 67.5% vs. 50/97, 51.5%], 400 [35/50, 70.0% vs. 69/127, 54.3%], and 500 cells/μL [29/39, 74.4% vs. 75/138, 54.3%]). Comparisons of groups divided according to blood eosinophil counts of 400 cells/μL and 500 cells/μL showed that the risk of GINA step-up (compared to step-down) was higher in the high eosinophil group. However, the ICS doses were similar in the high and low eosinophil groups at all eosinophil cut-off values. The percentage of patients who experienced AEs was 14.6% (OPD visit, 12.4%; ED visit, 2.1%; and admission to a ward, 1.7%). No patient was admitted to an ICU. The percentages of patients who experienced AEs were similar between the high and low eosinophil groups at all blood eosinophil cut-off values. The percentages of patients who experienced moderate or severe asthmatic AEs were also similar.

Table 2. Clinical burden of study population

Clinical factors	All asthmatics (302 subjects)	Atopic asthmatics (124 subjects)	Non-atopic asthmatics (178 subjects)	Atopic vs. non-atopic P value
Asthma control status				
Asthma control state				0.323
Well-controlled	146 (48.3)	60 (48.4)	86 (48.3)	
Partially/Uncontrolled	38 (12.6)	19 (15.3)	19 (10.7)	
Change of asthma control state				0.148
Partially/Uncontrolled to well	24 (8.0)	7 (5.7)	17 (9.6)	
Well to partially/Uncontrolled	22 (7.3)	11 (8.9)	11 (6.2)	
ACT score, mean				0.539
≥ 20	256 (84.8)	107 (86.3)	149 (83.7)	
< 19	46 (15.2)	17 (13.7)	29 (16.3)	
Medication demand				
Medication step, GINA				0.591
Steps 1–3	128 (42.4)	55 (44.4)	73 (41.0)	
Steps 4, 5	173 (57.3)	69 (55.6)	104 (58.4)	
Change of GINA step				0.510
Steps 4, 5 to 1–3	34 (11.3)	11 (8.9)	23 (12.9)	
Steps 1–3 to 4, 5	32 (10.6)	8 (6.5)	24 (13.5)	
ICS dose				0.587
Low dose	101 (33.4)	39 (31.5)	62 (34.8)	
Medium-to-high dose	145 (48.0)	61 (49.2)	84 (47.2)	
Asthma AE				
Asthma AEs				0.275
No	252 (83.4)	100 (80.6)	152 (85.4)	
Yes	50 (16.6)	24 (19.4)	26 (14.6)	
Severity of AE				0.630
Moderate	41 (13.6)	19 (15.3)	22 (12.4)	
Severe	11 (3.6)	6 (4.8)	5 (2.8)	

Data are presented as number (%).

ACT = asthma control test, GINA = Global Initiative for Asthma, ICS = inhaled corticosteroid, AE = acute exacerbation.

Quantitative relationships between blood eosinophil levels and the clinical burden of asthma

Changes in the clinical burden of asthma when the blood eosinophil counts increased in steps of 100 cells/ μ L, compared to the clinical burden of asthma in the group with blood eosinophils < 100 cells/ μ L, are shown in **Table 6**. Asthma control state, GINA medication step, and the occurrences of AEs were all analyzed after adjustments for age, sex, BMI, smoking status, baseline FEV₁, baseline GINA medication step, and mean drug compliance. The risk of GINA steps 4 or 5 was (roughly) quantitatively dependent on the increase in blood eosinophil counts in non-atopic asthmatics. In terms of the asthma control state of all and non-atopic asthmatics, as well as moderate exacerbation in atopic asthmatics, some (insignificant) tendencies toward positive or negative relationships with blood eosinophil levels were presented. However, we found no quantitatively dependent relationship.

DISCUSSION

The main purpose of this study was to evaluate the association between the clinical burden of asthma and blood eosinophil counts in Korean adult asthmatics. T_H2 inflammation is usually defined by reference to atopy and eosinophilic inflammation.¹⁶ Our atopic and non-atopic asthmatics partially differed in terms of age, sex, and smoking history. We sought associations between the clinical burden of asthma and blood eosinophil counts by dividing all patients into atopic and non-atopic asthmatics. We enrolled only asthmatics with good

Table 3. Comparison of clinical burden according to the blood eosinophil count in all asthmatics (n = 302)

Clinical burden	Blood eosinophil count, cells/ μ L	OR (95% CI) ^a	P value ^a
Asthma control status			
Asthma control state (Well-controlled vs. Partially/Uncontrolled)	< 100 vs. \geq 100	1.903 (0.557–6.507)	0.305
	< 200 vs. \geq 200	0.883 (0.384–2.028)	0.769
	< 300 vs. \geq 300	0.698 (0.322–1.514)	0.363
	< 400 vs. \geq 400	0.707 (0.305–1.641)	0.420
	< 500 vs. \geq 500	0.549 (0.212–1.420)	0.216
Change of asthma control state (Partially/Uncontrolled to well vs. Well to partially/Uncontrolled)	< 100 vs. \geq 100	0.275 (0.607–10.767)	0.490
	< 200 vs. \geq 200	0.467 (0.068–3.223)	0.440
	< 300 vs. \geq 300	0.359 (0.060–2.147)	0.261
	< 400 vs. \geq 400	0.158 (0.016–1.529)	0.111
	< 500 vs. \geq 500	0.040 (0.001–1.292)	0.069
ACT score, mean (\geq 20 vs. < 19)	< 100 vs. \geq 100	1.055 (0.438–2.540)	0.904
	< 200 vs. \geq 200	0.947 (0.46–1.932)	0.881
	< 300 vs. \geq 300	1.561 (0.786–3.101)	0.203
	< 400 vs. \geq 400	1.386 (0.678–2.831)	0.371
	< 500 vs. \geq 500	0.867 (0.396–1.899)	0.722
Medication demand			
Medication step, GINA (Steps 1–3 vs. Steps 4, 5)	< 100 vs. \geq 100	1.697 (0.823–3.500)	0.152
	< 200 vs. \geq 200	1.676 (0.918–3.030)	0.092
	< 300 vs. \geq 300	1.425 (0.798–2.545)	0.232
	< 400 vs. \geq 400	1.637 (0.859–3.118)	0.134
	< 500 vs. \geq 500	1.728 (0.846–3.528)	0.133
Change of GINA step (Steps 4, 5 to 1–3 vs. Steps 1–3 to 4, 5)	< 100 vs. \geq 100	2.579 (0.538–12.369)	0.236
	< 200 vs. \geq 200	2.599 (0.776–8.701)	0.121
	< 300 vs. \geq 300	1.520 (0.531–4.352)	0.436
	< 400 vs. \geq 400	2.515 (0.779–8.118)	0.123
	< 500 vs. \geq 500	2.431 (0.699–8.450)	0.162
ICS dose (Low dose vs. Medium-to-high dose)	< 100 vs. \geq 100	1.026 (0.442–2.381)	0.953
	< 200 vs. \geq 200	1.317 (0.673–2.579)	0.421
	< 300 vs. \geq 300	0.848 (0.449–1.602)	0.611
	< 400 vs. \geq 400	0.851 (0.425–1.705)	0.649
	< 500 vs. \geq 500	0.740 (0.340–1.608)	0.447
Asthma AE			
Asthma AEs (No vs. Yes)	< 100 vs. \geq 100	0.849 (0.396–1.819)	0.674
	< 200 vs. \geq 200	1.090 (0.565–2.103)	0.797
	< 300 vs. \geq 300	1.189 (0.630–2.244)	0.594
	< 400 vs. \geq 400	0.849 (0.421–1.712)	0.647
	< 500 vs. \geq 500	0.718 (0.326–1.583)	0.412
Severity of AE (No vs. Moderate)	< 100 vs. \geq 100	1.237 (0.503–3.039)	0.643
	< 200 vs. \geq 200	1.362 (0.653–2.844)	0.410
	< 300 vs. \geq 300	1.582 (0.790–3.167)	0.196
	< 400 vs. \geq 400	1.033 (0.485–2.201)	0.933
	< 500 vs. \geq 500	0.806 (0.341–1.908)	0.624
Severity of AE (No vs. Severe)	< 100 vs. \geq 100	0.185 (0.043–0.790)	0.023
	< 200 vs. \geq 200	0.417 (0.106–1.639)	0.210
	< 300 vs. \geq 300	0.335 (0.073–1.545)	0.161
	< 400 vs. \geq 400	0.543 (0.116–2.534)	0.437
	< 500 vs. \geq 500	0.729 (0.153–3.472)	0.692

OR = odd ratio, CI = confidential interval, ACT = asthma control test, GINA = Global Initiative for Asthma, ICS = inhaled corticosteroid, AE = acute exacerbation. ^aAdjusted factors were age, sex, body mass index, currently smoking, baseline forced expiratory volume in 1 second, baseline GINA medication step and mean drug compliance during 1 year. All patients had no history of acute asthma exacerbation during one year before enrollment. Baseline GINA medication step was excluded in adjusting in analyses of the change of GINA step, because there were not enough subjects to adjust.

compliance; poor compliance is a major risk factor for future asthma AEs.^{17,18} Age, sex, BMI, smoking status, baseline FEV₁, baseline GINA medication step and mean drug compliance were adjusted. All enrolled patients did not have an history of asthma AE during the year before the enrollment. No patient had an asthma AE during the year before enrollment, probably because most patients who experienced AEs immediately before enrollment were

Table 4. Comparison of clinical burden according to the blood eosinophil count in atopic asthmatics (N = 124)

Clinical burden	Blood eosinophil count, cells/ μ L	OR (95% CI) ^a	P value ^a
Asthma control status			
Asthma control state (Well controlled vs. Partially/Uncontrolled)	< 100 vs. \geq 100	2.508 (0.190–33.166)	0.485
	< 200 vs. \geq 200	0.375 (0.102–1.377)	0.140
	< 300 vs. \geq 300	0.288 (0.083–0.991)	0.048
	< 400 vs. \geq 400	0.243 (0.063–0.928)	0.039
	< 500 vs. \geq 500	0.132 (0.024–0.715)	0.019
Change of asthma control state (Partially/Uncontrolled to well vs. Well to partially/Uncontrolled)	< 100 vs. \geq 100	NA	0.999
	< 200 vs. \geq 200	NA	1.000
	< 300 vs. \geq 300	NA	1.000
	< 400 vs. \geq 400	NA	1.000
	< 500 vs. \geq 500	NA	0.999
ACT score, mean (\geq 20 vs. < 19)	< 100 vs. \geq 100	1.186 (0.262–5.363)	0.824
	< 200 vs. \geq 200	1.554 (0.403–5.969)	0.522
	< 300 vs. \geq 300	1.561 (0.456–5.342)	0.478
	< 400 vs. \geq 400	2.074 (0.611–6.861)	0.246
	< 500 vs. \geq 500	0.463 (0.116–1.850)	0.276
Medication demand			
Medication step, GINA (Steps 1–3 vs. Steps 4, 5)	< 100 vs. \geq 100	0.650 (0.142–2.981)	0.579
	< 200 vs. \geq 200	0.635 (0.198–2.034)	0.444
	< 300 vs. \geq 300	0.678 (0.231–1.990)	0.480
	< 400 vs. \geq 400	0.561 (0.184–1.708)	0.309
	< 500 vs. \geq 500	0.651 (0.189–2.246)	0.497
Change of GINA step (Steps 4, 5 to 1–3 vs. Steps 1–3 to 4, 5)	< 100 vs. \geq 100	1.013 (0.952–1.077)	0.692
	< 200 vs. \geq 200	0.121 (0.001–13.579)	0.381
	< 300 vs. \geq 300	0.687 (0.054–8.806)	0.773
	< 400 vs. \geq 400	0.176 (0.008–4.005)	0.276
	< 500 vs. \geq 500	0.560 (0.056–5.561)	0.620
ICS dose (Low dose vs. Medium-to-high dose)	< 100 vs. \geq 100	0.635 (0.131–3.074)	0.572
	< 200 vs. \geq 200	1.021 (0.328–3.175)	0.972
	< 300 vs. \geq 300	0.861 (0.302–2.457)	0.780
	< 400 vs. \geq 400	0.620 (0.211–1.822)	0.384
	< 500 vs. \geq 500	0.731 (0.231–2.321)	0.596
Asthma AE			
Asthma AEs (No vs. Yes)	< 100 vs. \geq 100	0.753 (0.226–2.510)	0.644
	< 200 vs. \geq 200	1.058 (0.380–2.948)	0.914
	< 300 vs. \geq 300	1.791 (0.682–4.703)	0.237
	< 400 vs. \geq 400	1.380 (0.532–3.578)	0.508
	< 500 vs. \geq 500	0.937 (0.326–2.691)	0.904
Severity of AE (No vs. Moderate)	< 100 vs. \geq 100	1.825 (0.343–9.702)	0.480
	< 200 vs. \geq 200	2.448 (0.623–9.619)	0.200
	< 300 vs. \geq 300	3.558 (1.083–11.686)	0.036
	< 400 vs. \geq 400	2.260 (0.741–6.889)	0.152
	< 500 vs. \geq 500	1.245 (0.386–4.018)	0.714
Severity of AE (No vs. Severe)	< 100 vs. \geq 100	0.173 (0.023–1.303)	0.089
	< 200 vs. \geq 200	0.122 (0.013–1.164)	0.068
	< 300 vs. \geq 300	0.324 (0.043–2.466)	0.277
	< 400 vs. \geq 400	0.424 (0.051–3.489)	0.425
	< 500 vs. \geq 500	0.750 (0.087–6.460)	0.793

OR = odd ratio, CI = confidential interval, ACT = asthma control test, GINA = Global Initiative for Asthma, ICS = inhaled corticosteroid, AE = acute exacerbation, NA = not assessed.

^aAdjusted factors were age, sex, body mass index, currently smoking, baseline forced expiratory volume in 1 second, baseline GINA medication step and mean drug compliance during 1 year. All patients had no history of acute asthma exacerbation during one year before enrollment. Baseline GINA medication step was excluded in adjusting in analyses of the change of GINA step, because there were not enough subjects to adjust.

excluded on the basis of systemic corticosteroid use. Among all asthmatics, the risk of severe AEs was higher in patients with blood eosinophil levels < 100 cells/ μ L than in patients with blood eosinophil levels \geq 100 cells/ μ L. Among atopic asthmatics, the risk of moderate AEs was higher in patients with blood eosinophil levels \geq 300 cells/ μ L than in patients with blood eosinophil levels < 300 cells/ μ L. The risk of partially/uncontrolled asthma state was higher in

Table 5. Comparison of clinical burden (asthma control status, medication demand and asthma AEs) according to the blood eosinophil count in non-atopic asthmatics (N = 178)

Clinical burden	Blood eosinophil count, cells/ μ L	OR (95% CI) ^a	P value ^a
Asthma control status			
Asthma control state (Well controlled vs. Partially/Uncontrolled)	< 100 vs. \geq 100	1.314 (0.294–5.870)	0.721
	< 200 vs. \geq 200	1.428 (0.407–5.015)	0.578
	< 300 vs. \geq 300	1.236 (0.398–3.836)	0.714
	< 400 vs. \geq 400	1.505 (0.415–5.461)	0.534
	< 500 vs. \geq 500	1.247 (0.296–5.252)	0.764
Change of asthma control state (Partially/Uncontrolled to well vs. Well to partially/Uncontrolled)	< 100 vs. \geq 100	NA	0.999
	< 200 vs. \geq 200	NA	0.991
	< 300 vs. \geq 300	NA	0.993
	< 400 vs. \geq 400	0.000 (0.000–303.515)	0.254
	< 500 vs. \geq 500	0.000 (0.000–158.449)	0.223
ACT score, mean (\geq 20 vs. < 19)	< 100 vs. \geq 100	1.191 (0.388–3.656)	0.760
	< 200 vs. \geq 200	0.824 (0.327–2.075)	0.681
	< 300 vs. \geq 300	1.609 (0.650–3.982)	0.303
	< 400 vs. \geq 400	1.087 (0.391–3.020)	0.873
	< 500 vs. \geq 500	1.258 (0.417–3.796)	0.683
Medication demand			
Medication step, GINA (Steps 1–3 vs. Steps 4, 5)	< 100 vs. \geq 100	2.534 (1.056–6.081)	0.037
	< 200 vs. \geq 200	2.500 (1.154–5.418)	0.020
	< 300 vs. \geq 300	2.154 (1.011–4.591)	0.047
	< 400 vs. \geq 400	3.165 (1.262–7.936)	0.014
	< 500 vs. \geq 500	3.462 (1.238–9.680)	0.018
Change of GINA step (Steps 4, 5 to 1–3 vs. Steps 1–3 to 4, 5)	< 100 vs. \geq 100	2.294 (0.445–11.828)	0.321
	< 200 vs. \geq 200	3.104 (0.764–12.617)	0.113
	< 300 vs. \geq 300	2.674 (0.652–10.968)	0.172
	< 400 vs. \geq 400	24.617 (1.985–305.227)	0.013
	< 500 vs. \geq 500	12.825 (1.265–130.075)	0.031
ICS dose (Low dose vs. Medium-to-high dose)	< 100 vs. \geq 100	1.365 (0.490–3.803)	0.552
	< 200 vs. \geq 200	1.392 (0.579–3.345)	0.459
	< 300 vs. \geq 300	0.783 (0.338–1.815)	0.569
	< 400 vs. \geq 400	0.9599 (0.360–2.557)	0.933
	< 500 vs. \geq 500	0.684 (0.217–2.156)	0.516
Asthma AE			
Asthma AEs (No vs. Yes)	< 100 vs. \geq 100	0.976 (0.331–2.874)	0.964
	< 200 vs. \geq 200	1.092 (0.423–2.820)	0.856
	< 300 vs. \geq 300	0.770 (0.297–1.994)	0.590
	< 400 vs. \geq 400	0.386 (0.110–1.347)	0.135
	< 500 vs. \geq 500	0.566 (0.150–2.137)	0.402
Severity of AE (No vs. Moderate)	< 100 vs. \geq 100	1.043 (0.334–3.262)	0.942
	< 200 vs. \geq 200	0.961 (0.358–2.579)	0.937
	< 300 vs. \geq 300	0.850 (0.318–2.268)	0.745
	< 400 vs. \geq 400	0.336 (0.085–1.329)	0.120
	< 500 vs. \geq 500	0.489 (0.115–2.077)	0.332
Severity of AE (No vs. Severe)	< 100 vs. \geq 100	0.021 (0.000–0.757)	0.121
	< 200 vs. \geq 200	0.710 (0.057–8.813)	0.790
	< 300 vs. \geq 300	1.151 (0.058–23.028)	0.927
	< 400 vs. \geq 400	6.732 (0.173–262.056)	0.307
	< 500 vs. \geq 500	17.783 (0.244–1296.987)	0.188

OR = odd ratio, CI = confidential interval, ACT = asthma control test, GINA = Global Initiative for Asthma, ICS = inhaled corticosteroid, AE = acute exacerbation, NA = not assessed.

^aAdjusted factors were age, sex, body mass index, currently smoking, baseline forced expiratory volume in 1 second, baseline GINA medication step and mean drug compliance during 1 year. All patients had no history of acute asthma exacerbation during one year before enrollment. Baseline GINA medication step was excluded in adjusting in analyses of the change of GINA step, because there were not enough subjects to adjust.

patients with low eosinophil levels. Among non-atopic asthmatics, the risk of a future need for a higher-step medication (GINA 4 or 5) was higher in patients with high blood eosinophil levels than in patients with low blood eosinophil levels. The risk of medication step-up

Table 6. Odd ratio of clinical burden (asthma control state, GINA medication step and asthma AE) by blood eosinophil counts comparing with blood eosinophil counts < 100 cells/ μ L

Clinical burden (blood eosinophil counts, cells/ μ L)	All asthmatics	Atopic asthmatics	Non-atopic asthmatics
Asthma control state (Partially/Uncontrolled)			
100–200	3.417 (0.764–15.284), 0.108	17.366 (0.641–470.172), 0.090	0.933 (0.107–8.121), 0.950
200–300	2.684 (0.607–11.869), 0.193	5.692 (0.268–121.50), 0.265	1.418 (0.199–10.100), 0.727
300–400	1.639 (0.340–7.908), 0.538	2.098 (0.081–4.641), 0.656	1.083 (0.169–6.632), 0.933
400–500	2.771 (0.485–15.832), 0.252	5.295 (0.191–146.730), 0.325	2.124 (0.207–21.803), 0.526
\geq 500	1.163 (0.281–4.821), 0.835	0.763 (0.034–17.129), 0.865	1.488 (0.236–9.392), 0.672
GINA medication step (Steps 4 or 5)			
100–200	1.244 (0.484–3.199), 0.651	0.929 (0.127–6.793), 0.942	1.573 (0.506–4.894), 0.434
200–300	1.820 (0.709–4.671), 0.213	0.705 (0.110–4.499), 0.712	2.496 (0.737–8.449), 0.142
300–400	1.371 (0.495–3.798), 0.543	1.309 (0.107–16.056), 0.833	1.809 (0.544–6.011), 0.333
400–500	1.730 (0.526–5.686), 0.367	0.464 (0.060–3.560), 0.460	3.280 (0.604–17.806), 0.169
\geq 500	2.348 (0.948–5.817), 0.065	0.517 (0.086–3.130), 0.473	5.792 (1.692–19.829), 0.005
History of asthma AE (One or More)			
100–200	0.653 (0.226–1.888), 0.431	0.429 (0.063–2.930), 0.388	0.883 (0.224–3.492), 0.860
200–300	0.771 (0.267–2.225), 0.630	0.288 (0.045–1.845), 0.189	1.739 (0.406–7.448), 0.456
300–400	1.528 (0.539–4.327), 0.425	1.640 (0.251–10.693), 0.605	1.649 (0.406–6.071), 0.485
400–500	1.109 (0.324–3.794), 0.869	1.438 (0.291–7.096), 0.656	NA
\geq 500	0.670 (0.253–1.774), 0.420	0.715 (0.180–2.848), 0.635	0.653 (0.135–3.153), 0.596
Moderate asthma AE (One or More)			
100–200	0.949 (0.288–3.126), 0.932	0.604 (0.043–8.524), 0.709	1.134 (0.277–4.644), 0.862
200–300	0.891 (0.255–3.114), 0.857	0.699 (0.077–6.376), 0.751	1.375 (0.264–7.166), 0.705
300–400	2.346 (0.745–7.389), 0.145	4.940 (0.461–52.988), 0.187	2.023 (0.480–8.532), 0.337
400–500	1.766 (0.472–6.606), 0.398	4.177 (0.535–32.638), 0.173	NA
\geq 500	0.983 (0.321–3.009), 0.975	1.865 (0.297–11.701), 0.506	0.601 (0.111–3.251), 0.555

Data are presented as adjusted odd ratio (95% confidence interval), *P* value. Asthma control status, GINA medication step, experience of AE and moderate AE was used to analyze. Age, sex, body mass index, smoking status, baseline forced expiratory volume in 1 second, baseline GINA medication step and mean drug compliance were adjusted.

GINA = Global Initiative for Asthma, AE = acute exacerbation, NA = not assessed.

(compared to step-down) was higher in patients with high eosinophil levels. Asthma AEs were not affected by the baseline eosinophil counts in non-atopic asthmatics.

Not all asthmatics with atopy exhibit high blood eosinophil counts and/or eosinophilic inflammation. A 2016 study by Tran et al.¹⁹ suggested that the atopic, eosinophilic, and T_H2-high asthma phenotypes overlapped. In that study, T_H2-high asthma was defined as a total serum IgE \geq 100 IU/mL and a blood eosinophil count \geq 140 cells/ μ L. Although the extent of overlap in the real world remains unclear, this overlap may explain why the mean blood eosinophil counts were similar between atopic and non-atopic asthmatics in our study. Various factors that are difficult to quantify (e.g., air pollution, allergen exposure, and inhaler technique) may affect the clinical burden of asthma in a complicated manner. It may be difficult to accurately predict the future clinical burden on the basis of blood eosinophil count alone. However, many studies have found that blood eosinophil levels reflect the risk of asthma AEs.^{6-8,20,21} Our work is meaningful in that we analyzed the association between the clinical burden of asthma and blood eosinophil counts (which are not affected by systemic corticosteroids) in a Korean adult asthma cohort; we studied atopic and non-atopic asthmatics separately. We excluded systemic corticosteroid-dependent patients with severe asthma, as well as patients with poor compliance. Therefore, we facilitated a good understanding of the association between clinical burden and blood eosinophil counts in most asthmatics.

We found no difference in ICS dose between groups divided according to the baseline blood eosinophil levels (both atopic and non-topic asthmatics). A 2015 study by Price et al.⁷

showed that the ICS dose per day was similar between groups in a UK cohort that was divided according to a blood eosinophil count of 400 cells/ μ L. In our study, although the ICS dose steps were similar, the risk of a need for high-step medication (GINA step 4 and 5) was higher in the high eosinophil group of non-atopic asthmatics. This is presumably because these patients also used other agents such as a leukotriene modifier or a long-acting muscarinic antagonist. In nonatopic asthmatics, clinicians may tend to prescribe a bronchodilator (rather than increasing the ICS dose) to control the symptoms of patients with high eosinophil counts. Airway remodeling was inhibited in IL-5-deficient mice, compared with wild-type mice.²² Patients with non-atopic asthma who experience weaker allergen-related effects might choose medications that dilate a remodeled airway, rather than control inflammation. It is unknown whether the blood eosinophil count exhibits a relationship with the extent of airway remodeling. Further studies are needed to explore such an association and define its details.

In most previous studies, baseline blood eosinophil counts were not affected by systemic corticosteroid use.⁵⁻⁷ Our finding was similar in the present study. In atopic asthmatics, the blood eosinophil level was associated with the risk of moderate AEs. In all asthmatics, the risk of severe AEs was higher in the low eosinophil group (< 100 cells/ μ L) than in the high eosinophil group (\geq 100 cells/ μ L), perhaps because patients with non-eosinophilic asthma tend to not respond to conventional treatment and often develop severe AEs.^{23,24} The risk of moderate AEs was higher in the group with high eosinophil levels (\geq 300 cells/ μ L) than in the group with low eosinophil levels (< 300 cells/ μ L), consistent with previous findings.⁵⁻⁷ However, any effect of the eosinophil level disappeared when cutoffs of 400 and 500 cells/ μ L were used. We found no quantitatively dependent relationship between any asthma burden and the blood eosinophil level. A blood eosinophil cutoff of 300 cells/ μ L may predict the risk of moderate AEs. However, at higher cutoffs, other risk factors for AE may offset the predictive power of the baseline blood eosinophil count. A 2014 study from the USA reported a difference in the risk of asthma AEs at an eosinophil cutoff of 300 cells/ μ L; however, the risks of AEs were similar at a cutoff of 400 cells/ μ L (OR, 1.49; 95% CI, 0.82–2.71).⁶

It remains unclear why the baseline blood eosinophil count does not strongly predict the future clinical burden of asthma. Price et al.⁷ found that the level of severe AEs was 2.32-fold (95% CI, 1.99–2.71) higher in a group with blood eosinophil levels \geq 1,000 cells/ μ L than in a group with blood eosinophil levels < 1,000 cells/ μ L. Zeiger et al.⁵ reported a 1.31-fold (95% CI, 1.07–1.60) increase in a group with blood eosinophil levels \geq 400 cells/ μ L, compared to a group with blood eosinophil levels < 400 cells/ μ L. Direct comparisons are difficult; the group features and the adjustment factors varied. However, the results do not suggest a very strong association between the clinical burden of asthma and blood eosinophil counts. Furthermore, eosinophil stability was not considered. Blood eosinophil counts from the same person vary over time. Jung et al.²⁵ reported that a single eosinophil count may not suffice when managing eosinophilic asthma; several factors (including technical considerations) may influence the count. Toledo-Pons et al.²⁶ reported that, compared with the absolute count, eosinophil variability was a better indicator of hospital episode risk. Because eosinophil stability may be problematic, other biomarkers that accurately reflect eosinophilic inflammatory status are needed. A high blood eosinophil count does not suggest that eosinophilic inflammation is severe. Depending on the patient, relatively low levels of eosinophils may affect the clinical course; some patients may be asymptomatic despite high blood eosinophil numbers.^{27,28} A recent Korean study compared patients with severe and non-severe asthma; the serum eosinophil-derived neurotoxin level reflected severity better

than did the blood eosinophil count.²⁹ Biomarkers that directly reflect the eosinophilic inflammatory state are needed to predict future clinical burden.

This study had several limitations. First, the influence of ICS on the blood eosinophil count was not considered. Inhaled high-dose budesonide (1,600 µg/day for 14 days) decreased the blood eosinophil count by approximately 200/µL in 10 asthmatics.³⁰ The effects of other doses and types of ICS on eosinophils are unknown. Second, the 1-year period differed among patients. Seasonal effects would have been equally reflected. However, environmental factors such as air pollution and fine dust, which differ from year to year, were not considered. The numbers of patients followed up during the same year were too small to analyze. Third, more patients than expected were excluded because of poor compliance or the use of systemic corticosteroids. The impacts of these excluded patients on the outcomes were not analyzed. Furthermore, the association between the clinical burden and blood eosinophil count in asthmatics who often used systemic corticosteroids was not evaluated.

In conclusion, among atopic asthmatics who were not exposed to systemic corticosteroids at enrollment in the COREA cohort, a high blood eosinophil count (≥ 300 cells/µL) could help to predict the risk of moderate AEs. Among non-atopic asthmatics, a high blood eosinophil count ($\geq 100, 200, 300, 400$ and 500 cells/µL) could help to predict the risk of a future need for higher-step medication. The baseline blood eosinophil count may help to predict the future clinical burden of asthma.

ACKNOWLEDGMENTS

We thank the members of the study centers for participating in this study. The COREA Study Group includes the following investigators: Woo-Jung Song, Hyouk-Soo Kwon, and You Sook Cho (Asan Medical Center, University of Ulsan, Seoul, Korea); Byoung Whui Choi (Chung-Ang University, Seoul, Korea); An-Soo Jang (Soonchunhyang University Bucheon Hospital, Bucheon, Korea); Sang-Hoon Kim and So Young Park (Eulji University, Seoul, Korea); Taehoon Lee (University of Ulsan, Ulsan, Korea); Jeong-Hee Choi (Hallym University Dongtan Sacred Heart Hospital, Hwaseong, Korea); Young-Hee Nam (Dong-A University, Busan, Korea); Sun-Young Yoon (Konkuk University Chungju Hospital, Chungju, Korea); Min-Suk Yang (Seoul National University Boramae Medical Center, Seoul, Korea); Jaechun Lee (Jeju National University, Jeju, Korea); Gyu Young Hur (Korea University, Seoul, Korea); Hee-Kyoo Kim (Kosin University, Busan, Korea); and Sang Ha Kim (Yonsei University, Wonju, Korea).

REFERENCES

1. Ong KY. What's new in the Global Initiative for Asthma 2018 report and beyond. *Allergo J Int* 2019;28(2):63-72. [CROSSREF](#)
2. Kuruvilla ME, Lee FE, Lee GB. Understanding asthma phenotypes, endotypes, and mechanisms of disease. *Clin Rev Allergy Immunol* 2019;56(2):219-33. [PUBMED](#) | [CROSSREF](#)
3. Corren J, Weinstein S, Janka L, Zangrilli J, Garin M. Phase 3 study of reslizumab in patients with poorly controlled asthma: effects across a broad range of eosinophil counts. *Chest* 2016;150(4):799-810. [PUBMED](#) | [CROSSREF](#)

4. Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet* 2012;380(9842):651-9.
[PUBMED](#) | [CROSSREF](#)
5. Zeiger RS, Schatz M, Li Q, Chen W, Khattry DB, Gossage D, et al. High blood eosinophil count is a risk factor for future asthma exacerbations in adult persistent asthma. *J Allergy Clin Immunol Pract* 2014;2(6):741-50.
[PUBMED](#) | [CROSSREF](#)
6. Tran TN, Khattry DB, Ke X, Ward CK, Gossage D. High blood eosinophil count is associated with more frequent asthma attacks in asthma patients. *Ann Allergy Asthma Immunol* 2014;113(1):19-24.
[PUBMED](#) | [CROSSREF](#)
7. Price DB, Rigazio A, Campbell JD, Bleecker ER, Corrigan CJ, Thomas M, et al. Blood eosinophil count and prospective annual asthma disease burden: a UK cohort study. *Lancet Respir Med* 2015;3(11):849-58.
[PUBMED](#) | [CROSSREF](#)
8. Zeiger RS, Schatz M, Dalal AA, Chen W, Sadikova E, Suruki RY, et al. Blood eosinophil count and outcomes in severe uncontrolled asthma: a prospective study. *J Allergy Clin Immunol Pract* 2017;5(1):144-153.e8.
[PUBMED](#) | [CROSSREF](#)
9. Kim TB, Park CS, Bae YJ, Cho YS, Moon HB; COREA Study Group. Factors associated with severity and exacerbation of asthma: a baseline analysis of the Cohort for Reality and Evolution of Adult Asthma in Korea (COREA). *Ann Allergy Asthma Immunol* 2009;103(4):311-7.
[PUBMED](#) | [CROSSREF](#)
10. Park SY, Jung H, Kim JH, Seo B, Kwon OY, Choi S, et al. Longitudinal analysis to better characterize asthma-COPD overlap syndrome: findings from an adult asthma cohort in Korea (COREA). *Clin Exp Allergy* 2019;49(5):603-14.
[PUBMED](#) | [CROSSREF](#)
11. Park SY, Jung HW, Lee JM, Shin B, Kim HJ, Kim MH, et al. Novel trajectories for identifying asthma phenotypes: a longitudinal study in Korean asthma cohort, COREA. *J Allergy Clin Immunol Pract* 2019;7(6):1850-1857.e4.
[PUBMED](#) | [CROSSREF](#)
12. Jang AS, Kim SH, Kim TB, Park HW, Kim SH, Chang YS, et al. Impact of atopy on asthma and allergic rhinitis in the cohort for reality and evolution of adult asthma in Korea. *Allergy Asthma Immunol Res* 2013;5(3):143-9.
[PUBMED](#) | [CROSSREF](#)
13. Adinoff AD, Rosloniec DM, McCall LL, Nelson HS. Immediate skin test reactivity to Food and Drug Administration-approved standardized extracts. *J Allergy Clin Immunol* 1990;86(5):766-74.
[PUBMED](#) | [CROSSREF](#)
14. Schatz M, Sorkness CA, Li JT, Marcus P, Murray JJ, Nathan RA, et al. Asthma Control Test: reliability, validity, and responsiveness in patients not previously followed by asthma specialists. *J Allergy Clin Immunol* 2006;117(3):549-56.
[PUBMED](#) | [CROSSREF](#)
15. Hogan AD, Bernstein JA. GINA updated 2019: landmark changes recommended for asthma management. *Ann Allergy Asthma Immunol* 2020;124(4):311-3.
[PUBMED](#) | [CROSSREF](#)
16. Nelson RK, Bush A, Stokes J, Nair P, Akuthota P. Eosinophilic asthma. *J Allergy Clin Immunol Pract* 2020;8(2):465-73.
[PUBMED](#) | [CROSSREF](#)
17. Chongmelaxme B, Chaiyakunapruk N, Dilokthornsakul P. Association between adherence and severe asthma exacerbation: a systematic review and meta-analysis. *J Am Pharm Assoc (2003)* 2020;60(5):669-685.e2.
[PUBMED](#) | [CROSSREF](#)
18. Stern L, Berman J, Lumry W, Katz L, Wang L, Rosenblatt L, et al. Medication compliance and disease exacerbation in patients with asthma: a retrospective study of managed care data. *Ann Allergy Asthma Immunol* 2006;97(3):402-8.
[PUBMED](#) | [CROSSREF](#)
19. Tran TN, Zeiger RS, Peters SP, Colice G, Newbold P, Goldman M, et al. Overlap of atopic, eosinophilic, and T_H2-high asthma phenotypes in a general population with current asthma. *Ann Allergy Asthma Immunol* 2016;116(1):37-42.
[PUBMED](#) | [CROSSREF](#)
20. Katz LE, Gleich GJ, Hartley BF, Yancey SW, Ortega HG. Blood eosinophil count is a useful biomarker to identify patients with severe eosinophilic asthma. *Ann Am Thorac Soc* 2014;11(4):531-6.
[PUBMED](#) | [CROSSREF](#)
21. Casciano J, Krishnan J, Dotiwala Z, Li C, Sun SX. Clinical and economic burden of elevated blood eosinophils in patients with and without uncontrolled asthma. *J Manag Care Spec Pharm* 2017;23(1):85-91.
[PUBMED](#) | [CROSSREF](#)

22. Cho JY, Miller M, Baek KJ, Han JW, Nayar J, Lee SY, et al. Inhibition of airway remodeling in IL-5-deficient mice. *J Clin Invest* 2004;113(4):551-60.
[PUBMED](#) | [CROSSREF](#)
23. Esteban-Gorgojo I, Antolín-Amérigo D, Domínguez-Ortega J, Quirce S. Non-eosinophilic asthma: current perspectives. *J Asthma Allergy* 2018;11:267-81.
[PUBMED](#) | [CROSSREF](#)
24. Chipps BE, Jarjour N, Calhoun WJ, Iqbal A, Haselkorn T, Yang M, et al. A comprehensive analysis of the stability of blood eosinophil levels. *Ann Am Thorac Soc* 2021;18(12):1978-87.
[PUBMED](#) | [CROSSREF](#)
25. Jung JW, Kim SH, Kwon JW, Kim TW, Kang HR, Park HW, et al. Clinical characteristics and long-term outcomes related to sputum eosinophilia in Korean asthmatics. *Asia Pac Allergy* 2011;1(1):16-24.
[PUBMED](#) | [CROSSREF](#)
26. Toledo-Pons N, van Boven JFM, Muncunill J, Millan A, Roman-Rodriguez M, Lopez-Andrade B, et al. Impact of blood eosinophil variability in asthma: a real-life population study. *Ann Am Thorac Soc*. Forthcoming 2021. DOI: 10.1513/AnnalsATS.202103-409OC.
[PUBMED](#) | [CROSSREF](#)
27. Chen YY, Khoury P, Ware JM, Holland-Thomas NC, Stoddard JL, Gurprasad S, et al. Marked and persistent eosinophilia in the absence of clinical manifestations. *J Allergy Clin Immunol* 2014;133(4):1195-202.
[PUBMED](#) | [CROSSREF](#)
28. Rothenberg ME, Hogan SP. The eosinophil. *Annu Rev Immunol* 2006;24(1):147-74.
[PUBMED](#) | [CROSSREF](#)
29. An J, Lee JH, Sim JH, Song WJ, Kwon HS, Cho YS, et al. Serum eosinophil-derived neurotoxin better reflect asthma control status than blood eosinophil counts. *J Allergy Clin Immunol Pract* 2020;8(8):2681-2688.e1.
[PUBMED](#) | [CROSSREF](#)
30. Evans PM, O'Connor BJ, Fuller RW, Barnes PJ, Chung KF. Effect of inhaled corticosteroids on peripheral blood eosinophil counts and density profiles in asthma. *J Allergy Clin Immunol* 1993;91(2):643-50.
[PUBMED](#) | [CROSSREF](#)