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Risk Factors Predicting Severe Asthma Exacerbations in Adult Asthmatics: A Real-World Clinical Evidence

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ABSTRACT

Purpose: Minimizing the future risk of asthma exacerbation (AE) is one of the main goals of asthma management. We investigated prognostic factors for risk of severe AE (SAE) in a real-world clinical setting.
Methods: This is an observational study evaluating subjects who were diagnosed with asthma and treated with anti-asthmatic medications from January 1995 to June 2018. Risk factors for SAE were analyzed in 2 treatment periods (during the initial 2 years and the following 3–10 years of treatment) using the big data of electronic medical records.
Results: In this study, 5,058 adult asthmatics were enrolled; 1,335 (28.64%) experienced ≥ 1 SAE during the initial 2 years of treatment. Female sex, higher peripheral eosinophil/basophil counts, and lower levels of forced expiratory volume in 1 second (FEV1; %) were factors predicting the risk of SAEs ($P < 0.001$ for all). Higher serum total immunoglobulin E levels increased the risk of SAEs among the patients having ≤ 2 SAEs ($P = 0.025$). Patients with more frequent SAEs during the initial 2 years of treatment had significantly higher risks of SAEs during the following years of treatment ($P < 0.001$, for all) (patients with ≥ 4 SAEs, odds ratio [OR], 29.147; those with 3 SAEs, OR, 14.819; those with 2 SAEs, OR, 9.867; those with 1 SAE, OR, 5.116), had higher maintenance doses of systemic steroids, and showed more gradual decline in FEV1 (%) and FEV1/forced vital capacity levels maintained during the following years of treatment ($P < 0.001$ for all).
Conclusions: Asthmatics having risk factors for SAEs (female sex, higher peripheral eosinophil/basophil counts, and lower FEV1) should be strictly monitored to prevent future risk and improve clinical outcomes.

Keywords: Asthma; adults; female; eosinophils; basophils; IgE; risk factors; steroids; respiratory function tests

INTRODUCTION

The long-term goal of asthma treatment is to achieve good control of symptoms and to minimize the future risk of asthma exacerbations (AEs).[1] Asthma is a heterogeneous disease

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with various responses to treatment and clinical outcomes.[2,3] AEs are a prominent feature of severe asthmatics; however, frequent AEs have also been reported in mild asthmatics.[4]

Estimated annual rates of AEs per patient were reported to be 0.34 to 0.91 even in adult asthmatics having been treated with anti-asthmatic medications.[5] The annual AE rates ranged between 25% and 35% in the analysis of National Health Insurance Service-National Sample Cohort in Korea.[6] AE has the greatest impact on health care utilization and treatment costs for asthmatics. The costs related to asthma care were 3 times higher in patients with AEs than in those without.[3] Thus, there have been several studies reporting risk factors that can predict AEs[3,7,8] and lung function decline.[9-11]

To date, many studies have consistently shown that type 2-driven biomarkers, including peripheral/sputum eosinophilia and high Fractional exhaled nitric oxide (FeNO) level (≥20 ppb), could predict AEs and lung function decline.[3,9,12] Most of the biomarkers identified were studied in limited populations of asthmatics in randomized, controlled trials. These biomarkers have limitation to be applied in real clinical settings; therefore, the biomarkers that can be used in the chronic management of asthmatics in daily practice are needed.

This is an observational study to identify predictors for patients with frequent AEs among adult asthmatics (who had been treated by asthma specialists according to the treatment guidelines in the Asthma Center of a University Hospital setting) by analyzing medical big data of electronic medical records (EMR), which will provide an insight to the long-term management of adult asthmatics in real-world practice.

MATERIALS AND METHODS

Subjects

Patients aged ≥ 17 years diagnosed as having bronchial asthma (with J45-J46 code of International classification of Diseases, 10th edition [ICD-10] on EMR) and who had been treated by allergy or respiratory specialists at Ajou University Hospital from January 1995 to June 2018 were screened. Subjects who fulfilled both of the following criteria were finally enrolled: 1) who had ≥ 2 visits and ≥ 2 prescriptions of anti-asthmatic medications during the study period and 2) who had been monitored for 3–10 years. Any of the single prescriptions of the following medications were regarded as anti-asthmatic medications based on the Global Initiative for Asthma guideline[1]; short-acting beta2-agonists, inhaled corticosteroids (ICSs), ICS/long-acting beta$_2$-agonists, and leukotriene receptor antagonists. The follow-up period was calculated as the time between the first day and the last day of prescription of anti-asthmatic medications.

Clinical data collection

Clinical data on demographics, age at asthma diagnosis, asthma follow-up duration, pulmonary function test results (forced expiratory volume in 1 second [FEV1]% pred. and FEV1/forced vital capacity [FVC]) and laboratory findings (total immunoglobulin E [IgE], specific IgE to *Dermatophagoides pteronyssinus* [Dp], specific IgE to *Dermatophagoides farinae* [Df], peripheral eosinophil/neutrophil/basophil/lymphocyte/platelet counts, eosinophil cationic protein [ECP], and sputum eosinophil/neutrophil counts) were extracted from the EMR database. The levels of total IgE, specific IgE, and ECP were measured by the ImmunoCAP system (ThermoFisher Scientific, Waltham, MA, USA). Neutrophil-lymphocyte ratio (NLR)

or eosinophil-lymphocyte ratio (ELR) was defined as the absolute neutrophil or eosinophil counts divided by the absolute lymphocyte count. All of the repetitive lung function and laboratory results during the follow-up period were collected and the mean value of each year was used to be analyzed. To exclude drug-induced effects, total IgE levels (which were examined within 5 years of omalizumab treatment) or peripheral eosinophil counts (which were examined within 5 months of anti-interleukin [IL]-5 antibody treatment) were not used for this analysis.[13] Peripheral eosinophil or neutrophil count data that were examined within 1 month of systemic steroid prescription were also excluded from the analysis.

The repetitive data on lung function results and laboratory findings were analyzed in 2 ways: 1) by using the cross-sectional data collected at the initial visit to investigate the differences among the study subjects and to assess the cutoff levels that can predict the risk or frequency of AEs, and 2) by analyzing longitudinal follow-up data on maintained anti-asthmatic medications during the following 3 to 10 years of treatment according to the risk or frequency of AEs to overcome the limitation of initial cross-sectional data and to represent the real-world clinical data. This study was approved by the Ethical Review Board of Ajou University (AJIRB-TEMP-TEMP-18-404).

The 3 study groups according to the frequency of SAEs

Systemic steroid prescription histories extracted from EMR data were used to assess severe AEs (SAEs). An SAE in the present study was defined when a systemic steroid estimated (prednisolone-equivalent dose ≥ 15 mg per day for 7 consecutive days) per patient was prescribed. Extracted EMR data were condensed, depending on the frequency of SAEs for 2 years. Study subjects were categorized into 3 groups according to the frequency of SAEs during the initial 2 years of treatment: those with no SAE (non-exacerbators, group 1), those with 1–2 SAEs (non-frequent exacerbators, group 2), and those with ≥ 3 SAEs (frequent exacerbators, group 3). The EMR data were managed by SAS according to the internal guideline proposed by Ajou University Medical Center (SAS® 9.4; SAS Institute Inc., Cary, NC, USA).

Study outcomes

The primary outcomes were prognostic factors for predicting SAE during initial 2 years of treatment. The secondary outcomes were factors predicting SAE during initial 2 years which were analyzed in eosinophilic asthma and non-eosinophilic asthma separately, considering that peripheral eosinophil count is a critical factor predicting the risk of SAEs. Eosinophilic asthma was defined when the mean value of peripheral eosinophil counts collected during the first year of treatment was ≥ 300/μL. Subgroup analysis for factors predicting SAE during initial 2 years were analyzed each in the group 1–3 to investigate whether there is a difference in factors predicting SAE according to the frequencies of SAE. Prognostic factors for the risk of SAEs during 10 years of treatment were also evaluated. In order to evaluate whether the previous history of SAEs affect the following period SAEs, SAE risk during following 3 to 10 years were assessed according to the frequencies of SAEs during the initial 2 years of treatment. In addition, changes in systemic steroid requirements, lung functions during 10 years of treatment were compared among the 3 groups to evaluate the long-term prognosis according to the frequency of SAE during initial 2 years of treatment.

Statistical analysis

Analysis of variance with Tukey tests was performed to compare the baseline characteristics and clinical data according to the frequency of SAE during the initial 2 years of treatment. To find factors predicting the risk of SAEs (based on clinical/laboratory parameters), a

generalized estimating equation (GEE) with a binary logistic/Poisson loglinear model was employed according to the presence/frequency of SAEs during the 2 initial years of treatment. Multivariate logistic regression analysis was performed to adjust for confounding factors. The receiver operating characteristic (ROC) curves with area under the curve (AUC) were applied to assess the optimal cutoff levels of prognostic factors predicting SAEs. The optimal cutoff values predicting the risk of SAEs were obtained from maximum Youden J (SPSS 23; IBM Corporation, Chicago, IL, USA). Longitudinal changes in systemic steroid requirements (mg) prescribed per year, FEV1 (%) and FEV1/FVC (%) levels during the following years of treatment (up to 10 years) were estimated by GEE with a linear model.

RESULTS

Characteristics of the study subjects

A total of 5,058 subjects were enrolled and 28,349 repeated measurements, including lung function test results and laboratory findings (evaluated at the initial and final visits), were generated during the study period. The mean follow-up duration was 5.52 ± 4.79 years, and the mean age at asthma diagnosis was 39.25 ± 16.84 years. Mean baseline FEV1 level (% pred.) was 94.51% ± 18.12%, and FEV1/FVC (%) was 83.68% ± 8.52%. Of the total study subjects, 1,335 (28.64%) experienced ≥ 1 SAE and 317 (8.51%) showed frequent SAEs (≥ 3) during the initial 2 years of treatment. The changes in number of asthmatics and the level of peripheral eosinophil count of each group during 10 years are presented in **Supplementary Fig. S1**. Asthmatics who had ever experienced SAEs during the initial 2 years of treatment had older age, higher prevalence of late-onset asthma, higher levels of total IgE and peripheral eosinophil/neutrophil/basophil/platelet counts, lower levels of specific IgE to Dp/Df, FEV1, and FEV1/FVC than those who did not. Differences in the baseline characteristics of the study subjects among the study groups are presented in **Table 1**.

Prognostic factors predicting SAE during the initial 2 years of treatment

Fig. 1 summarizes the prognostic factors analyzed to predict the risk of SAEs during the initial 2 years of treatment. Age at enrollment, age at diagnosis, female sex, follow-up duration, ECP levels, peripheral eosinophil/neutrophil/basophil/platelet counts, sputum eosinophil counts, NLR (%) and ELR (%) were significant factors predicting the risk of SAEs ($P < 0.001$ for all); the lower levels of specific IgE to Dp/Df, FEV1 (% pred.) and FEV1/FVC were significant factors predicting the risk of SAEs ($P < 0.001$ for both). In addition, when prognostic factors were analyzed to predict the frequency of SAEs during the initial 2 years of treatment, age at enrollment, age at diagnosis, follow-up duration, ECP levels, peripheral eosinophil/neutrophil/basophil/platelet counts, sputum eosinophil counts, NLR (%), and ELR (%) were significant factors predicting the frequency of SAE ($P < 0.05$) (**Supplementary Table S1**), which were comparable to prognostic factors for the risk of SAE listed in **Table 1**. When subgroup analysis for group 1/2 subjects was performed to evaluate prognostic factors predicting the risk of SAEs, the serum total IgE level was found to be a risk factor for SAE (odds ratio [OR], 1.000, $P = 0.025$; **Fig. 2**), and other predictors are presented in **Fig. 1**.

Multivariate analysis for predicting the risk of SAEs during the initial 2 years of treatment was performed using a GEE with a linear model composing sex, age at diagnosis, peripheral eosinophil/basophil counts, and FEV1 (%pred.) value. Female sex, peripheral eosinophil/basophil counts, and FEV1 (%) value were significant risk factors for SAE (**Table 2**). ROC analysis was performed to discriminate asthmatics with SAEs from those without during

Table 1. Clinical characteristics of the study subjects and their comparisons between the groups

Variables	Total (n = 5,058)	Group 1 (non-exacerbator; n = 3,723)	Group 2 (non-frequent exacerbator; n = 1,018)	Group 3 (frequent exacerbator; n = 317)	*P* value			
					Total	Group 1 vs. 2	Group 1 vs. 3	Group 2 vs. 3
Age at enrollment (yr)	50.80 ± 17.35	49.44 ± 17.22/3,723	53.80 ± 17.47/1,018	57.14 ± 15.95/317	< 0.001	< 0.001	< 0.001	0.007
Sex (female)	2,890 (57.14)	2,074 (55.71)/3,723	619 (60.81)/1,018	197 (62.15)/317	0.003	0.012	0.081	1.000
Age at diagnosis (yr)	39.25 ± 16.84	37.76 ± 16.69/3,723	42.39 ± 16.90/1,018	46.68 ± 15.00/317	< 0.001	< 0.001	< 0.001	< 0.001
Follow-up duration (yr)	5.52 ± 4.79	5.45 ± 4.76/3,723	5.66 ± 4.89/1,018	5.84 ± 4.77/317	0.215	0.425	0.350	0.835
Total IgE (kU/L)	493.03 ± 840.52	472.67 ± 813.46/2,203	567.01 ± 947.96/615	489.96 ± 775.46/213	0.048	0.037	0.956	0.481
Specific IgE to Dp (kU/L)	12.39 ± 24.11	13.60 ± 25.02/2,628	10.35 ± 22.29/765	5.56 ± 16.87/238	< 0.001	0.003	< 0.001	0.020
Specific IgE to Df (kU/L)	16.73 ± 29.31	18.36 ± 30.37/2,649	14.05 ± 27.62/781	7.43 ± 18.37/238	< 0.001	0.001	< 0.001	0.006
Peripheral eosinophil count (× 10^3/μL)	0.30 ± 0.29	0.28 ± 0.25/2,940	0.34 ± 0.35/911	0.39 ± 0.36/282	< 0.001	< 0.001	< 0.001	0.026
Peripheral neutrophil count (× 10^3/μL)	4.38 ± 1.84	4.06 ± 1.58/2,938	5.06 ± 2.15/910	5.55 ± 2.19/282	< 0.001	< 0.001	< 0.001	< 0.001
Peripheral basophil count (× 10^3/μL)	0.04 ± 0.02	0.04 ± 0.02/2,938	0.04 ± 0.02/910	0.05 ± 0.02/282	0.001	0.043	0.005	0.290
Peripheral lymphocyte count (× 10^3/μL)	2.16 ± 0.62	2.19 ± 0.60/2,940	2.09 ± 0.66/911	2.14 ± 0.72/282	< 0.001	< 0.001	0.409	0.470
Peripheral platelet count (× 10^3/μL)	257.59 ± 59.01	255.40 ± 57.04/2,953	260.21 ± 61.74/914	272.08 ± 67.42/282	< 0.001	0.079	< 0.001	0.009
ECP (μg/L)	33.86 ± 42.95	29.40 ± 30.63/1,326	44.38 ± 67.93/432	41.85 ± 37.44/170	< 0.001	< 0.001	0.001	0.788
NLR (%)	2.47 ± 2.07	2.14 ± 1.60/2,938	3.22 ± 2.80/910	3.55 ± 2.64/282	< 0.001	< 0.001	< 0.001	0.039
ELR (%)	0.14 ± 0.14	0.13 ± 0.12/2,940	0.17 ± 0.17/911	0.19 ± 0.21/282	< 0.001	< 0.001	< 0.001	0.007
Sputum eosinophils (%)	33.57 ± 31.74	32.09 ± 31.52/928	34.81 ± 31.82/302	42.08 ± 31.96/118	0.004	0.394	0.004	0.087
FEV1 (%)	94.51 ± 18.12	97.66 ± 15.52/1,810	89.08 ± 21.53/544	80.96 ± 19.93/203	< 0.001	< 0.001	< 0.001	< 0.001
FEV1/FVC (%)	83.68 ± 8.52	84.96 ± 7.82/1,257	81.38 ± 8.81/374	77.24 ± 10.29/115	< 0.001	< 0.001	< 0.001	< 0.001

Values are presented as mean ± standard deviation or number (%). Group 1: asthmatics experienced no SAE during the initial 2 years of asthma treatment; Group 2: asthmatics experienced 1–2 SAE during the initial 2 years of asthma treatment; Group 3: asthmatics experienced ≥ 3 SAE during the initial 2 years of asthma treatment.
IgE, immunoglobulin E; Df, *Dermatophagoides farinae*; Dp, *Dermatophagoides pteronyssinus*; ECP, eosinophil cationic protein; ELR, eosinophil-lymphocyte ratio; NLR, neutrophil-lymphocyte ratio; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; SAE, severe asthma exacerbation.

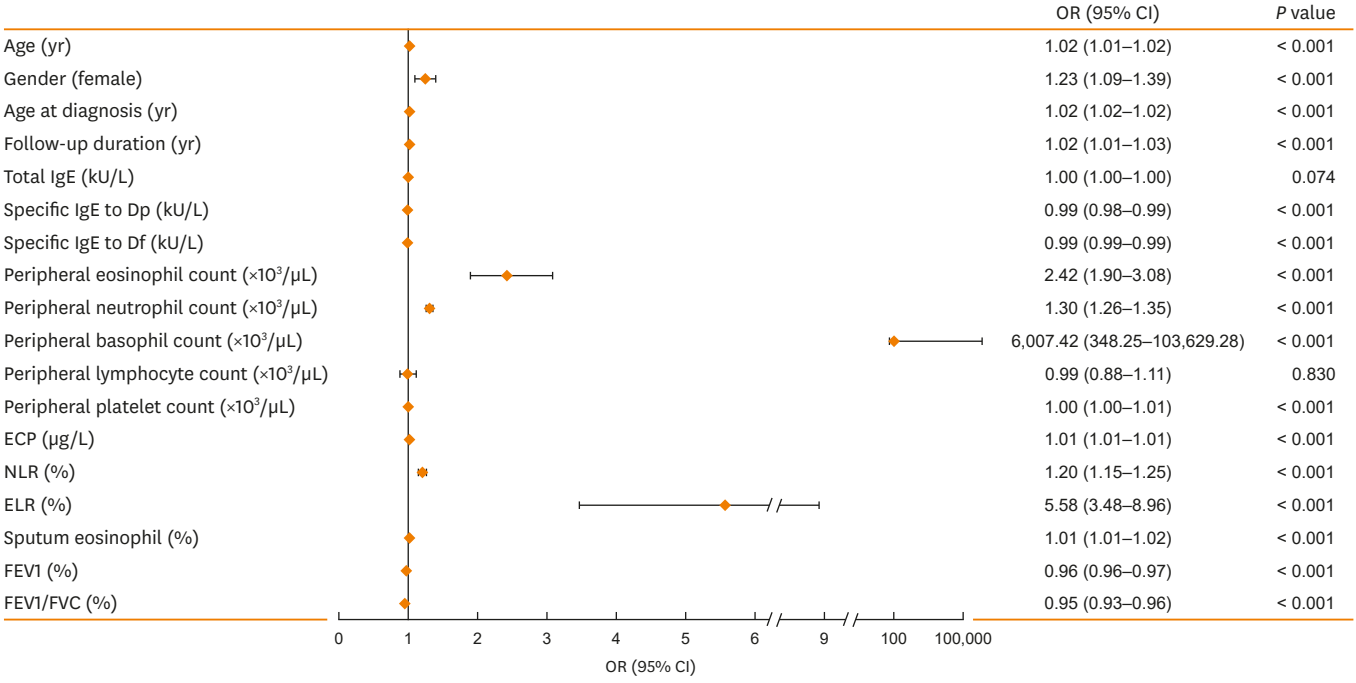

Fig. 1. Prognostic factors predicting the risk of severe asthma exacerbations during the initial 2 years of treatment in the study subjects.
IgE, immunoglobulin E; Df, *Dermatophagoides farina*; Dp, *Dermatophagoides pteronyssinus*; ECP, eosinophil cationic protein; ELR, eosinophil-lymphocyte ratio; NLR, neutrophil-lymphocyte ratio; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; OR, odds ratio; CI, confidence interval.

the initial 2 years of treatment (**Supplementary Table S2**). The cutoff values with sensitivity/specificity for individual factors predicting the frequency of SAEs were 239.42 kU/L for total IgE ($P = 0.010$, AUC = 0.530, 50% sensitivity with 57% specificity), 406/μL for peripheral

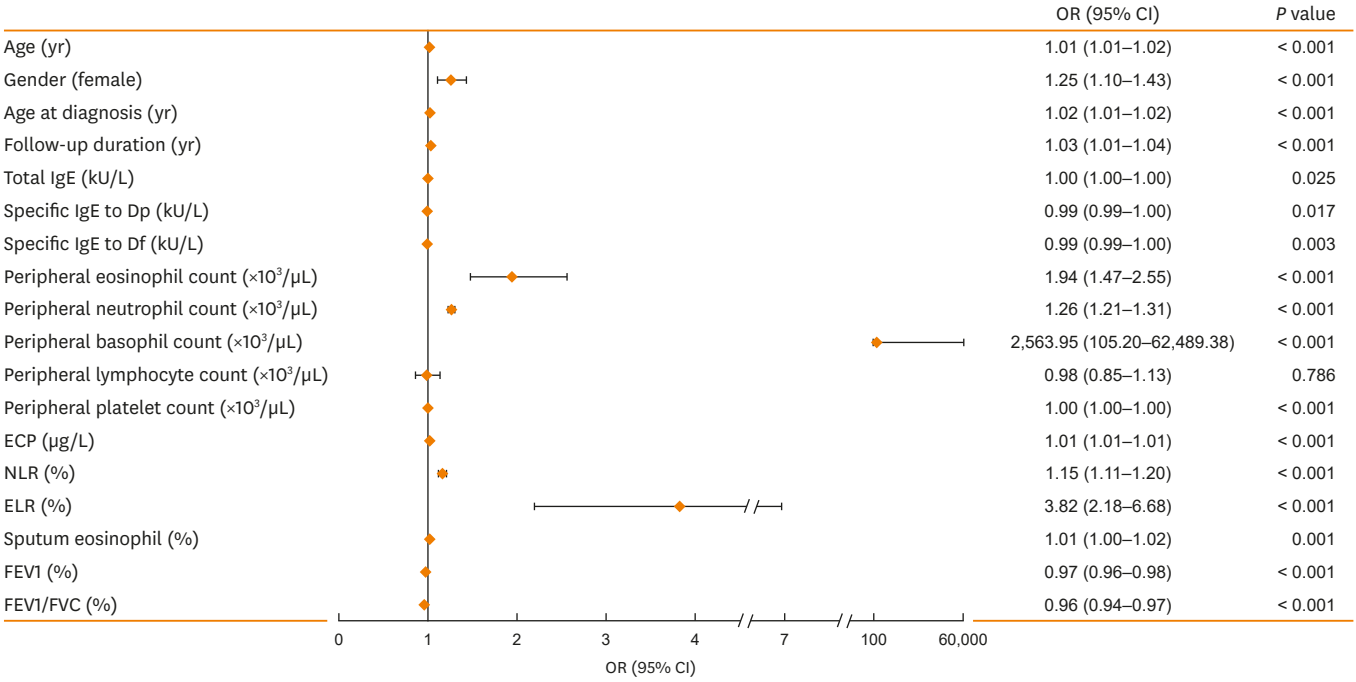

Fig. 2. Prognostic factors predicting the risk of SAEs during the initial 2 years of treatment in group 1 and 2 subjects. Group 1: asthmatics experienced no SAE during the initial 2 years of asthma treatment; Group 2: asthmatics experienced 1–2 SAE during the initial 2 years of asthma treatment.
SAE, severe asthma exacerbation; IgE, immunoglobulin E; Df, *Dermatophagoides farina*; Dp, *Dermatophagoides pteronyssinus*; ECP, eosinophil cationic protein; ELR, eosinophil-lymphocyte ratio; NLR, neutrophil-lymphocyte ratio; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; OR, odds ratio; CI, confidence interval.

Table 2. Multivariate analysis of prognostic factors for predicting the risk of severe asthma exacerbation during initial 2 years' treatment period

Variables	B	*P* value	Exp (B)	95% CI for Exp (B)	
				Lower	Upper
Sex (female)	0.487	< 0.001	1.627	1.295	2.045
Age at diagnosis (yr)	0.005	0.160	1.005	0.998	1.012
Peripheral eosinophil count (× 10³/μL)	0.860	< 0.001	2.362	1.625	3.434
Peripheral basophil count (× 10³/μL)	4.964	0.022	143.184	2.031	10,095.818
FEV1 (%)	−0.036	< 0.001	0.964	0.958	0.971

Factors used in multivariate analysis were sex, age at diagnosis, peripheral eosinophil/basophil count, and FEV1 (% pred.) value.
FEV1, forced expiratory volume in 1 second; CI, confidence interval.

eosinophils ($P < 0.001$, AUC = 0.544, 32.3% sensitivity with 78.2% specificity), and 89.62% for FEV1% pred. ($P < 0.001$, AUC = 0.668, 32.3% sensitivity with 78.2% specificity).

Comparison of prognostic factors predicting the risk of SAEs during the initial 2 years of treatment between patients with eosinophilic asthma and those with non-eosinophilic asthma

Their clinical characteristics according to the frequency of SAEs are summarized in **Supplementary Table S3**. **Fig. 3** compares prognostic factors predicting the risk of SAEs during the initial 2 years of treatment between patients with eosinophilic and those with non-eosinophilic asthma. Age at enrollment, age at diagnosis, female sex, follow-up duration, serum ECP level, peripheral eosinophil/neutrophil/basophil/platelet counts, NLR (%), and ELR (%) were factors predicting the risk of SAEs in patients with eosinophilic asthma, and lower levels of specific IgE to Dp, Df, FEV1 and FEV1/FVC were factors predicting the risk of AEs (**Fig. 3**). Although sputum eosinophil count was not a significant predictor of SAEs, it predicted the frequency of SAEs (OR, 1.008, $P = 0.020$). In patients with non-eosinophilic

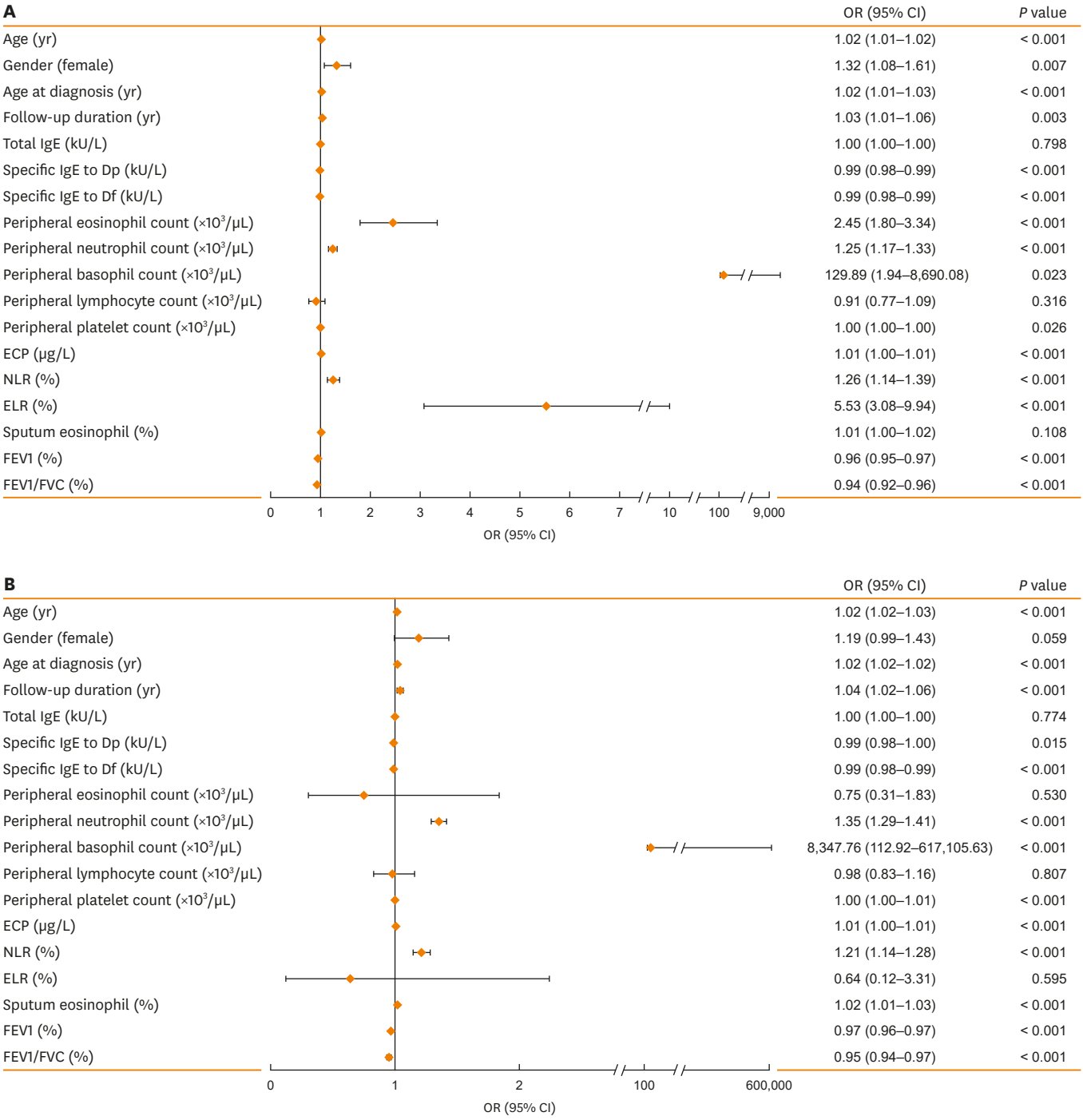

Fig. 3. Prognostic factors predicting the risk of severe asthma exacerbation during the initial 2 years of treatment in patients with eosinophilic (A) and non-eosinophilic asthma (B).
IgE, immunoglobulin E; Df, *Dermatophagoides farina*; Dp, *Dermatophagoides pteronyssinus*; ECP, eosinophil cationic protein; ELR, eosinophil-lymphocyte ratio; NLR, neutrophil-lymphocyte ratio; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; OR, odds ratio; CI, confidence interval.

asthma, female sex, peripheral eosinophil count and ELR did not predict the risk of SAEs. Meanwhile, sputum eosinophil count was found to be a significant prognostic factor predicting the risk and frequency of SAEs (OR, 1.019, $P < 0.001$; OR, 1.014, $P < 0.001$). Multivariate analysis for predicting SAEs in patients with eosinophilic asthma and those

Table 3. Multivariate analysis of prognostic factors for predicting the risk of severe asthma exacerbation during initial 2 years' treatment period in patients with eosinophilic and non-eosinophilic asthma

Variables	B	*P* value	Exp (B)	95% CI for Exp (B)	
				Lower	Upper
Eosinophilic asthma					
Sex (female)	0.578	0.001	1.783	1.255	2.533
Age at diagnosis (yr)	0.004	0.532	1.004	0.992	1.016
Peripheral eosinophil count ($\times 10^3$/μL)	0.986	< 0.001	2.682	1.665	4.320
Peripheral basophil count ($\times 10^3$/μL)	0.480	0.870	1.616	0.005	510.495
FEV1 (%)	−0.042	< 0.001	0.959	0.946	0.971
Non-eosinophilic asthma					
Sex (female)	0.474	0.004	1.606	1.166	2.214
Age at diagnosis (yr)	0.007	0.143	1.007	0.998	1.016
Peripheral neutrophil count ($\times 10^3$/μL)	0.282	< 0.001	1.325	1.234	1.424
Peripheral basophil count ($\times 10^3$/μL)	5.977	0.073	394.222	0.568	273,443.216
FEV1 (%)	−0.027	< 0.001	0.973	0.965	0.982

FEV1, forced expiratory volume in 1 second; CI, confidence interval.

with non-eosinophilic asthma during the initial 2 years of treatment was performed using a GEE with a linear model. Female sex, peripheral eosinophil count and FEV1 (%) level were found to be factors for the risk of SAEs in patients with eosinophilic asthma; female sex, peripheral neutrophil count, and FEV1 (%) were factors for the risk of SAEs in those with non-eosinophilic asthma (**Table 3**).

Prognostic factors for the risk of SAE during 10 years of treatment

In order to evaluate whether SAEs during the initial 2 years of treatment may predict long-term prognoses, we analyzed prognostic factors predicting the risk of SAE during the following 3 to 10 years of treatment. Asthmatics with more frequent SAEs during the initial 2 years of treatment had significantly higher risks of SAEs during the following years of treatment compared to those who did not (OR of patients with 1 SAE was 5.116, $P < 0.001$; OR of those with 2 SAEs was 9.867, $P < 0.001$; OR of those with 3 SAEs was 14.819, $P < 0.001$; and OR of those with ≥ 4 SAEs was 29.147, $P < 0.001$) even though all patients had maintained anti-asthmatic medications with regular monitoring, indicating that the frequency of SAEs during the initial 2 years of treatment could affect significantly the risk of SAEs during the following years of treatment (**Fig. 4**). In addition, asthmatics with older age, late-onset

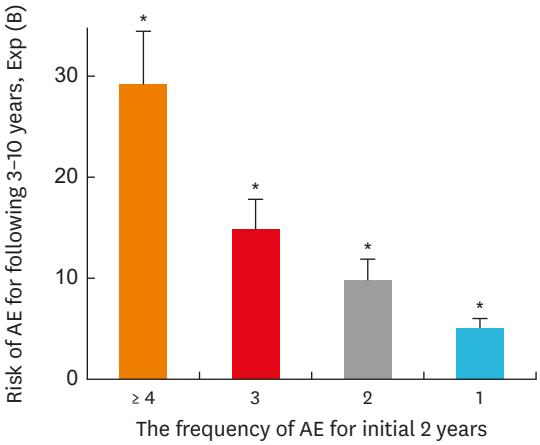

Fig. 4. Comparison of SAE risks during the following 10 years of treatment according to the frequency of SAEs during the initial 2 years of treatment.
SAE, severe asthma exacerbation; CI, confidence interval; AE, asthma exacerbation.
*P value < 0.001, error bar means upper of 95% CI for Exp (B).

asthma, higher levels of serum ECP, higher peripheral eosinophil/neutrophil/basophil/platelet counts, higher NLR (%)/ELR(%)/sputum eosinophil count as well as lower levels of specific IgE to Dp, Df, FEV1 (%) and FEV1/FVC were significantly associated with the risk of SAEs during the 10 years of treatment ($P < 0.001$ for all) (**Supplementary Table S4**), which were similar to prognostic factors during the initial 2 years of treatment as noted in **Fig. 1**.

Comparison of long-term changes in systemic steroid requirements, FEV1 (%) and FEV1/FVC (%) during the following years of treatment among the 3 groups

When longitudinal changes in systemic steroid requirements during the following 3–10 years were compared among the 3 groups, remarkable differences were noted among the 3 groups even with regular maintenance medications. Group 1 patients consistently showed the lowest doses with little changes, while group 2 patients showed a decreasing tendency for a few years and then maintained similar levels during the following years of treatment (higher doses than group 1 patients). Group 3 patients had the highest dose at baseline and then showed a decreasing tendency, but still had the highest dose compared to group 1 and 2 patients ($P < 0.001$ for each, **Fig. 5A**), indicating that asthmatics suffering from frequent SAEs required persistently higher doses of systemic steroids during the following years of treatment, even with maintained anti-asthmatic medications. Active interventional strategies are critical to reduce systemic steroid requirements for group 3 patients.

Longitudinal changes in FEV1 (%) and FEV1/FVC during the following 10 years of treatment were compared among the 3 groups as shown in **Fig. 5B and C**. The mean baseline values of FEV1 (%) and FEV1/FVC were 94.39% ± 1.78% and 82.99% ± 1.35% in the group 1, 86.76% ± 2.49% and 79.92% ± 1.30% in the group 2, and 74.43% ± 6.10% and 74.29% ± 2.48% in the group 3, with statistically significant differences. In addition, significantly different changes in FEV1 (%) and FEV1/FVC (%) with gradual declining curves were noted among the 3 groups; group 2/3 patients showed more gradual declines (group 3 patients showed the steeper slope than group 2 patients), while the group 1 patients showed a slightly decreasing tendency (which may have been attributed to aging as noted in healthy controls) ($P < 0.001$ for all).

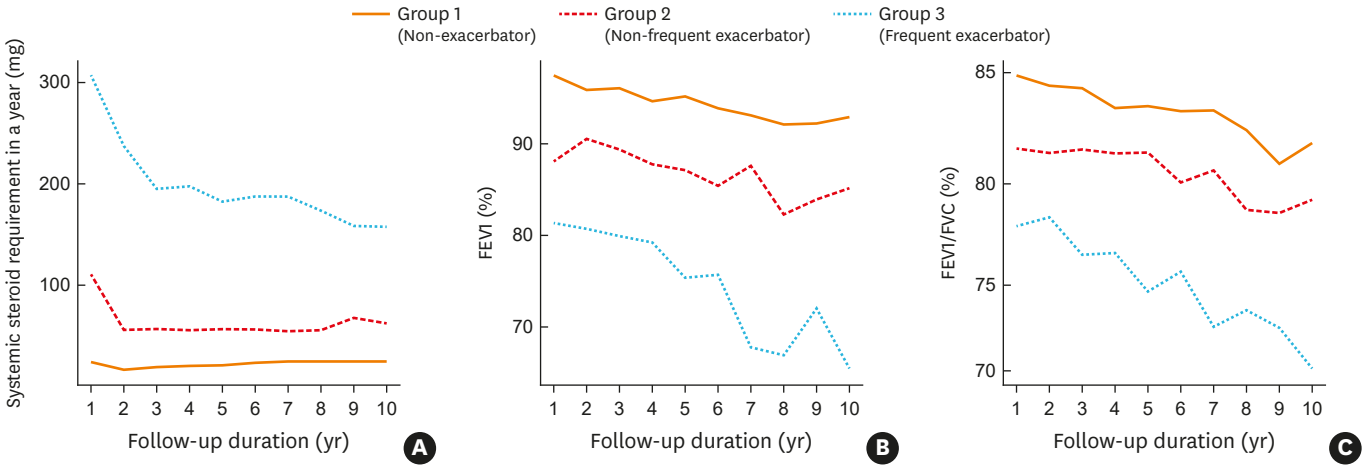

Fig. 5. Changes in systemic steroid requirements (mg) (A), FEV1 (%) (B), and FEV1/FVC (%) (C) in the 3 study groups during the 10 years of treatment. Group 1: asthmatics experienced no SAE during the initial 2 years of treatment; Group 2: asthmatics experienced 1–2 SAEs; Group 3, asthmatics experienced ≥ 3 SAEs. The mean systemic steroid requirements were presented and estimated by a generalized estimating equation.
FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; SAE, severe asthma exacerbation.

DISCUSSION

AEs are the most critical factor for asthma-associated morbidity and mortality and may contribute to the increased healthcare cost of asthmatics and government public health agencies.[14] Despite optimal guideline-directed management and irrespective of asthma severity, asthmatics experience AEs which are triggered by various factors.[14-16] Therefore, identifying prognostic factors for AE is essential for improving the management level of asthma in real-world practice. In the present study, we analyzed clinical parameters and laboratory findings that affected SAEs (requiring systemic steroids for > 7 days) in 5,058 adult asthmatics, who had maintained anti-asthmatic medications following the guidelines, and had been cared by asthma specialists in a single tertiary asthma center. The strength of the present study is utilizing the large scaled real-world data: 1) cross-sectional extensive laboratory findings (peripheral comprehensive data on clinical/laboratory findings including clinical characteristics, pulmonary function tests and sputum eosinophil counts and peripheral neutrophils/basophils/lymphocytes/platelet counts) and 2) longitudinal changes in systemic steroid uses and FEV1 (%) and FEV1/FVC (%) during the following 10 years of treatment. In addition, prognostic factors for SAE were analyzed according to the presence or frequency of SAEs and to peripheral eosinophilia (≥ 300/μL vs. < 300/μL), during the 2 treatment periods (the initial 2 years vs. the following 10 years). Therefore, the present study provides insights to identify factors predicting SAEs based on the previous histories of SAEs and the degree of eosinophilic inflammation in real-world practice of asthma specialists.

The rate of AEs per year has been reported to be 17% in a study analyzing UK EMR[8] and 59% in the population of the International Severe Asthma Registry.[17] In the present study, 28.64% of asthmatics experienced 1–2 SAEs and 8.51% showed ≥ 3 SAEs (frequent SAEs) during the initial 2 years of treatment. We used the definition of SAE as prescription of a prednisolone-equivalent dose of ≥ 15 mg per day for ≥ 7 days, which is longer prescription days of prednisolone compared to that previously reported (systemic corticosteroid uses for > 3 days are recommended for defining AE by the American Thoracic Society/European Respiratory Society).[18] We employed a real-world dataset in the present study for a long-term period (up to 10 years) to avoid the over-estimation of the SAE rate. According to the statement of the American Thoracic Society/European Respiratory Society,[18] the definition of SAE inevitably needs the systemic steroid prescription, therefore we used the unified definition for SAE with/without ER visit or hospitalization. In addition, compared to the previous studies on SAE predictors,[8,19] the present study included 2 time points: the initial 2 years vs. the following years in order to evaluate whether initial treatment outcome could affect the long-term outcomes (the risk of SAEs, systemic steroid requirements, and changes in lung functions). Given that SAEs more frequently developed during the initial treatment period, we analyzed initial prognostic factors (collected at the initial visit) to predict the SAE risk during the initial 2 years of treatment, and then analyzed long-term prognostic factors predicting the SAE risk during the following years of treatment, indicating that initial SAE risk factors could lead to a higher long-term SAE risk during the following years of treatment. These results emphasize the importance of evaluating ever-previous history of SAE at the initial visit and at each visit. Special attention should be paid to the management of asthmatics who have risk factors for SAE.

Consistent with the previous studies that determined the predictors of AE in patients with asthma[8,20,21] or severe asthma,[19] type 2/eosinophil inflammation (blood/sputum eosinophilia) was a key risk factor for AE in the present study. Peripheral blood/sputum eosinophil

counts (along with ECP levels) were significant predictors of SAE in asthmatics during the initial 2 years of treatment, and remained significant predictors for the risk or frequency of SAEs during the following 10 years of treatment, although they could be decreased after ICS treatment, and show variable changes according to symptom severity or medications. Considering that it is not easy to monitor sputum eosinophil counts, these results collectively imply that strict monitoring of peripheral eosinophil counts (with sputum eosinophil count, if possible) is critical for preventing SAEs in the long-term management of adult asthmatics.

Although the prevalence of AE is high in eosinophilic asthmatics as previously reported,[8,19,20] a substantial proportion of non-eosinophilic asthmatics (about 26%) experienced SAEs. In the present study, we performed subgroup analysis according to peripheral eosinophil counts (300/μL) to determine whether there are factors predicting SAEs different from peripheral eosinophil counts. Most of the SAE predictors listed in **Fig. 1** were replicated as significant factors (except sputum eosinophil counts) in patients with eosinophilic asthma, which may be attributed to the higher baseline levels of sputum eosinophil counts noted in patients with eosinophilic asthma; therefore, sputum eosinophil counts may affect the frequency of SAEs but not the risk of SAEs ($P = 0.020$; OR, 1.008) (data not shown). In patients with non-eosinophilic asthma, sputum eosinophils affected the frequency of SAEs, but peripheral eosinophil counts did not. This may be attributed to the treatment effect of ICSs which considerably decreased 2-year peripheral eosinophil counts in those with non-eosinophilic asthma. Since sputum eosinophils were not fully suppressed by ICSs, and thus remained in the sputum, they may affect the development of SAE.[22-24] Collectively, in terms of assessing eosinophilic inflammation, we suggest that both systemic (peripheral) and local (sputum) eosinophil counts be monitored for the prevention of SAEs in clinical practice, especially in asthmatics on the maintenance ICS therapy.

There is no consistency among studies in the role of total IgE as a predictor of AE.[19,25-27] Although the total IgE level has been shown to have a positive correlation with asthma[28,29] and a negative correlation with FEV1/FVC level,[30] the correlation between IgE level and AE is not conclusive. Several studies reported a lack of the correlation between the total IgE level and AE/asthma control status/disease severity.[26,27,31] Moreover, an inverse relationship between the serum total IgE level and the risk of AEs has been described in a study of factors associated with the frequency of AEs in Severe Asthma Research Program-3.[19] A recent study on the long-term predictors of poorly-controlled asthmatics demonstrated that higher total IgE levels were noted in patients with poorly-controlled persistent asthmatics than in other asthmatics.[25] Similarly, the present study showed that a higher level of serum total IgE was found to be a significant predictor of SAE; therefore, anti-IgE antibody therapy can be an effective option for preventing SAEs in asthmatics with less frequent SAEs.

Along with higher eosinophil counts and serum total IgE levels, specific IgE to Dp and Df, peripheral basophil/platelet counts were found to be associated with the risk of SAEs in the present study. Dp and Df are major allergens for allergic asthma, and asthmatics with elevated levels of specific IgE to Dp and Df may be considered as allergic asthma. Allergic asthma has been reported to have more benign course than non-allergic asthma.[32,33] Based on the results of previous reports, higher levels of specific IgE to Dp and Df can be used to predict lower risk of SAE. Previous studies reported positive associations between increased sputum basophil counts in adult asthmatics as well as increased peripheral basophil counts in childhood asthmatics and previous SAEs.[34-36] Although basophils are rare and account for <1% of leukocytes in peripheral blood, they have been considered an important effector

cell in asthma pathogenesis via IgE, IL-25 and IL-33.[37,38] In this context, increased levels of peripheral basophil counts can be applicable in real-world clinical practice as a predictor for SAE. In addition, our results provide indirect evidence that anti-IgE and anti-IL-33 antibodies may decrease the frequency of SAEs by acting with basophils. Platelets have also been found to contribute to the pathogenesis of asthma by secreting a wide range of inflammatory mediators and by facilitating granulocyte recruitment and activation.[39,40] Platelets promote eosinophil recruitment to the airways, and the platelet-eosinophil complex are increased in patients with allergic asthma.[41] To the best of our knowledge, this is the first study to report that higher peripheral platelet counts could be a significant risk factor predicting SAEs in a large cohort of adult asthmatics. Based on these results, drugs targeting platelets can be a novel promising therapeutic option for preventing SAE in patients with uncontrolled asthma.

The present study has several limitations. First, because all the study subjects were enrolled from a single tertiary center, it is likely that our results represent prognostic factors for SAE in patients with uncontrolled or severe asthma rather than in those with mild-moderate asthma seen in primary care settings. However, considering that all the study subjects were treated by the experienced asthma specialists consistently, our clinical and laboratory data are highly standardized and qualified. Secondly, although the present study was a real-world clinical study that utilized the extracted EMR data, text information such as smoking status or body mass index were not available in the EMR. In addition, the comorbidities extracted from EMR by ICD-10 code in a single tertiary center can make the skewed results. Therefore, we focused on the risk factors of SAE regarding the numeric data such as demographic/laboratory data and pulmonary function test results which can be accurately transformed from EMR data.

In conclusion, we demonstrated relevant risk factors for SAE (female sex, higher peripheral eosinophil/basophil counts, and lower FEV1) based on a large-scale cross-sectional/longitudinal comprehensive data, which can be easily obtained and used to reduce the future risk in everyday practice of adult asthmatics.

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SUPPLEMENTARY MATERIALS

Supplementary Table S1

Prognostic factors for predicting the frequency of severe asthma exacerbation during initial 2 years' treatment period

Click here to view

Supplementary Table S2

Receiver operating characteristic analysis of prognostic factors for predicting the risk of severe asthma exacerbation during initial 2 years' treatment period

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Supplementary Table S3

Clinical characteristics of patients with eosinophilic and those with non-eosinophilic asthma according to the frequency of SAE

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Supplementary Table S4

Prognostic factors for predicting the risk of severe asthma exacerbation for 10 years of treatment

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Supplementary Fig. S1

Numbers of asthmatics (A) and the levels of peripheral eosinophil counts (B) of 3 study groups during 10 years of treatment. Group 1: asthmatics experienced no SAE during the initial 2 years of treatment; Group 2: asthmatics experienced 1–2 SAEs; Group 3: asthmatics experienced ≥ 3 SAEs. The mean systemic steroid requirements were presented and estimated by a generalized estimating equation.

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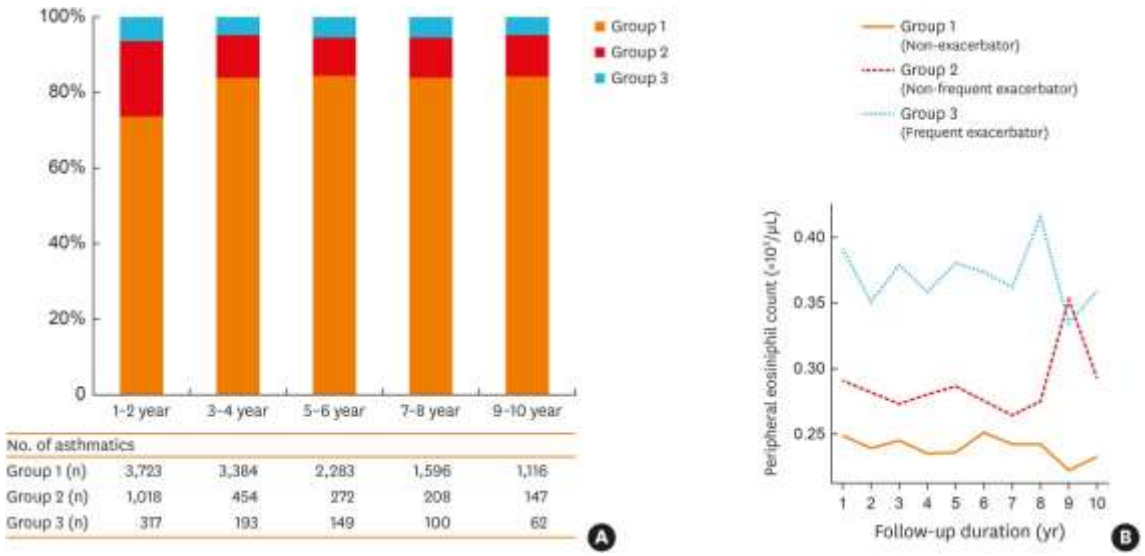

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