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Youngsoo Lee, MD, Youjin Park, PharmD, Chungsoo Kim, PharmD, Eunyoung Lee, MS, Hyun Young Lee, PhD, Seong-Dae Woo, MD, Seng Chan You, MD, Rae Woong Park, MD, PhD, Hae-Sim Park, MD, PhD

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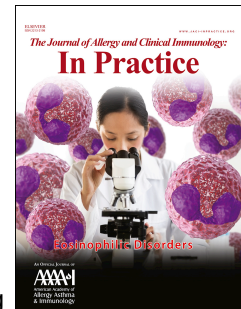
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Longitudinal outcomes of severe asthma: real-world evidence of multidimensional analyses

Youngsoo Lee, MD,^{1*} Youjin Park, PharmD,^{2*} Chungsoo Kim, PharmD,² Eunyoung Lee, MS,^{3,4} Hyun Young Lee, PhD,⁵ Seong-Dae Woo, MD,¹ Seng Chan You, MD,³ Rae Woong Park, MD, PhD,^{2,3} and Hae-Sim Park, MD, PhD^{1†}

*Youngsoo Lee and Youjin Park contributed equally as co-first authors.

¹Department of Allergy & Clinical Immunology, Ajou University School of Medicine, Suwon, Korea.

²Department of Biomedical Sciences, Ajou University Graduate School of Medicine, Suwon, Korea.

³Department of Biomedical Informatics, Ajou University School of Medicine, Suwon, Korea. ⁴Office of Biostatistics, Medical Research Collaboration Center, Ajou Research Institute for Innovative Medicine, Ajou University Medical Center, Suwon, Korea. ⁵Department of Statistics, Clinical Trial Center, Ajou University Medical Center, Suwon, Korea.

Youngsoo Lee¹ (Email: thejadelight@gmail.com)

Youjin Park² (Email: dbwls5223@ajou.ac.kr)

Chungsoo Kim² (Email: ted9219@gmail.com)

Eunyoung Lee^{3,4} (Email: eylee@aumc.ac.kr)

Hyun Young Lee⁵ (Email: ajoustat@gmail.com)

Seong-Dae Woo¹ (Email: nextera@naver.com)

Seng Chan You³ (Email: applegna@gmail.com)

Rae Woong Park^{2,3} (Email: veritas@ajou.ac.kr)

Hae-Sim Park¹ (Email: hspark@ajou.ac.kr)

[†]**Corresponding Author:** Hae-Sim Park

Department of Allergy & Clinical Immunology, Ajou University School of Medicine

164 Worldcup-ro, Yeongtong-gu, Suwon 16499, Korea

E-mail: hspark@ajou.ac.kr

Tel: +82 31 219 5000

Fax: +82 31 216 6380

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Abstract

Background: There have been few studies assessing long-term outcomes of asthma based on regular follow-up data.

Objective: We aimed to demonstrate clinical outcomes of asthma by multidimensional analyses of a long-term real-world database and a prediction model of severe asthma using machine learning.

Methods: The database included 567 severe and 1,337 nonsevere adult asthmatics, who had been monitored during a follow-up of up to 10 years. We evaluated longitudinal changes in eosinophilic inflammation, lung function, and the annual number of asthma exacerbation (AE) using linear mixed effects model. Least absolute shrinkage and selection operator logistic regression was used to develop a prediction model for severe asthma. Model performance was evaluated and validated.

Results: Severe asthmatics had higher blood eosinophil ($P = 0.020$) and neutrophil ($P < 0.001$) counts at baseline than nonsevere asthmatics; blood eosinophil counts showed significantly slower declines in severe asthmatics than nonsevere asthmatics throughout the follow-up ($P = 0.009$). Severe asthmatics had a lower level of forced expiratory volume in 1 second ($P < 0.001$), which declined faster than nonsevere asthmatics ($P = 0.033$). Severe asthmatics showed a higher annual number of severe AE than nonsevere asthmatics. The prediction model for severe asthma consisted of 17 variables, including novel biomarkers.

Conclusions: Severe asthma is a distinct phenotype of asthma with persistent eosinophilia, progressive lung function decline, and frequent severe AEs even on regular asthma medication. We suggest a useful prediction model of severe asthma for research and clinical purposes.

Key words: severe asthma; clinical outcome; asthma exacerbation; eosinophil; inflammation; real-world evidence

Abbreviations

AE: asthma exacerbation

FEV1: forced expiratory volume in 1 second (%)

OMOP CDM: the Observational Medical Outcome Partnership Common Data Model

ICD-10: the 10th revision of the International Statistical Classification of Diseases and Related Health

ICS: inhaled corticosteroid

LABA: long-acting β_2 -agonist

CS: corticosteroid

SAE: severe asthma exacerbation

HiEP: highly exacerbation-prone

EP: exacerbation-prone

LMM: linear mixed effects model

Lasso: least absolute shrinkage and selection operator

Highlights box**1. What is already known about this topic?**

Severe asthmatics are suffering from frequent respiratory symptoms and acute asthma exacerbations and are at risk of rapid lung function decline, which is attributed to a higher level of eosinophilic airway inflammation.

2. What does this article add to our knowledge?

This study presents real-world longitudinal data from severe asthmatics concerning eosinophilic inflammation, asthma exacerbation, and lung function, which have hardly been addressed. Based on the observation, a novel prediction model for severe asthma using a machine learning technique was established.

3. How does this study impact current management guidelines?

The study results emphasized that earlier and more active treatment strategies are needed for severe asthmatics. The prediction model of severe asthma in our study may help identify and better manage severe asthmatics.

INTRODUCTION

Asthma is a chronic inflammatory disease of the airways affecting more than 300 million people worldwide [1]. Remarkable advances in asthma treatment over the last decade enabled many asthmatics to maintain well-controlled status [2]. However, some asthmatics are still suffering from persistent symptoms and asthma exacerbations (AEs) despite the treatment. They are referred to as severe asthmatics, who are a minority of the overall asthmatics but are responsible for more than half of the economic burdens of asthma [3]. There are 2 major components (airway eosinophilia and bronchoconstriction) in the pathogenesis of asthma [4]. Patients with severe asthma have higher blood/sputum eosinophil counts and lower levels of forced expiratory volume in 1 second (FEV1), both of which are closely related with frequent AEs even treated by multiple asthma medications [5].

Variable unmet needs exist in severe asthma due to the heterogeneity in epidemiology, pathophysiology, diagnosis, treatment, and prognosis. Although several large cohort studies of severe asthma have been performed, there is still much more to be disclosed [6–8]. Many efforts have recently been made to develop a prediction model for other acute or chronic diseases by applying machine learning techniques using clinical laboratory measurements of patients. However, there have hardly been real-world studies applying these techniques to detect severe adult asthmatics and the potential risk factors of severe asthma [9, 10].

We aimed to determine the differences in the clinical characteristics between severe and nonsevere asthmatics treated in a single tertiary hospital in Korea, using cross-sectional and longitudinal analyses with the linear mixed effects model (LMM) based on a large-scale database. In addition, the predictive model for severe asthma was implemented by applying a machine learning technique.

METHODS

Data source

It is a prospective study of adult asthmatics who had been treated by asthma specialists for 8.56 ± 5.22

years in the Department of Allergy and Clinical Immunology in Ajou University Medical Center (Suwon, South Korea). The study patients were informed that their medical information would be collected after signing the consent form at the first visit to our clinic. Our Institutional Review Board approved this study (AJIRB–MED–MDB–19–100).

We established a database named ICARUS (Immune/Inflammatory Disease Common Data Model Augmentation for Research Union System) for the in-depth analyses of refractory immune diseases. It contains real-world clinical data on biomarkers and lung functions from the medical records of patients with immune/inflammatory diseases, implemented with the Observational Medical Outcome Partnership Common Data Model (OMOP CDM) [11, 12]. The OMOP CDM incorporates data from heterogeneous healthcare databases in terminology and overall structure, which promotes research to improve human health.

Complete blood cell count with differentials (including absolute eosinophil counts), renal and liver function test, electrolytes, uric acid, albumin, erythrocyte sedimentation rate, and urinalysis were done at baseline. The serum levels of total IgE, specific IgE to house dust mite and environmental pollens, and eosinophil cationic protein were measured using ImmunoCAP® (ThermoFisher, Waltham MA, USA). The results of allergic skin prick tests to common inhalant allergens were also included. Atopy was defined according to the 10th revision of the International Statistical Classification of Diseases and Related Health (ICD–10) codes containing “allergic” or “atopic” or serum specific IgE level to a common inhalant allergen of over 0.35 kU/L [13]. All patients enrolled in the present study underwent pulmonary function and methacholine challenge tests as previously described [14, 15].

Definitions

The time point when asthma medications were first prescribed to each patient was designated as the baseline of this study. Asthmatics were defined as follows: (1) the presence of ICD–10 codes for asthma (J45–46) at baseline (2) the prescription of asthma medications for longer than 3 months from

baseline to index date (a year after baseline). Clinical information for up to 10 years after baseline was collected from the asthmatics. The asthma medications were as follows: short-acting β_2 -agonists, inhaled corticosteroids (ICS) alone, ICS with long-acting β_2 -agonists (ICS-LABA), leukotriene receptor antagonists, long-acting muscarinic antagonists, xanthine derivatives, and systemic corticosteroids (CS). Severe asthmatics were defined as (1) asthmatics being treated by medium- to high-dose ICS-LABA within 2 years after baseline date and (2) having more than 4 events of severe AEs (SAEs) within 2 years after baseline. Asthmatics who did not fulfill the criteria were defined as nonsevere asthmatics. Asthmatics who had been treated with any type 2-targeting biologics (omalizumab, mepolizumab, reslizumab, and dupilumab) for ≥ 6 months before baseline were excluded. SAE was defined as being prescribed systemic corticosteroids (oral prednisolone ≥ 15 mg per day or its equivalent for 3 consecutive days) or visiting the emergency or outpatient department due to worsened asthma symptoms. In addition, to characterize patients who had more frequent SAEs, we classified severe asthmatics as 2 groups based on the annual number of SAE within the first year after baseline: the highly exacerbation-prone group (HiEP group, annual number of SAE ≥ 4) and the exacerbation-prone group (EP group, $2 \leq$ annual number of SAE < 4). Severe asthmatics were also classified as severe eosinophilic asthma (baseline blood eosinophil count $\geq 300/\mu\text{L}$) and severe non-eosinophilic asthma (baseline blood eosinophil count $< 300/\mu\text{L}$). Late-onset asthma was defined by the age of asthma onset ≥ 40 years [16].

Comorbidities were defined as the presence of at least one ICD-10 code of the following during the study period: rhinitis/chronic rhinosinusitis (J00, J02, J30-J33), allergic conjunctivitis (H10), atopic dermatitis (L20, L23, L25), urticaria/angioedema (D69, D84, L27, L29, L50, T78), hypertension (I10), diabetes (E10-E14), osteoporosis (M80-82), depression (F32, F33), arthritis (M05-M09, M13), gastroesophageal reflux disease (GERD) (K21), and ischemic heart disease (I20-I25, except I20.1).

Multidimensional analysis

Cross-sectional analyses compared baseline characteristics, inflammatory profiles, comorbidities, and

the frequency of asthma medication of severe and nonsevere asthmatics. Continuous variables were assessed using student's t test or Wilcoxon-signed rank test after normality validation by Shapiro-Wilk test. Categorical variables were compared using the χ^2 test. A P value of < 0.05 was considered statistically significant.

Longitudinal analyses were conducted to assess the differences in long-term changes in the measurement values, medication use, and SAE between severe and nonsevere asthmatics. The LMM was used to assess the differences in long-term parameters (FEV1, blood eosinophil and neutrophil counts, and sputum inflammatory cell counts). It is suitable for real-world studies as it accounts for irregularly dispersed longitudinal data with different time points. In the LMM, we included each measurement, group, time, and time by group interaction as fixed effects and random intercept and slope as random effects, with the variance-covariance structures of autoregression (1). The best-fitting model was chosen with the smallest Bayesian Information Criterion. If normality was not assumed, data were log-transformed. To compare the annual number of SAE, we calculated the average number of SAEs in each year. The long-term pattern of the frequency of asthma medications in severe and nonsevere asthmatics for up to 10 years was demonstrated.

The prediction model utilizing a machine learning technique

Lasso (least absolute shrinkage and selection operator) logistic regression was used to develop a prediction model for severe asthma and to determine which baseline measurements and demographic data could differentiate severe and nonsevere asthmatics. It is a type of regression analysis for predictor selection in order of predictive strength and regularization. It shrinks coefficients of parameters to zero and minimizes overfitting data [17]. After reviewing the literature, predictors of severe asthma were chosen from clinically available data, including demographic characteristics, parameters of baseline blood/sputum/urine, and lung functions [18–22]. All continuous variables were normalized by Min–Max method. The data were randomly split into the training set (75% of the data) and the test set (25%) for internal validation of the model. The prediction model was built using Lasso

logistic regression at 3-fold cross-validation on the training set. The discriminability of the model was assessed by the receiver operating characteristic curves of the training and test sets. The effect of variables was confirmed by the covariate coefficients. All analyses were performed using R (version 3.5.1, R Project for Statistical Computing, Vienna, Austria).

RESULTS

Study subjects

The ICARUS database included 2,228 asthmatics, who had been followed up for longer than 2 years from 1994 to 2017 (Figure 1). Among them, 276 with no asthma medications and 48 who had been treated with any type 2-targeting biologics for longer than 6 months were excluded from the study. A total of 1,904 asthmatics were enrolled; 567 and 1,337 patients were classified as severe and nonsevere asthmatics, respectively. Among severe asthmatics, the HiEP and EP groups consisted of 189 and 378 severe asthmatics, respectively. With the exclusion of 88 patients whose initial blood eosinophil counts were not available, the number of severe eosinophilic and non-eosinophilic asthmatics were 221 and 258, respectively.

Comparison of demographic and baseline clinical characteristics between severe and nonsevere asthmatics

The demographic and baseline clinical characteristics were compared between severe and nonsevere asthmatics and between the HiEP and EP groups (Table 1). Severe asthmatics were older, had a longer duration of asthma, and showed a higher proportion of females (all $P < 0.001$). Baseline body mass index was higher in severe asthmatics ($P = 0.023$). Baseline FEV1(%) and FEV1/FVC were significantly lower in severe asthmatics (all $P < 0.001$). The onset age of asthma and the proportion of late-onset asthma were higher in severe asthmatics ($P < 0.001$ and $P = 0.055$, respectively). The HiEP group demonstrated a shorter asthma duration and a lower baseline FEV1/FVC ($P = 0.033$ and $P <$

0.001, respectively).

Baseline blood and sputum eosinophil counts tended to be higher in severe asthmatics than in nonsevere asthmatics, which was not statistically significant. Baseline blood neutrophil counts (not sputum neutrophils; $P = 0.473$) were higher in severe asthmatics than in nonsevere asthmatics ($P < 0.001$) (Table 2). Severe asthmatics had lower rates of allergic comorbidities than nonsevere asthmatics (Table 3): atopy, rhinitis/chronic rhinosinusitis, allergic conjunctivitis, atopic dermatitis, and urticaria/angioedema (all $P < 0.001$). Hypertension ($P = 0.006$), diabetes mellitus ($P = 0.012$), osteoporosis ($P = 0.001$) and GERD ($P = 0.005$) were more prevalent in severe asthmatics.

Longitudinal changes in inflammatory profiles and lung function

The LMM analyses showed that blood eosinophil counts, sputum eosinophils (%), and neutrophil counts decreased during the follow-up, with negative coefficients of time effect. Severe asthmatics showed higher blood eosinophil and neutrophil counts than nonsevere asthmatics ($P = 0.020$ and $P < 0.001$, respectively), but not for sputum eosinophils (%) ($P = 0.079$). Blood eosinophil counts of severe and nonsevere asthmatics diverged ($P = 0.009$), but the changes in sputum eosinophil (%) and blood neutrophil counts between severe and nonsevere asthmatics throughout the follow-up did not exhibit statistical significance ($P = 0.556$ and $P = 0.113$, respectively) (Figure 2 and Table E1).

Figure 3 shows comparisons of longitudinal changes in FEV1(%) for up to 10 years between severe and nonsevere asthmatics as analyzed by the LMM. Baseline FEV1(%) was lower in severe asthmatics than in nonsevere asthmatics ($P < 0.001$), although there were significant differences in FEV1(%) decrease throughout the follow-up ($P = 0.033$) (Table E1 and Table E2). No significant differences were noted in FEV1(%) decreases between the HiEP and EP groups ($P = 0.738$) and between severe eosinophilic and non-eosinophilic asthmatics throughout the follow-up ($P = 0.256$) (Table E1 and Figure E1).

Comparison of medication use and the annual number of SAE between severe and nonsevere asthmatics

The changes in the annual number of SAE for up to 10 years were compared between severe and nonsevere asthmatics and between the HiEP and EP groups (Figure 4 and Table E3). Severe asthmatics had a higher annual number of SAE than nonsevere asthmatics. They persistently experienced SAEs more than once a year despite asthma medications, whereas nonsevere asthmatics experienced less than once a year during the study period. In addition, the annual number of SAE remained higher in the HiEP group (higher than once a year) than in the EP group (once a year) during the follow-up of the last few years. The changes in the annual number of SAE for severe eosinophilic and non-eosinophilic asthmatics and nonsevere asthmatics are presented in Figure E2.

All the asthma medications, including medium- to high-dose ICS-LABA and systemic CS, were prescribed more frequently in severe asthmatics than in nonsevere asthmatics (all $P < 0.001$) (Figure 5 and Table E4). The cumulative dose of systemic CS for 2 years after baseline was also significantly higher in severe asthmatics than in nonsevere asthmatics and in the HiEP group than in the EP group (all $P < 0.001$). The frequency of asthma medications in severe eosinophilic and non-eosinophilic asthmatics are shown in Figure E3.

The prediction model of severe asthma

Predictive factors for severe asthma were identified by using the Lasso logistic regression model (Figure 6 and Table E5). They included baseline blood leukocyte count, age, blood eosinophil count, urine leukocyte count, platelet count, blood urea nitrogen, serum uric acid, blood basophil percentage, and female sex. The lower levels of FEV1(%), lower serum specific IgE levels to American and European house dust mites, and lower urine erythrocyte and blood lymphocyte counts were suggested to contribute to severe asthma. The area under the curve of the training and test sets were comparable (0.703 for the training set, 0.704 for the test set).

DISCUSSION

The present study demonstrated long-term clinical outcomes of 567 severe asthmatics for up to 10 years about bronchoconstriction, airway inflammation, and the annual number of SAE, as compared to 1,337 nonsevere asthmatics. Severe asthmatics were older and had a longer duration of asthma, a higher proportion of females, and a greater body mass index. They were more likely to suffer from comorbid disorders. They had lower FEV1(%) at baseline, which declined more steeply despite higher doses of ICS and systemic CS and the higher annual number of SAE. Taken together, this is the first real-world evidence for the long-term clinical outcomes of severe and nonsevere asthmatics by multidimensional analyses, suggesting that new therapeutic interventions are critical for improving the clinical outcomes of severe asthma. The prediction model of severe asthma implemented in this study may help provide new insights into the management of severe asthma.

Our study showed the differences in long-term outcomes between severe and nonsevere asthmatics: reductions in FEV1(%), blood and sputum eosinophil counts, and the annual number of SAE. FEV1(%) declined more steeply despite asthma medications in severe asthmatics, while it decreased by the ordinary rate in nonsevere asthmatics (approximately 22.4 mL/year) [23]. The increased numbers of blood and sputum eosinophils did not fall to zero by medium- to high-dose ICS/systemic CS in severe asthmatics, while they fell to zero in nonsevere asthmatics [24, 25]. Although both severe and nonsevere asthmatics experienced SAEs during the first year of treatment, severe asthmatics experienced more frequent SAEs than nonsevere asthmatics throughout the follow-up. It suggests that airway inflammation may not be sufficiently suppressed within a year and provides the rationale for the optimal use of long-term maintenance of asthma medications. Since severe asthmatics with uncontrolled eosinophilic airway inflammation suffered from frequent SAEs that accelerated lung function declines, more active interventions, such as biologics targeting type 2 inflammation, are required to prevent SAEs and lung function declines in severe asthmatics [26, 27].

Eosinophilic airway inflammation is major pathophysiology of severe asthma [28, 29]. Blood

eosinophil count has been widely used as a useful biomarker for eosinophilic airway inflammation, and its clinical implications have been reported in the clinical studies [30–32]. In these studies, IL-5-targeting biologics effectively reduced AEs and eosinophilia, implying that blood eosinophils may play an important role in the clinical severity and pathogenesis of airway inflammation. However, the cutoff values of blood eosinophil count defining severe eosinophilic asthma were variable by each clinical trial [33, 34]. Although sputum eosinophil count is expected to reflect airway inflammation and has been considered a biomarker for severe asthma, several studies suggested that blood eosinophil counts were more suitable to define severe eosinophilic asthma [35, 36]. In our study, blood eosinophil counts remained higher and showed a slower decline in severe asthmatics than in nonsevere asthmatics. Sputum eosinophil (%) was not significantly different between severe and nonsevere asthmatics. It suggests that blood and sputum eosinophil count may partly reflect airway inflammation and clinical severity in asthma. We observed that no difference was found in FEV1(%) decline, the annual number of SAE, or the frequency of asthma medication between severe eosinophilic and non-eosinophilic asthmatics (Table E3 and Table E4). Nevertheless, we found that blood neutrophil counts decreased in severe and nonsevere asthmatics but remained higher in severe asthmatics than in nonsevere asthmatics throughout the follow-up. The role of neutrophils in asthma has not been completely elucidated, even though a few studies have reported neutrophilic inflammation and eosinophil–neutrophil interactions could play a role in severe asthma [37, 38]. Our findings suggest that activated eosinophils are critical for developing severe asthma, but further studies are needed to determine the importance of other effector cells in asthma, including neutrophils or structural components.

The remarkably higher annual number of SAE in severe asthmatics is also noteworthy. The annual number of SAE in severe asthmatics decreased in the first several years of treatment but remained higher than once a year afterward. In the HiEP group, the annual number of SAE was persistently higher and more variable throughout the study period. The HiEP group had lower FEV1(%) and FEV1/FVC levels, and higher basophil and platelet counts than the EP group. There have been a few studies suggesting that activated mast cells may play a role in severe asthmatics refractory to

treatment and that platelet–leukocytes aggregates are involved in type 2 airway inflammation [39, 40]. The present study also showed that patients with variable comorbidities and related poly-medications had poor clinical outcomes, especially in the elderly population, indicating that comorbidities should be considered in the management of severe asthma [41]. Taken together, AE leads to persistent airway inflammation/structural changes in the airways, both of which are very heterogeneous in severe asthma. The exact mechanisms of AE according to different inflammatory phenotypes (neutrophilic or pauci-granulocytic phenotypes) and the exact role of mast cells, basophils, and platelets remain to be determined.

Our prediction model of severe asthma proposed that multiple components would be related to the pathogenesis of severe asthma. Previous studies showed that severe asthmatics were older and more likely to be female, which is in line with our results [20]. Our prediction model further suggested several potential biomarkers and new targets of severe asthma, which have not been detected in some previous studies: increased platelets and basophil counts and higher blood urea nitrogen and uric acid levels. Platelet–eosinophil aggregates were reported to participate in eosinophil activation in patients with aspirin-exacerbated respiratory disease [42, 43]. Basophil is considered as a key effector cell of type 2 airway inflammation [44]. Uric acid was suggested to induce type 2 inflammation in a mouse asthma model [45]. Although further studies in other cohorts are required, we suggest that our prediction model may help identify new diagnostic and therapeutic targets of severe asthma.

There are some limitations to our study. First, since asthmatic patients were enrolled at a single tertiary hospital, their clinical characteristics may not represent the general population of asthmatics.

However, our asthma center is the largest one in our country to which many severe asthmatics are being referred, and the prevalence of severe asthma was estimated at 43.4% in our cohort, which is higher than that of a previous study [46]. In this study, patients had been treated by the same team of asthma specialists during a period of up to 10 years with the same treatment guidelines; therefore, our prediction model of severe asthma could be appropriate for assessing the longitudinal outcomes of severe asthmatics with close monitoring of SAE, comorbidities, and laboratory/spirometry findings in

real-world clinical practice. Secondly, the fraction of exhaled nitric oxide was not included in our study because it has been approved since 2018 in Korea. Although considered a surrogate for the measurement of eosinophilic inflammation, it is neither specific for asthma nor reflective of non-eosinophilic airway inflammation [47, 48]. Thirdly, this is an observational study, and some patients lost their follow-up, or some clinical data were missing. However, this limitation is inevitable due to the nature of real-world data. Notwithstanding these limitations, we successfully established a real-world database of severe asthma with the largest and longest scale and reported significant differences in clinical outcomes between severe and nonsevere asthmatics. Additional translational research is needed to validate these findings, thereby resolving the unmet needs for new therapeutic targets of severe asthma.

In conclusion, severe asthma can be regarded as a distinct phenotype of asthma with persistent eosinophilia and progressive lung function decline even on regular asthma medications. We suggest a useful prediction model of severe asthma for research and clinical purposes.

Author contributions: Literature search: all authors; Study design: all authors; data analysis: Youjin Park, Chungsoo Kim, Eunyoung Lee, Hyun Young Lee, and Seng Chan You; data interpretation: all authors; writing: Youngsoo Lee, Youjin Park; Rae Woong Park and Hae-Sim Park supervised all the process.

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FIGURE LEGENDS

Figure 1. Study populations.

HiEP, highly exacerbation-prone; EP, exacerbation-prone.

Figure 2. Longitudinal changes in inflammatory parameters during a follow-up of up to 10 years as estimated by the linear mixed effects model in severe (*solid line with closed circle*) and nonsevere (*dashed line with open circle*) asthmatics. (A) blood eosinophil counts, (B) sputum eosinophil (%), and (C) blood neutrophil counts.

Error bars indicate 95% confidence interval.

Figure 3. Longitudinal changes in FEV1(%) during a follow-up of up to 10 years as estimated by the linear mixed effects model. (A) severe (*solid line with closed circle*) and nonsevere (*dashed line with open circle*) asthmatics, (B) the highly exacerbation-prone (HiEP, *bold black line with closed triangle*) and exacerbation-prone (EP, *grey line with open triangle*) groups.

Error bars indicate 95% confidence interval. The slope of severe asthmatics (the sum of the parameters corresponding to the time and time $\times$ cohort) is -0.365 (-0.072 to -0.293), and the slope for nonsevere asthmatics (the parameter corresponding to the time) is -0.072 . The slope of the HiEP group (the sum of the parameters corresponding to the time and time $\times$ cohort) is -0.402 (-0.320 to $+0.082$), and the slope for the EP group (the parameter corresponding to the time) is -0.320 . FEV1, forced expiratory volume in 1 second (%).

Figure 4. Annual number of severe asthma exacerbation during a follow-up of up to 10 years. (A) Severe asthmatics (*grey bar with closed circle*), (B) nonsevere asthmatics (*white bar with white circle*). The highly exacerbation-prone (*grey bar with closed triangle*) and exacerbation-prone (*white bar with open triangle*) groups. Error bars indicate 95% confidence interval. SAE, severe asthma exacerbation.

Figure 5. Frequency of asthma medications during a follow-up of up to 10 years. (A) severe asthmatics, (B) nonsevere asthmatics, (C) the highly exacerbation-prone group, (D) the exacerbation-prone group.

Systemic steroids (*bold line*), high-dose ICS–LABA (*closed square*), medium-dose ICS–LABA (*open circle*), SABA (*dotted line*).

ICS, inhaled corticosteroids; LABA, long-acting β_2 -agonists; SABA, short-acting β_2 -agonists.

Figure 6. The prediction model of severe asthma. (A) Eighteen variables included in the prediction model, (B) receiver operating curves of the training (*solid line*) and test (*dotted line*) sets.

Der p, *dermatophgoides pteronyssinus*; *der f*, *dermatophagoides farinae*; AUC, area under the curve.

TABLES

Variable	Severe asthmatics			Nonsevere asthmatics (n=1337)	P value*	P value [†]
	Total (n=567)	HiEP group (n=189)	EP group (n=378)			
Female, %	62.6	66.7	60.6	52.5	< 0.001	0.187
Age, years	43.94 ± 14.16	43.94 ± 14.60	43.94 ± 13.95	36.29 ± 14.21	< 0.001	0.991
Asthma onset age, years	36.44 ± 13.17	37.42 ± 14.23	35.85 ± 12.51	32.07 ± 14.92	< 0.001	0.405
Years of follow-up	10.32 ± 5.51	9.61 ± 5.65	10.67 ± 5.41	6.68 ± 4.72	< 0.001	0.033
Late onset asthma [‡] , %	40.4	45.2	37.4	31.5	0.055	0.311
Smoking history	241	95	146	327		
Current or ex-smoker, %	108 (44.8)	47 (49.5)	61 (41.8)	188 (57.5)	0.004	0.298
Baseline BMI, kg/m ²	24.30 ± 4.05	23.91 ± 4.08	24.50 ± 4.05	23.71 ± 3.55	0.023	0.075
Baseline FEV1, %	85.65 ± 19.67	81.57 ± 24.74	86.95 ± 17.63	94.29 ± 18.62	< 0.001	0.152
Baseline FEV1/FVC	80.97 ± 10.06	74.68 ± 12.70	82.45 ± 8.74	85.05 ± 9.13	< 0.001	< 0.001
Baseline PC ₂₀ , mg/mL	8.30 ± 13.44	5.41 ± 9.42	9.84 ± 14.95	9.68 ± 16.51	0.163	0.004

Table 1. Baseline clinical characteristics of severe and nonsevere asthmatics and the highly exacerbation-prone and exacerbation-prone groups

Data are presented as mean ± SD or n (%).

HiEP, highly exacerbation-prone; EP, exacerbation-prone; BMI, body mass index; FEV1, forced expiratory volume in 1 second (%); FVC, forced vital capacity (%); PC₂₀, provocative concentration of methacholine inducing a fall of 20% decline in FEV1(%).

*Comparison between severe and nonsevere asthmatics.

[†]Comparison between the HiEP and EP groups.

Table 2. Baseline laboratory profiles of severe and nonsevere asthmatics and the highly exacerbation-prone and exacerbation-prone groups

Variable	Severe asthmatics			Nonsevere asthmatics (n=1337)	P value*	P value [†]
	Total (n=567)	HiEP group (n=189)	EP group (n=378)			
Total IgE, kU/L	431.16 ± 696.93	383.42 ± 636.48	449.54 ± 719.03	439.78 ± 673.28	0.047	0.429
Der <i>p</i> -specific IgE, kU/L	8.50 ± 19.13	8.10 ± 18.45	8.63 ± 19.38	17.99 ± 25.95	< 0.001	0.497
Der <i>f</i> -specific IgE, kU/L	10.27 ± 21.28	10.54 ± 22.41	10.18 ± 20.92	23.20 ± 30.54	< 0.001	0.381
Skin prick test						
Positive to <i>der p</i>	92 (28.6)	22 (27.8)	70 (28.8)	477 (53.4)	< 0.001	0.984
Positive to <i>der f</i>	101 (31.3)	24 (28.9)	77 (32.1)	509 (58.0)	< 0.001	0.690
Blood eosinophil count, /μL	413.37 ± 565.00	429.45 ± 439.18	404.30 ± 610.88	382.06 ± 387.44	0.901	0.710
Blood neutrophil count, /μL	4742.07 ± 2562.62	5159.48 ± 3272.21	4566.13 ± 2177.34	4200.14 ± 1995.03	< 0.001	0.092
Blood basophil, %	0.61 ± 0.36	0.57 ± 0.36	0.62 ± 0.36	0.59 ± 0.31	0.848	0.053
Platelet count, 10 ³ /μL	266.07 ± 63.60	274.74 ± 65.56	262.30 ± 62.41	261.78 ± 63.01	0.151	0.059
Sputum eosinophils, %	43.74 ± 35.20	46.68 ± 38.11	42.83 ± 34.33	38.09 ± 34.31	0.068	0.397
Sputum neutrophils, %	58.59 ± 32.65	57.56 ± 34.70	58.94 ± 32.00	60.55 ± 31.93	0.473	0.794

Data are presented as mean ± SD or n (%).

HiEP, highly exacerbation-prone; EP, exacerbation-prone; *Der p*, *dermatophagoides pteronyssinus*; *Der f*, *dermatophagoides farinae*.

*Comparison between severe and nonsevere asthmatics.

[†]Comparison between the HiEP and EP groups.

Table 3. Baseline comorbidities of severe and nonsevere asthmatics and the highly exacerbation-prone and exacerbation-prone groups

Comorbidity	Severe asthmatics			Nonsevere asthmatics (n=1337)	P value*	P value [†]
	Total (n=567)	HiEP group (n=189)	EP group (n=378)			
Atopy	420 (74.1)	139 (73.5)	281 (74.3)	1108 (82.9)	< 0.001	0.919
Allergic rhinitis/chronic rhinosinusitis	378 (66.7)	125 (66.1)	253 (66.9)	1038 (77.6)	< 0.001	0.850
Allergic conjunctivitis	94 (16.6)	27 (14.3)	67 (17.7)	342 (25.6)	< 0.001	0.299
Atopic dermatitis	67 (11.8)	17 (9.0)	50 (13.2)	277 (20.7)	< 0.001	0.141
Urticaria/angioedema	32 (5.6)	14 (7.4)	18 (4.8)	158 (11.8)	< 0.001	0.198
Hypertension	65 (11.5)	26 (13.8)	41 (10.8)	100 (7.5)	0.006	0.382
Diabetes mellitus	20 (3.5)	6 (3.2)	14 (3.7)	21 (1.6)	0.012	0.936
Osteoporosis	20 (3.5)	7 (3.7)	13 (3.4)	17 (1.3)	0.001	0.872
Depression	3 (0.5)	1 (0.5)	2 (0.5)	3 (0.2)	0.157	
Arthritis	12 (2.1)	3 (1.6)	9 (2.4)	16 (1.2)	0.122	0.536
GERD	34 (6.0)	11 (5.8)	23 (6.1)	43 (3.2)	0.005	0.901
Ischemic heart disease	8 (1.4)	2 (1.1)	6 (1.6)	12 (0.9)	0.371	0.615

Data are presented as n (%).

HiEP, highly exacerbation-prone; EP, exacerbation-prone; GERD, gastroesophageal reflux disease.

*Comparison between severe and nonsevere asthmatics.

[†]Comparison between the HiEP and EP groups.

