The prevalence and disease burden of severe eosinophilic asthma in Japan

Tadao Nagasaki, MD, PhD, Keiko Sato, PhD, Naoto Kume, PhD, Tsuyoshi Oguma, MD, PhD, Hironobu Sunadome, MD, Isao Ito, MD, PhD, Yumi Izuhara, MD, PhD, Kazuya Okamoto, PhD, Shinji Kobayashi, MD, PhD, Tomoya Ohno, PhD, Akiko Mizukami, MPharm, Akihiro Kobayashi, MPharm, Toshihiko Kaise, PhD, Tomohiro Kuroda, PhD, Michiaki Mishima, MD, PhD, and Hisako Matsumoto, MD, PhD

Abstract

Background: There are limited data on the prevalence and burden of severe eosinophilic asthma (SEA) both in Japan and globally. This study aimed to assess the prevalence and burden of SEA in Japan. Methods: This study was a retrospective, observational cohort analysis using health records or health insurance claims from patients with severe asthma treated at Kyoto University Hospital. The primary outcome was the prevalence of SEA, defined as a baseline blood eosinophil count $\geq 300$ cells/µL. Secondary outcomes included frequency and risk factors of asthma exacerbations, and asthma-related healthcare resource utilization and costs. Results: Overall, 217 patients with severe asthma were included; 160 (74%) had eosinophil assessments. Of these, 97 cases (61%), 54 cases (34%), and 33 cases (21%) had a blood eosinophil count $\geq 150$, $\geq 300$, and $\geq 500$ cells/µL, respectively. Proportion of SEA was 34%. Blood eosinophil count was not associated with a significantly increased frequency of exacerbations. In the eosinophilic group, lower % forced expiratory volume in 1 second and higher fractional exhaled nitric oxide were predictive risk factors, while the existence of exacerbation history was a predictive risk factor for asthma exacerbations in the non-eosinophilic group. Severe asthma management cost was estimated as ¥357,958/patient-year, and asthma exacerbations was ¥26,124/patient-year. Conclusions: Approximately, one-third of patients with severe asthma in Japan have SEA. While risk factors for exacerbations differed between SEA and severe non-eosinophilic asthma, both subgroups were associated with substantial disease and economic burden. From subgroup analysis, blood eosinophil counts could be an important consideration in severe asthma management.

Introduction

Asthma is a heterogeneous chronic inflammatory disorder of the airways that affects over 300 million people worldwide [1–4], and is associated with airway hyper-responsiveness and variable airflow obstruction [1]. In Japan, approximately 6%–7% of patients with asthma have severe asthma [5,6], which is characterized by frequent exacerbations and poor symptom control, despite the regular intensive use of maintenance therapies such as high-dose inhaled corticosteroids (ICS) or long-acting $\beta_2$-agonists (LABA) and additional controller medications [7]. In severe asthma, these medications are required to either prevent progression to uncontrolled asthma, or where asthma remains uncontrolled despite these clinical interventions [7]. Recent advances in asthma diagnosis have attempted to characterize asthma phenotypes based on inflammation and pulmonary function [7–9]. One phenotype identified is severe eosinophilic asthma (SEA), characterized by eosinophilic, inflammation, higher Global Initiative for Asthma (GINA) step treatments, low symptom control, poor quality of life, and morbidity [3,7,10–14].

Previous United Kingdom (UK) and United States (US)-based studies have demonstrated that patients with severe asthma and elevated blood eosinophil...
counts have an increased risk of future exacerbations [12,15]. Consequently, the condition is associated with high healthcare resource utilization (HCRU) and costs, presenting a substantial burden on healthcare systems [16,17]. However, currently there are few data on the prevalence and the associated burden of disease of SEA in Japan or in Asia. These data would be informative for improving disease characterization and management. This study aimed to determine the prevalence of SEA and the associated burden of disease in Japan.

**Methods**

**Study design**

This was a retrospective, observational cohort analysis using medical chart data and health insurance claims data from patients with severe asthma treated at Kyoto University Hospital, Japan, from 1 January 2009 to 31 May 2015. The baseline period, from which eligible patients were identified, was defined as the 12 months prior to each index date (not including the date itself). In the baseline period, patients with severe asthma were identified and those patients’ demographics were collected. The follow-up period was defined as the 12 months after each index date. In the follow-up period, factors that may predict subsequent asthma exacerbations and healthcare costs were investigated. In order to maximize the study population, two index dates were selected (1 January 2013 and 1 January 2014) to create two different populations: patients ≥15 years of age at Index Date 1 with at least one record for asthma during the 12-month baseline period prior to Index Date 1 (between January 2013 and December 2013) were assigned to Population 1, and similarly those with at least one record for asthma between January 2012 and December 2012 were assigned to Population 2 (Figures 1 and 2). To be certain that patients received continuous asthma therapy at Kyoto University during the study period, patients were selected if they had outpatient records ICD-10 code J45 from before the baseline period to after the follow-up period. Patients with severe asthma were identified by the following prescriptions in the baseline period: a ≥240-day prescription for high-dose ICS as defined by the Japanese guidelines for adult asthma (2014) [18], and at least one ≥240-day prescription of non-ICS asthma controller medication (LABA, leukotriene receptor antagonist, theophylline, anti-immunoglobulin E [IgE] monoclonal antibody, or continuous systemic corticosteroids [SCS; denoting either oral corticosteroids (OCS) or intravenous corticosteroids]). Exclusion criteria were: a diagnosis of respiratory cancer, or any malignant disease undergoing treatment, autoimmune disease, and cystic fibrosis. Finally, patients were assessed if they had blood eosinophil data during the 12-month baseline period prior to each Index Date. The final populations were combined for the analysis. In this study, patients with blood eosinophil data were categorized as SEA if the count was ≥300 cells/μL or non-eosinophilic if the count was <300 cells/μL.

**Variables**

Blood eosinophil count data were collected during the baseline period. If a patient had multiple records of blood eosinophil count data, the data closest to index date were used in statistical analysis. When patients

![Figure 1. Study design. Records from patients treated at Kyoto University Hospital between 1 Jan 2009 and 31 May 2015 were analyzed. Index dates (1 January 2013 and 1 January 2014) were preceded by a 1-year baseline period (used to identify eligibility) and succeeded by a 1-year follow-up period. Patients identified using one index date were excluded from searches using the other index date.](image)
were prescribed SCSs for more than 240 days, patients’ blood eosinophil counts data were used. Because blood eosinophil count data fluctuate with conditions such as asthma exacerbations or infectious diseases, blood eosinophil data collected under such circumstances were not used in the analysis. For serum total...
IgE, atopic status (allergen-specific IgE and skin test results), fractional exhaled nitric oxide (FeNO), body mass index (BMI), and respiratory function, the data closest to the index date were used in statistical analysis. If data were only collected before the baseline period, they were included in the analysis. In particular, atopic status data could be used from the first visit; serum total IgE data could be used from the first visit or before the start of omalizumab therapy.

Four categories were used for smoking status: current (smoking during baseline period), past (smoked before baseline period), never, or unknown.

Omalizumab treatment and/or OCS treatment status were categorized as: current (record of treatment within 6 months prior to index date), past (record of treatment from January 2009 to 6 months before index date), or never.

Information of comorbidities such as eosinophilic granulomatosis with polyangitiis, allergic bronchopulmonary aspergillosis, gastroesophageal reflux disease, allergic rhinitis, nasal polyposis, dermatitis, and Chronic Obstructive Pulmonary Disease (COPD) were obtained from the medical chart database.

Exacerbations were defined as any event associated with a worsening of asthma requiring an emergency room (ER) or hospital admission or the administration of SCS treatment (intravenous or oral administration of corticosteroids for at least 3 days, or a doubling of the existing dose for ≥3 days in patients already receiving maintenance SCS therapy). An exacerbation occurring within 7 days after the end of the previous event was recorded as a single event.

The study investigators reviewed all potential exacerbation events by using medical chart information to confirm that the events were asthma-related. HCRU and medical costs included those relating to asthma management (outpatient visits, asthma-related medications, laboratory examinations, and home healthcare rehabilitation) and asthma exacerbations (hospital admissions, ER, and SCS treatment). Asthma management-related medical costs were analyzed separately from exacerbation-related costs. Medical costs were based on the 2014 medical fee point scheme for each medical service and National Health Insurance (Japan) drug prices [19].

**Objectives**

The primary outcome was the prevalence of SEA (defined as a blood eosinophil count ≥300 cells/μL in this study) during the baseline period using the eosinophil count closest to the index date, and of severe non-eosinophilic asthma (<300 cells/μL) in patients with severe asthma. Secondary outcomes included: the frequency of asthma exacerbations during the baseline period and the follow-up period in patients with SEA and severe non-eosinophilic asthma; the risk factors for asthma exacerbations in patients with SEA and severe non-eosinophilic asthma during the follow-up period; and asthma-related HCRU and medical costs during the follow-up period in all patients with severe asthma.

**Statistical analyses**

Because our primary endpoint was to describe the prevalence of SEA and severe non-eosinophilic asthma, we collected subjects who fulfilled inclusion criteria from the hospital database without sample size calculation based on any statistical assumptions.

Baseline characteristics are presented as n (%) for categorical variables and mean (standard deviation) for continuous variables. Statistical comparisons were performed using the Wilcoxon rank-sum test, t-test, or Chi-squared test where appropriate on JMP® Pro Version 12, (SAS Institute Inc. Cary, NC, USA). Exacerbations during the follow-up period are presented as mean (95% confidence interval [CI]) and n (%). For this analysis, formal statistical comparisons were not performed, but significant differences were inferred from non-overlapping 95% CIs. All tests were two-sided, and a p value of <0.05 was considered to indicate statistical significance.

To determine factors associated with exacerbation risk during the follow-up period, univariate and multivariate analyses using a Lasso negative binomial regression model were performed. Covariates included age ≥40 years, gender, atopic status (defined as the presence of one or more positive specific IgE antibodies against common inhaled allergens during the baseline period), current omalizumab or SCS therapy, the presence of an exacerbation during the baseline period, percent predicted forced expiratory volume in 1 second (FEV₁) < 60%, FeNO ≥25 parts per billion (ppb), and eosinophil count ≥300 cells/μL. Variables with a rate ratio (RR) equal to 1.00 had a coefficient equal to zero by Lasso and were removed from the final model. Significant predictors identified in the univariate analysis, together with clinically important factors (age, gender) were incorporated into the multivariate models. Patients with missing data were excluded from the analysis. The p values of <0.1 and <0.05 were considered significant for the univariate and multivariate analyses, respectively.
**Results**

**Distribution of blood eosinophil counts and prevalence of SEA**

From 7117 patients who had at least one record of asthma, 217 patients with severe asthma were identified \((n = 147\) as Population 1, and \(n = 70\) as Population 2).

During the identification process, 12 patients who did not have blood eosinophil data in 2013 but had in 2012 were included in Population 2. Meanwhile, 60 patients had blood eosinophil data both in 2012 and in 2013, those patients were assigned to Population 1 (data not shown in Figure 2). Among the 217 patients with severe asthma, 160 (74%) had eosinophil assessments (Figure 2). Of these, 97 (61%) patients had a blood eosinophil count \(\geq 150\) cells/\(\mu\)L, 54 (34%) patients had a blood eosinophil count \(\geq 300\) cells/\(\mu\)L, and 33 (21%) patients had a blood eosinophil count \(\geq 500\) cells/\(\mu\)L (Figure 3). Therefore, 54 (34%) were classified as patients with SEA.

**Baseline demographics and characteristics**

Age, age of asthma onset, BMI, and current medications were similar across patients with severe asthma (baseline demographics and characteristics are summarized in Table 1). Several significant differences were observed between patients with SEA and severe non-eosinophilic asthma: the SEA group had a more balanced gender distribution (patients with severe non-eosinophilic asthma were predominantly female), longer smoking history, increased serum total IgE levels, increased FeNO, and reduced FEV\(_1\)/forced vital capacity ratio, compared with the severe non-eosinophilic asthma group. Average daily doses of OCS did not differ between patients with SEA and those with severe non-eosinophilic asthma \((n = 12, 4.9 \pm 3.0\) mg for SEA; \(n = 22, 6.6 \pm 4.9\) mg for severe non-eosinophilic asthma).

The mean annual number of exacerbations during the baseline period was similar for patients with severe asthma (including those without eosinophil data), SEA, and severe non-eosinophilic asthma \((0.47–0.61; \text{Table 1})\), as was the number of exacerbations requiring hospitalization or an ER visit \((0.02–0.07; \text{Table 1})\). Indeed, the proportion of patients experiencing \(\geq 1\) exacerbation was also similar across these three groups \((27%–31%; \text{Table 1})\).

**Exacerbation frequencies during the follow-up period**

During the 12-month follow-up period, in the severe asthma population with eosinophil data, the annual rate of exacerbations was 0.50 \((95\%\text{ CI: 0.33, 0.67})\) and 25% of these patients experienced at least one exacerbation \((\text{Table 2})\). 95\% CIs of the annual rate of exacerbations during the 12-month follow-up period were not overlapping between patients who had experienced one exacerbation during the baseline period \((1.20 [95\%\text{ CI: 0.74, 1.65}]\) and those who had not \((0.22 [95\%\text{ CI: 0.10, 0.34}]\) \((\text{Table 2})\). This finding indicates the presence of a significant difference in the annual rate of exacerbations between the two patient groups, and is supported by multivariate analyses to determine predictors of exacerbations during the 12-month follow-up period \((\text{Table 3})\). However, exacerbations requiring hospitalization or ER visit were not increased in patients who had experienced these
Exacerbation types during the baseline period (Table 2).

**Exacerbation risk factors**

The results of the univariate and multivariate analyses to identify risk factors for exacerbations during the follow-up period in patients with eosinophil data are summarized in Table 3. Multivariate analyses showed the presence of baseline exacerbations to be a significant risk factor for follow-up exacerbations in the severe asthma group. In the subgroup analyses, a low percent predicted FEV₁ (<60%) and a high FeNO (≥25 ppb) were significant risk factors for follow-up exacerbations in the SEA group, whereas the presence
of baseline exacerbations was a significant risk factor for follow-up exacerbations in the non-eosinophilic asthma group (Table 3). In patients with severe asthma who had eosinophil data, baseline eosinophilia $\geq$300 cells/$\mu$L was not a significant predictive factor for exacerbations during the 12-month follow-up period (Table 3).

**HCRU and medical costs**

HCRU and medical costs associated with asthma management and exacerbations are summarized for all patients with severe asthma (both with and without eosinophil data), SEA, and severe non-eosinophilic asthma in Table 4 and Figure 4. Overall, severe asthma management was estimated to have a mean annual cost of ¥357,958 (US$3,113 [conversion rate: ¥115/US$1 at the time of submission]) per patient-year, and ¥26,124 (US$227 [conversion rate: ¥115/US$1 at the time of submission]) for asthma exacerbations per patient-year.

For SEA and non-eosinophilic subgroups, HCRU and medical costs associated with asthma management both exerted a substantial healthcare burden. Mean overall medical costs per patient-year for SEA were ¥346,554 (US$3,014, conversion rate as ¥115/US$1 at the time of submission) and severe non-eosinophilic asthma costs per patient-year were ¥479,338 (US$4,168 [conversion rate: ¥115/US$1 at the time of submission]) (Table 4, Figure 4).

**Discussion**

The results of this retrospective, cohort study in a university hospital in Japan showed that approximately one-third of patients with severe asthma had an eosinophil count $\geq$300 cells/$\mu$L. The threshold of $\geq$300 cells/$\mu$L used in this study to define SEA was informed by other studies [20,21]; however, several other studies have investigated different thresholds [12,15].

We identified several significant differences in patient characteristics between eosinophilic and non-eosinophilic groups. The marked difference in gender distribution and increased serum total IgE levels in the eosinophilic group are in line with several previous studies [22,23], with serum total IgE elevation potentially associated with hidden allergens, such as *Staphylococcus aureus* enterotoxins [23–25]. However, this finding is in contrast to one previous study of 179 patients with severe asthma, which reported no significant differences in baseline characteristics between eosinophilic ($\geq$400 cells/$\mu$L) and non-eosinophilic groups, despite the use of a higher eosinophilia boundary to define eosinophilic asthma [17]. Nevertheless, patients in the severe non-eosinophilic asthma group in this study may have had a different severity of asthma from that of those who were in the present study. Finally, several studies have not considered the duration of treatment ($\geq$240 days on high-dose ICS and controller[s]) during the 1-year baseline period in the definition of severe asthma [12,17].

### Table 2. Summary of exacerbations during the 12-month follow-up period (severe asthma population with eosinophil data).

| Number of patients, n | Annual rate of exacerbations (95% CI) | Number of exacerbations |
|-----------------------|--------------------------------------|------------------------|
| Overall, mean (CI)    |                                      |                        |
| Age, years            |                                      |                        |
| <40                   | 16 (0.03, 1.60) | 0.40 (0.00, 0.08) 45 (71) 9 (14) 14 (26) |
| ≥40                   | 144 (0.03, 1.60) | 0.80 (0.00, 0.08) 34 (74) 4 (8) 2 (5) |
| Gender                |                                      |                        |
| Male                  | 61 (0.03, 1.60) | 0.20 (0.00, 0.08) 46 (75) 13 (16) 11 (13) |
| Female                | 99 (0.03, 1.60) | 0.50 (0.00, 0.08) 34 (74) 4 (8) 2 (5) |
| Eosinophil counts, cells/$\mu$L |            |                        |
| <300                  | 106 (0.03, 1.60) | 0.60 (0.00, 0.08) 34 (74) 4 (8) 2 (5) |
| ≥300                  | 54 (0.03, 1.60) | 0.40 (0.00, 0.08) 34 (74) 4 (8) 2 (5) |
| Atopic status*       |                                      |                        |
| Yes                   | 106 (0.03, 1.60) | 0.60 (0.00, 0.08) 34 (74) 4 (8) 2 (5) |
| No                    | 46 (0.03, 1.60) | 0.40 (0.00, 0.08) 34 (74) 4 (8) 2 (5) |
| Current omalizumab    |                                      |                        |
| Yes                   | 46 (0.03, 1.60) | 0.60 (0.00, 0.08) 34 (74) 4 (8) 2 (5) |
| and/or SCS therapy    | 114 (0.03, 1.60) | 0.40 (0.00, 0.08) 34 (74) 4 (8) 2 (5) |
| Exacerbation during   |                                      |                        |
| baseline period       | 114 (0.03, 1.60) | 0.60 (0.00, 0.08) 34 (74) 4 (8) 2 (5) |
| ≥2 exacerbations dur- | 114 (0.03, 1.60) | 0.60 (0.00, 0.08) 34 (74) 4 (8) 2 (5) |
| ing baseline period   | 140 (0.03, 1.60) | 0.60 (0.00, 0.08) 34 (74) 4 (8) 2 (5) |
| % FEV$_1$ of predicted* |                                      |                        |
| <60                   | 27 (0.03, 1.60) | 0.60 (0.00, 0.08) 34 (74) 4 (8) 2 (5) |
| ≥60                   | 127 (0.03, 1.60) | 0.60 (0.00, 0.08) 34 (74) 4 (8) 2 (5) |
| FeNO (ppb)$^\dagger$  |                                      |                        |
| <25                   | 63 (0.03, 1.60) | 0.60 (0.00, 0.08) 34 (74) 4 (8) 2 (5) |
| ≥25                   | 127 (0.03, 1.60) | 0.60 (0.00, 0.08) 34 (74) 4 (8) 2 (5) |

*Data missing for 14 patients.

$^\dagger$Data missing for 6 patients.

$^\dagger$Data missing for 28 patients.

ER: emergency room; ppb: parts per billion; SCS: systemic corticosteroid.
Patients with persistent eosinophilic inflammation have a poor prognosis despite treatment with ICS [3,7,14]. In the current study, baseline eosinophilia ≥300 cells/µL was not a significant predictive factor for exacerbations during the 12-month follow-up period in either univariate or multivariate analyses. This finding is in contrast to two large studies of medical records in the US and UK where baseline eosinophil count was predictive of exacerbation frequency [12,15]. Because both studies used a threshold of >400 (or ≥400) cells/µL to define eosinophilic asthma, the observed differences between these studies and the present study may relate to the severity of asthma in the eosinophilic subgroups. For example, a study by Berry et al. highlighted the pathophysiological differences between the two groups and concluded that patients with severe non-eosinophilic asthma had a poorer response to SCS treatment than those with eosinophilic asthma, suggesting that patients with a threshold of <300 cells/µL may be intrinsically more difficult to treat [26]. However, considering the difference in study size, patient eligibility, and the definition of severe asthma between studies, it is difficult to compare the results; and further investigation is necessary.

Table 3. Summary of univariate and multivariate analyses to determine predictors of exacerbations during the 12-month follow-up period.

| Variable during baseline period | Univariate analysis (N = 160) | Multivariate analysis (N = 142) |
|--------------------------------|-----------------------------|-------------------------------|
|                                | RR  | 95% CI | p value | RR  | 95% CI | p value |
| Age >40 years                  | 1   | –      | –       | 1.58 | 0.50, 5.02 | 0.44 |
| Gender, male                   | 1.09| 0.38, 3.12 | 0.88 | 1.58 | 0.50, 5.02 | 0.44 |
| Atopic status                  | 2.81| 0.97, 8.10 | 0.06 | 1.58 | 0.50, 5.02 | 0.44 |
| Current omalizumab or SCS therapy | 3.45| 1.26, 9.43 | 0.02 | 2.00 | 0.54, 7.41 | 0.30 |
| % predicted FEV1 low (<60%)    | 3.66| 1.36, 9.87 | 0.01 | 3.33 | 1.16, 9.57 | 0.03 |
| FeNO high (>25 ppb)            | 48  | 321     | 3      | 19  | 988, 116,821 | <0.0001 |
| Blood eosinophil count, ≥300 cells/µL | 2.31| 1.11, 4.78 | 0.02 | 4.63 | 2.46, 8.73 | <0.0001 |

SEA (≥300 cells/µL)

| Variable during baseline period | Univariate analysis (N = 54) | Multivariate analysis (N = 47) |
|--------------------------------|-----------------------------|-------------------------------|
|                                | RR  | 95% CI | p value | RR  | 95% CI | p value |
| Age >40 years                  | NA  | –      | –       | 2.00 | 0.54, 7.41 | 0.30 |
| Gender, male                   | 1.09| 0.38, 3.12 | 0.88 | 1.58 | 0.50, 5.02 | 0.44 |
| Atopic status                  | 0.38| 0.10, 1.42 | 0.15 | 1.58 | 0.50, 5.02 | 0.44 |
| Current omalizumab or SCS therapy | 2.43| 1.05, 5.64 | 0.04 | 3.33 | 1.16, 9.57 | 0.03 |
| % predicted FEV1 low (<60%)    | 7.35| 3.15, 17.2 | <0.0001 | 3.33 | 1.16, 9.57 | 0.03 |
| FeNO high (>25 ppb)            | 1.33| 0.52, 3.44 | 0.55 | 3.33 | 1.16, 9.57 | 0.03 |

Severe non-EA (<300 cells/µL)

| Variable during baseline period | Univariate analysis (N = 106) | Multivariate analysis (N = 106) |
|--------------------------------|-----------------------------|-------------------------------|
|                                | RR  | 95% CI | p value | RR  | 95% CI | p value |
| Age >40 years                  | NA  | –      | –       | 2.00 | 0.54, 7.41 | 0.30 |
| Gender, male                   | 0.38| 0.10, 1.42 | 0.15 | 1.58 | 0.50, 5.02 | 0.44 |
| Atopic status                  | 3.45| 1.26, 9.43 | 0.02 | 2.00 | 0.54, 7.41 | 0.30 |
| Current omalizumab or SCS therapy | 2.43| 1.05, 5.64 | 0.04 | 3.33 | 1.16, 9.57 | 0.03 |
| % predicted FEV1 low (<60%)    | 7.35| 3.15, 17.2 | <0.0001 | 3.33 | 1.16, 9.57 | 0.03 |
| FeNO high (>25 ppb)            | 1.33| 0.52, 3.44 | 0.55 | 3.33 | 1.16, 9.57 | 0.03 |

Data missing for 14 patients.
Data missing for 6 patients.
Data missing for 28 patients.
Data missing for 5 patients.
Data missing for 7 patients.
Data missing for 9 patients.
Data missing for 6 patients.
Data missing for 21 patients.
1) Coefficient equal to zero by the Lasso.
2) Coefficients equal to zero by the Lasso, and deleted from final model.
3) All patients who experienced exacerbation during follow-up period were categorized as ≥25 ppb group.

Estimates in bold are statistically significant.
EA: eosinophilic asthma; ppb: parts per billion; RR: rate ratio; SCS: systemic corticosteroid; SEA: severe eosinophilic asthma.

The most recent data before the index date was used to compare with the 12-month follow-up period. In most cases this was during the 12-month baseline period. If data were taken from before the 12-month baseline period, but the investigators could confirm that the status of the variable had not changed, then the data could be included. Otherwise these data were treated as missing data.
In the current study, the proportion of patients who experienced exacerbations did not differ from previous studies [12,15]. However, low annual rates of exacerbations requiring hospitalization or ER visit were observed both during the baseline period and follow-up period. This might be why there was not an increased frequency of exacerbations requiring hospitalization or ER visit during the follow-up period compared with the baseline period. Furthermore, low annual rates of exacerbations requiring hospitalization or ER visit impacted on low cost of exacerbations (¥26,124 per patient-year).

From the multivariate analysis, in patients with blood eosinophil counts of $>300$ cells/μL, the current study demonstrated an association between future exacerbations and both low predicted FEV₁ and high FeNO ($>25$ ppb), which was in line with previous studies [27,28] that showed the presence of subgroups...
with SEA. Comparatively, exacerbations during the baseline period were associated with an increased frequency of exacerbations in the 12-month follow-up period in patients with non-eosinophilic asthma but not in those with SEA. The cause of the unexpectedly high correlation between high FeNO and future exacerbations in patients with SEA is unclear. One possible cause is the small sample size, which was intended to assess the prevalence of SEA, rather than the association of biological measurements with future exacerbations. However, the differences in exacerbation risk factors seen between eosinophilic and non-eosinophilic subgroups highlight the significance of using blood eosinophil count to stratify subgroups, and that these subgroups may require different management strategies.

Asthma-related costs were comparable in both eosinophilic and non-eosinophilic patient groups (¥346,554 [US$3,014] and ¥479,338 [US$4,168] per patient-year, respectively), with medications accounting for most costs in all treatment groups. The high medication costs in both patient groups may be explained by the requirement for all patients to have received ≥240 days of high-dose ICS or non-ICS asthma-controller therapy in the 12 months prior to the index date. In contrast to previous studies that reported significant differences between eosinophilic subgroups [16,17], in this study, the asthma-related costs and asthma exacerbations were similar in both SEA and severe non-eosinophilic subgroups, warranting further studies to investigate cost differences between these two patient subsets.

Severe asthma costs presented in this study were substantially higher than those in the general asthma population in Japan (¥73,000–¥265,000 per patient-year). While costs associated with severe asthma in countries outside of Japan cannot be directly compared with data from this study, Suruki et al. present data supporting this notion, showing that costs associated with SEA in the USA are approximately double than those reported in the overall asthma population [29].

**Summary of study limitations**

There are limitations inherent to the study design that should be considered. Because this was a retrospective analysis of data collected in routine clinical practice, some objective measurements of clinical variables, markers of disease control or symptomatology may not have been consistently recorded for all patients, and may have affected the patient population selection. Specifically, based on the baseline characteristics, there were 57 patients without eosinophil data who may have had a different prevalence of SEA compared with those patients for whom eosinophil data were available, leading to an over- or under-estimation of the prevalence of SEA. However, the prevalence of SEA reported here (34% of patients with severe asthma) is supported by the results of the previous studies [16,17,21,22].

Second, in this study, SEA was defined using a blood eosinophil count, which is an indirect measure of airway eosinophilic inflammation [21]. However, a previous report showed that patients with blood eosinophil counts ≥300 cells/μL almost always had a sputum eosinophil count ≥2%, which is an indicator of airway eosinophilic inflammation [30,31]. In patients with severe non-eosinophilic asthma who used SCS regularly, blood eosinophil counts might have been artificially lowered. However, in view of the similar daily doses of SCS between patients with SEA and those with severe non-eosinophilic asthma, the effects of SCS use on blood eosinophil counts may not meaningfully weaken from the value of our conclusion.

Finally, not all patients who experienced an asthma exacerbation may have visited Kyoto University Hospital for every treatment, which could contribute to an under-estimation of the frequency of exacerbations, HCRU, and medical costs.
Conclusion
Overall, the results of this study show that SEA (≥300 cells/μL) is present in approximately one-third of patients with severe asthma in Japan. Despite long-term ICS plus non-ICS controller medication, both SEA and severe non-eosinophilic asthma exert a substantial clinical and economic burden. There is clearly an unmet medical need for effective treatments for both SEA and severe non-eosinophilic asthma, and eosinophil count may be useful to inform clinical management.

Acknowledgement
Editorial support (in the form of writing assistance, including development of the initial draft based on author direction, assembling tables and figures, collating author comments, and grammatical editing and referencing) was provided by Chris Tan, PhD, at Fishawack Indicia Ltd, UK, and was funded by GSK.

Disclosure statements
KS, TOh, AM, AK, and TKa are employees of GlaxoSmithKline (GSK); KS, AK, and TKa hold stock/shares in GSK; HM received personal fees from GSK; NK, II, YI, TKu, HM, MM, TN, TOg, KO, SK and HS received research funding for the current study from GSK Japan.

Funding
This study was funded by GSK (205547/HO-15-15492). GSK employees contributed to the study design, analysis, and interpretation of data, the writing of the manuscript and the approval of the final version to be submitted. The decision to submit for publication was that of the authors alone. The sponsor did not place any restrictions on access to the data or on the statements made in the manuscript. The authors had full access to all the data in the study and had final responsibility to submit for publication.

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