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The prevalence and disease burden of severe eosinophilic asthma in Japan

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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 ≥ 300 cells/ μ L. 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, 97cases (61%), 54cases (34%), and 33cases (21%) had a blood eosinophil count ≥ 150 , ≥ 300 , and ≥ 500 cells/ μ L, 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 as ¥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.

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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 β_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

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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 (Figure 1). The study protocol was approved by the Ethical Committee of Kyoto University prior to the start of the study (Kyoto University ID: R0102, GSK ID: 205547/HO-15-15492), and patient anonymization occurred before the start of the study. Those who did not consent were not included in the study.

Study population

Patients with the diagnosis of asthma, which was defined according to the International Classification of

Diseases, 10th Revision (ICD-10) code J45, were selected from a health insurance claims database. Use of two index dates created 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/ μ L or non-eosinophilic if the count was < 300 cells/ μ L.

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

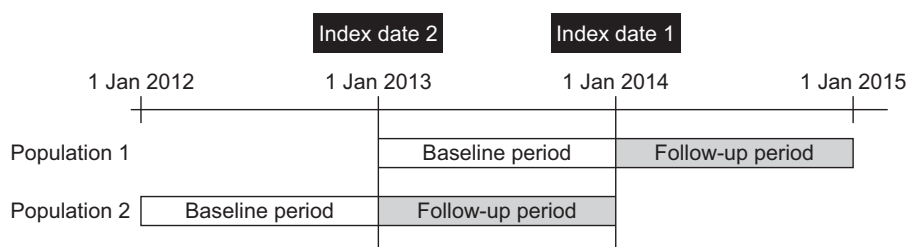
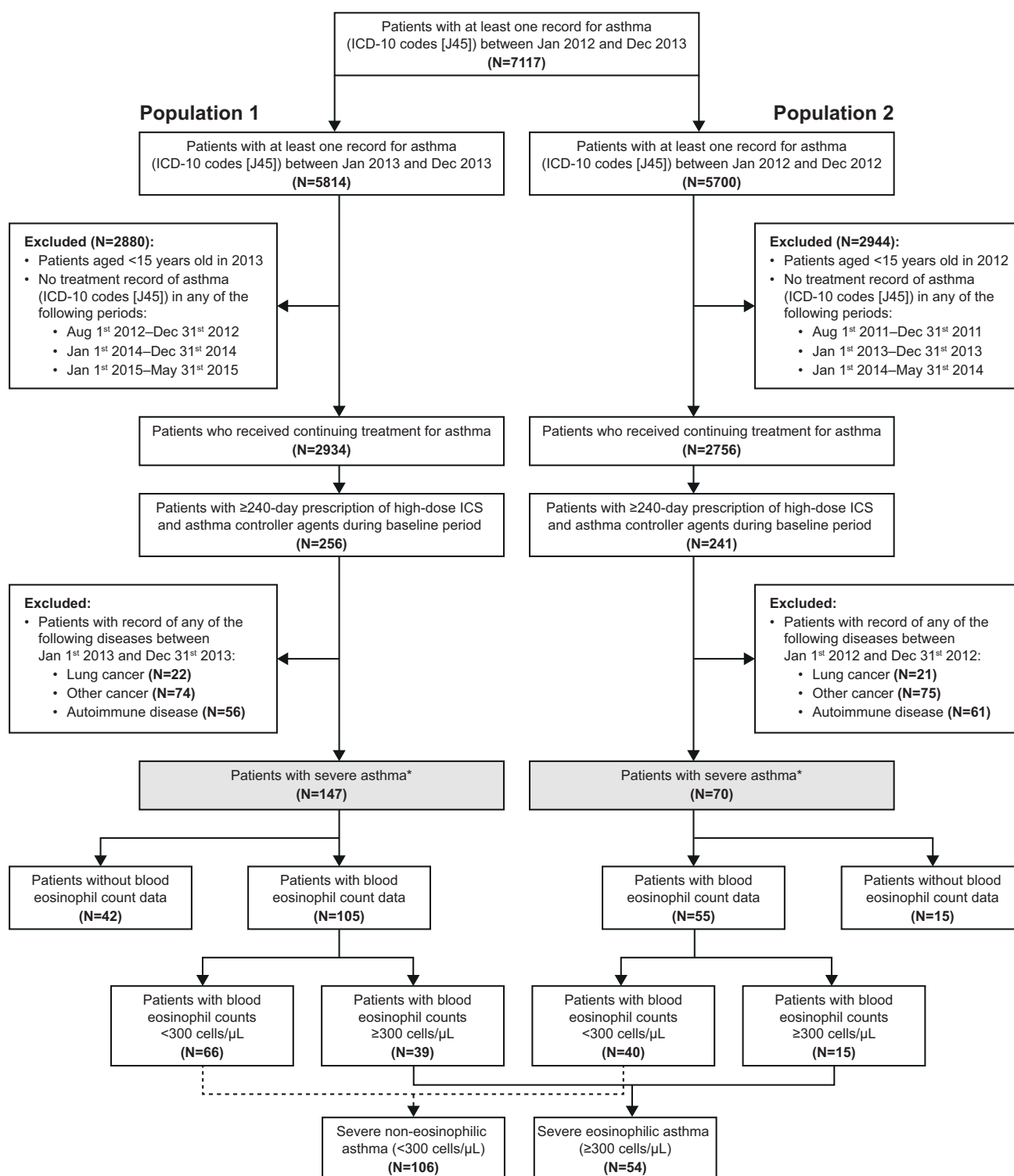


Figure 1. Study design. Records from patients treated at Kyoto University Hospital between 1 Jan 2009 and 31 May 2015 were analyzed. Index dates (1 January 2013 and 1 January 2014) were preceded by a 1-year baseline period (used to identify eligibility) and succeeded by a 1-year follow-up period. Patients identified using one index date were excluded from searches using the other index date.



*Patients who were eligible in both population were categorized in population 1 (without duplicate.)

Figure 2. Patient flow diagram. Patients with severe asthma were defined as those with a ≥240-day prescription for high-dose ICS as defined by the Japanese guideline for adult asthma (2014) [18], and at least one ≥240-day prescription of non-ICS asthma-controller medication (LABA, leukotriene receptor antagonist, theophylline, anti-IgE monoclonal antibody, continuous or near continuous systemic corticosteroid). ICD, International Classification of Diseases.

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 polyangiitis, 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/ μ L in this study) during the baseline period using the eosinophil count closest to the index date, and of

severe non-eosinophilic asthma (< 300 cells/ μ L) 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 values 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 ($FEV_{1\%}$) $< 60\%$, FeNO ≥ 25 parts per billion (ppb), and eosinophil count ≥ 300 cells/ μ L. 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 ≥ 150 cells/ μL , 54 (34%) patients had a blood eosinophil count ≥ 300 cells/ μL , and 33 (21%) patients had a blood eosinophil count ≥ 500 cells/ μL (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 FEV₁/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 ± 3.0 mg for SEA; $n=22$, 6.6 ± 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; Table 1), as was the number of exacerbations requiring hospitalization or an ER visit (0.02–0.07; Table 1). Indeed, the proportion of patients experiencing ≥ 1 exacerbation was also similar across these same groups (27%–31%; 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% CI: 0.33, 0.67) and 25% of these patients experienced at least one exacerbation (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% CI: 0.74, 1.65]) and those who had not (0.22 [95% CI: 0.10, 0.34]) (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 (Table 3). However, exacerbations requiring hospitalization or ER visit were not increased in patients who had experienced these

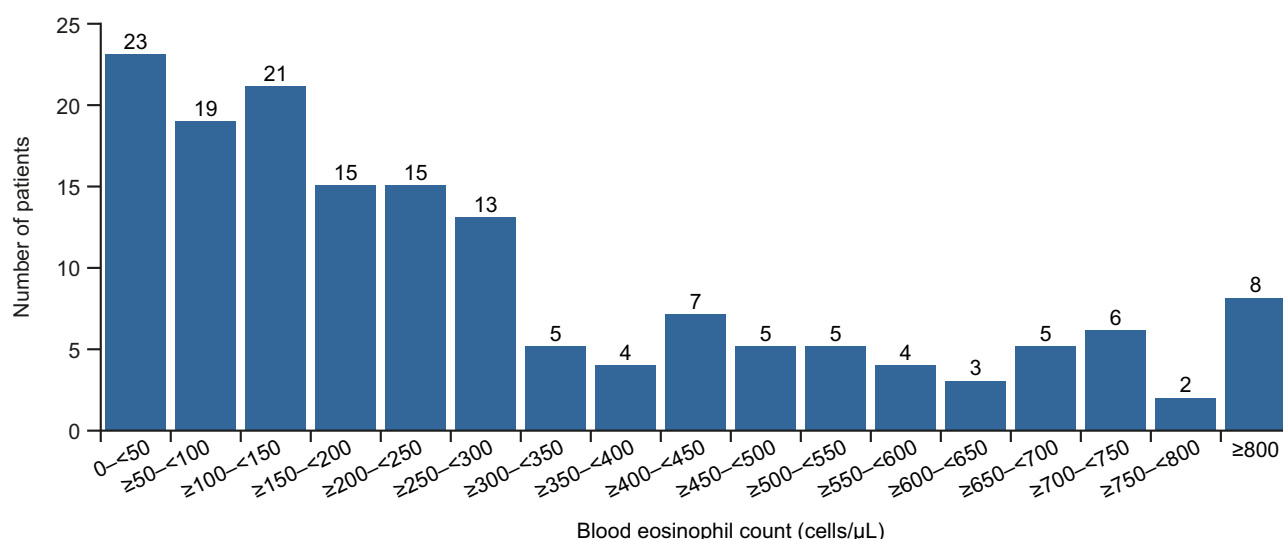


Figure 3. Distribution of blood eosinophil counts among patients with severe asthma ($n=160$).

Table 1. Patient demographics, characteristics, and exacerbations during the baseline period.

	All patients with severe asthma (<i>n</i> = 217)				
	Total (<i>n</i> = 217)	Patients with eosinophil data (<i>n</i> = 160)		Total (<i>n</i> = 160)	Patients with no eosinophil data (<i>n</i> = 57)
Age, years, mean (SD)	62 (15)	67 (10)	61 (17)	63 (15)	60 (15)
Gender, female, <i>n</i> (%)	129 (59)	25 (46)*	74 (70)	99 (62)	30 (53)
Age of asthma onset, years, mean (SD) ^a	45 (20)	46 (18)	46 (22)	46 (20)	40 (20)
Body mass index, kg/m ² , mean (SD) ^b	23 (4)	23 (4)	23 (5)	23 (4)	23 (5)
Smoking status, current or past/never/no data	83/130/4	26/27/1	33/73/0	59/100/1	24/30/3
Smoking pack-years, mean (SD) ^b	13 (24)	17 (25)*	10 (23)	12 (23)	14 (24)
Current medications, <i>n</i> (%)					
Omalizumab	20 (9)	6 (11)	14 (13)	20 (13)	0
SCS	38 (18)	12 (22)	22 (21)	34 (21)	4 (7)
Omalizumab and/or SCS	50 (23)	16 (30)	30 (28)	46 (29)	4 (7)
Disease characteristics					
Atopic Yes, <i>n</i> (%)	146 (73) ^c	39 (80) ^a	67 (69) ^d	106 (73) ^e	40 (75) ^b
Chronic rhinosinusitis, <i>n</i> (%)	26 (12)	8 (15)	8 (8)	16 (10)	10 (18)
Serum total IgE (IU/mL), median (min–max) ^f	245 (5–25 000)	411 (6–6000)*	115 (5–8700)	230 (5–8700)	290 (5–25 000)
FeNO, ppb, mean (SD) ^g	36 (36)	55 (36)*	25 (25)	36 (33)	35 (46)
Lung function					
% FEV ₁ of predicted ^h , %, mean (SD)	85 (26)	83 (27)	88 (26)	86 (27)	83 (25)
FEV ₁ /FVC ^h , %, mean (SD)	72 (13)	70 (10)*	75 (13)	73 (12)	71 (14)
%FEF _{25–75} ^h , %, mean (SD)	61 (37)	53 (31)*	69 (41)	64 (38)	55 (32)
Exacerbations during the baseline period					
Number of exacerbations, mean (SD)	0.55 (1.11)	0.61 (1.17)	0.56 (1.20)	0.58 (1.19)	0.47 (0.85)
Patients who experienced ≥1 exacerbation, <i>n</i> (%)	63 (29)	17 (31)	29 (27)	46 (29)	17 (30)
Patients who experienced an exacerbation, <i>n</i> (%)					
0	154 (71)	37 (69)	77 (73)	114 (71)	40 (70)
1	36 (17)	10 (19)	16 (15)	26 (16)	10 (18)
2	11 (5)	2 (4)	5 (5)	7 (4)	4 (7)
3	9 (4)	2 (4)	4 (4)	6 (4)	3 (5)
≥4	7 (3)	3 (6)	4 (4)	7 (4)	0
Number of exacerbations requiring hospitalization or an ER visit, mean (SD)	0.05 (0.39)	0.06 (0.23)	0.07 (0.52)	0.06 (0.44)	0.02 (0.13)

^aData missing for five patients.^bData missing for four patients.^cData missing for 18 patients.^dData missing for 9 patients.^eData missing for 14 patients.^fData missing for 13 patients.^gData missing for 35 patients.^hData missing for 8 patients.

*Statistically significant for SEA versus non-SEA with chi-square test for binary variable or *t*-test or the Wilcoxon rank-sum test for continuous variable; SEA was defined as a blood eosinophil count ≥ 300 cells/ μ L during the baseline period; non-SEA was defined as a blood eosinophil count < 300 cells/ μ L during the baseline period.

EA: eosinophilic asthma; ER: emergency room; FEF: forced expiratory flow; FVC: forced vital capacity; SCS: systemic corticosteroids; ppb: parts per billion; SEA: severe eosinophilic asthma.

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

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

		Annual rate of exacerbations (95% CI)			Number of exacerbations		
		Number of patients, <i>n</i>	All exacerbations	Exacerbations requiring hospitalization or ER visit	0	1	2+
					<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)
Overall, mean (CI)		160	0.50 (0.33, 0.67)	0.08 (0.02, 0.13)	120 (75)	21 (13)	19 (12)
Age, years	<40	16	0.81 (0.03, 1.60)	0.38 (−0.17, 0.92)	11 (69)	2 (13)	3 (19)
	≥40	144	0.47 (0.30, 0.63)	0.04 (0.01, 0.07)	109 (76)	19 (13)	16 (11)
Gender	Male	61	0.46 (0.20, 0.72)	0.02 (−0.02, 0.05)	46 (75)	8 (13)	7 (11)
	Female	99	0.53 (0.30, 0.75)	0.11 (0.02, 0.21)	74 (75)	13 (13)	12 (12)
Eosinophil counts, cells/μL	<300	106	0.46 (0.26, 0.66)	0.08 (0.00, 0.17)	81 (76)	14 (13)	11 (10)
	≥300	54	0.57 (0.26, 0.89)	0.06 (−0.01, 0.12)	39 (72)	7 (13)	8 (16)
Atopic status ^a	Yes	106	0.63 (0.40, 0.86)	0.11 (0.02, 0.20)	73 (69)	17 (16)	16 (15)
	No	40	0.23 (−0.01, 0.46)	0 (0, 0)	35 (88)	3 (8)	2 (5)
Current omalizumab and/or SCS therapy	Yes	46	0.67 (0.27, 1.08)	0.15 (−0.04, 0.34)	34 (74)	4(9)	8 (17)
	No	114	0.43 (0.26, 0.60)	0.04 (0.01, 0.08)	86 (75)	17(15)	11 (10)
Exacerbation during baseline period	Yes	46	1.20 (0.74, 1.65)	0.22 (0.02, 0.41)	23 (50)	8 (17)	15 (33)
	No	114	0.22 (0.10, 0.34)	0.02 (−0.01, 0.04)	97 (85)	13 (11)	4 (4)
≥2 exacerbations during baseline period	Yes	20	1.80 (1.02, 2.58)	0.35 (−0.09, 0.79)	7 (35)	2 (10)	11 (55)
	No	140	0.31 (0.18, 0.45)	0.04 (0.00, 0.07)	113 (81)	19 (14)	8 (6)
% FEV ₁ of predicted ^b	<60	27	0.93 (0.32, 1.54)	0.07 (−0.03, 0.18)	18 (67)	2 (7)	7 (26)
	≥60	127	0.40 (0.24, 0.56)	0.05 (0.01, 0.08)	97 (76)	19 (15)	11 (9)
FeNO (ppb) ^c	<25	69	0.46 (0.21, 0.72)	0.07 (0.01, 0.14)	52 (75)	11 (16)	6 (9)
	>25	63	0.54 (0.27, 0.81)	0.03 (−0.01, 0.08)	45 (71)	9 (14)	9 (14)

^aData missing for 14 patients.^bData missing for 6 patients.^cData missing for 28 patients.

ER: emergency room; ppb: parts per billion; SCS: systemic corticosteroid.

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 ≥ 300 cells/ μ 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 ≥ 300 cells/ μ L. The threshold of ≥ 300 cells/ μ 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 (≥ 400 cells/ μ 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 (≥ 240 days on high-dose ICS and controller[s]) during the 1-year baseline period in the definition of severe asthma [12,17].

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

All severe asthma with eosinophil data						
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⁾	—	—			
Gender, male	— ¹⁾	—	—			
Atopic status ^a	2.81	0.97, 8.10	0.06	1.58	0.50, 5.02	0.44
Current omalizumab or SCS therapy	— ¹⁾	—	—			
Exacerbation during baseline period	5.45	2.86, 10.4	<0.0001	4.63	2.46, 8.73	<0.0001
% predicted FEV ₁ low (<60%) ^b	2.31	1.11, 4.78	0.02	— ²⁾	—	—
FeNO high (≥25 ppb) ^c	— ¹⁾	—	—			
Blood eosinophil count, ≥300 cells/μL	— ¹⁾	—	—			
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 ^d	NA			NA		
Gender, male	1.09	0.38, 3.12	0.88			
Atopic status ^e	— ¹⁾	—	—			
Current omalizumab or SCS therapy	— ¹⁾	—	—			
Exacerbation during baseline period	3.45	1.26, 9.43	0.02	2.00	0.54, 7.41	0.30
% predicted FEV ₁ low (<60%)	3.66	1.36, 9.87	0.01	3.33	1.16, 9.57	0.03
FeNO high (≥25 ppb) ^f	48 321³⁾	19 988, 116 821	<0.0001	302	84, 1086	<0.0001
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	— ¹⁾	—	—			
Gender, male	— ¹⁾	—	—			
Atopic status ^g	0.38	0.10, 1.42	0.15			
Current omalizumab or SCS therapy	2.43	1.05, 5.64	0.04	— ²⁾	—	—
Exacerbation during baseline period	7.35	3.15, 17.2	<0.0001	6.94	2.97, 16.2	<0.0001
% predicted FEV ₁ low (<60%) ^h	— ¹⁾	—	—			
FeNO high (≥25 ppb) ⁱ	1.33	0.52, 3.44	0.55	—	—	—

^aData missing for 14 patients.^bData missing for 6 patients.^cData missing for 28 patients.^dAll patients with severe eosinophilic asthma (≥300 cells/μL) were over 40 years.^eData missing for 5 patients.^fData missing for 7 patients.^gData missing for 9 patients.^hData missing for 6 patients.ⁱData 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.

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 4. Asthma-related HCRU and medical costs in severe asthma during the 12-month follow-up period.

	All patients with severe asthma (n = 217)			
	Patients with eosinophil data			Patients with no eosinophil count data (N = 57)
	All severe asthma (N = 217)	SEA (N = 54)	Severe non-EA (N = 106)	
Asthma management HCRU				
Outpatient visits, n (%)	217 (100)	54 (100)	106 (100)	57 (100)
Mean frequency	7.6	7.9	8.7	5.3
Medications, n (%)				
ICS/LABA combination	184 (84.8)	48 (88.9)	83 (78.3)	53 (93.0)
ICS	119 (54.8)	29 (53.7)	72 (67.9)	18 (31.6)
SCS	61 (28.1)	23 (42.6)	29 (27.4)	9 (15.8)
LABA	29 (13.4)	5 (9.3)	20 (18.9)	4 (7.0)
Leukotriene receptor antagonists	145 (66.8)	32 (59.3)	73 (68.9)	40 (70.2)
Sustained release theophylline	69 (31.8)	20 (37.0)	35 (33.0)	14 (24.6)
Omalizumab	18 (8.3)	5 (9.3)	12 (11.3)	1 (1.8)
Other asthma controllers				
Others	110 (50.7)	25 (46.3)	61 (57.5)	24 (42.1)
	163 (75.1)	40 (74.1)	85 (80.2)	38 (66.7)
Laboratory examinations, n (%)				
Blood test	74 (34.1)	27 (50.0)	38 (35.8)	9 (15.8)
Respiratory function test	69 (31.8)	17 (31.5)	36 (34.0)	16 (28.1)
Bacterial test	28 (12.9)	5 (9.3)	20 (18.9)	3 (5.3)
X-ray	100 (46.1)	28 (51.9)	51 (48.1)	21 (36.8)
Cytology sputum test	13 (6.0)	5 (9.3)	7 (6.6)	1 (1.8)
Home healthcare, n (%)	17 (7.8)	2 (3.7)	14 (13.2)	1 (1.8)
Asthma exacerbation HCRU				
Hospital admissions, n (%)	3 (1.4)	1 (1.9)	2 (1.9)	0
Total admissions	6	1	5	0
Mean admission days/event	14.3	6.0	16.0	–
Mean (SD) cost/event, ¥	715 612 (281 397)	328 672 (–)	793 000 (232 515)	–
ER visits, n (%)	7 (3.2)	1 (1.9)	4 (3.8)	2 (3.5)
Total exacerbations	7	1	4	2
Mean outpatient visits/event	2.6	3.0	1.8	4.0
Mean (SD) cost/event, ¥	29 174 (28 412)	15 965 (–)	20 487 (26 720)	53 151 (32 794)
SCS use, n (%)	30 (13.8)	10 (18.5)	15 (14.2)	5 (8.8)
Total exacerbations	42	13	23	6
Mean outpatient visits/event	1.7	2.1	1.7	1.0
Mean (SD) cost/event, ¥	31 671 (36 822)	33 539 (36 316)	34 606 (40 886)	16 378 (16 374)
Asthma management costs, mean (SD) cost/patient-year, ¥				
Outpatient visits	5495 (4501)	5416 (3135)	6363 (5549)	3954 (2697)
Laboratory examinations	12 322 (18 193)	15 870 (17 112)	14 978 (21 664)	4023 (4894)
Medications omalizumab	83 175 (383 186)	111 413 (484 838)	102 336 (409 106)	20 790 (156 961)
Medications others	225 705 (176 709)	190 042 (102 043)	255 127 (217 136)	204 779 (137 389)
Home healthcare	26 366 (128 879)	4867 (25 208)	50 120 (180 370)	2561 (19 338)
Other costs	4894 (4386)	5049 (3731)	5434 (5224)	3744 (2815)
Total	357 958 (524 431)	332 656 (520 317)	434 357 (617 243)	239 851 (253 731)
Asthma exacerbation costs, mean (SD) cost/patient-year, ¥				
Hospital admissions	19 787 (212 810)	6087 (44 727)	37 406 (302 542)	0 (–)
ER visits	898 (6558)	296 (2173)	773 (5982)	1702 (9659)
SCS use	5439 (26 700)	7515 (21 747)	6803 (34 698)	937 (4042)
Total	26 124 (214 391)	13 897 (55 290)	44 981 (303 655)	2638 (11 353)
Overall costs, mean (SD) cost/patient-year, ¥				
Total	384 081 (611 625)	346 554 (522 656)	479 338 (757 717)	242 489 (262 531)

EA: eosinophilic asthma; ER: emergency room; HCRU: healthcare resource utilization; SCS: systemic corticosteroid; SEA: severe eosinophilic asthma.

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/ μ L, 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

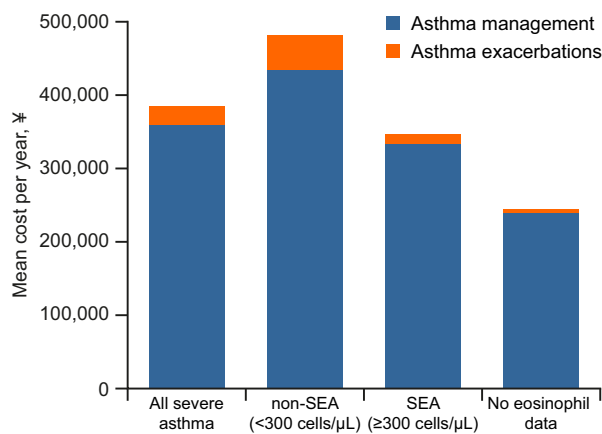


Figure 4. Severe asthma-related medical costs during the 12-month follow-up period, stratified by eosinophil count relating to asthma management and asthma exacerbations. HCRU was stratified into two categories relating to asthma-management (outpatient visits, laboratory examinations, asthma-controller medications, home healthcare, other [fees for rehabilitation, management, prescriptions and injections]) and asthma exacerbations (hospital admissions, ER visits, and SCS treatment). ER, emergency room; HCRU, healthcare resource utilization; SCS, systemic corticosteroid; SEA, severe eosinophilic asthma.

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/ μ L almost always had a sputum eosinophil count $\geq 2\%$, 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/ μ L) 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.

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