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Original Article

Prevalence, disease burden, and treatment reality of patients with severe, uncontrolled asthma in Japan

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ANOVA, analysis of variance; ATS, American Thoracic Society; CI, confidence interval; COPD, chronic obstructive pulmonary disease; ERS, European Respiratory Society; GERD, gastroesophageal reflux disease; ICS, inhaled corticosteroids; LABA, long-acting β_2 -agonist; LAMA, long-acting muscarinic antagonist; OCS, oral corticosteroids; SCA, severe, controlled asthma; SUA; severe, uncontrolled asthma; USD, United States Dollars

ABSTRACT

Background: The severe asthma and severe, uncontrolled asthma (SUA) populations in Japan are not well-studied. We investigated the prevalence of continuously treated severe asthma and SUA patients, their disease burden, and the treatment reality via a Japanese health insurance claims database.

Methods: Continuously treated asthma patients (patients prescribed inhaled corticosteroids for asthma ≥ 4 times in the past year) aged ≥ 17 years at the index date (latest visit between April 2014 and March 2015 for asthma treatment) were included in this analysis (KEIFU study, UMIN000027695). Asthma severity and control status at the index date were defined using modified criteria of ERS/ATS guidelines. Asthma hospitalization, oral corticosteroid (OCS) use, and total medical expenses were calculated using data up to 12 months post-index date.

Results: We identified 10,579 patients as continuously treated asthma patients. Of these, 823 (7.8%) had severe asthma; 267 (2.5%) and 556 (5.3%) patients had SUA and severe, controlled asthma (SCA), respectively. Compared with SCA and mild to moderate asthma patients, a greater percentage of SUA patients required hospitalization (13.7%, 6.2%, and 3.0%, respectively) and were prescribed OCSs (67.4%, 45.9%, and 16.2%, respectively). Yearly total medical expenses were also greater for SUA patients (mean [standard deviation]: 8346 [12,280], vs 5989 [10,483] and 3422 [8800] USD, respectively).

Conclusions: The percentages of severe asthma and SUA patients continuously treated in Japan were obtained through this large-scale analysis using a health insurance claims database. SUA patients had greater medical and economic burdens, suggesting more appropriate treatment is required according to the treatment guidelines.

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Introduction

Asthma is a chronic inflammatory airway disease.¹ According to the World Health Organization, approximately 235 million individuals currently suffer from asthma globally.² Respiratory

symptoms caused by asthma are not only numerous and varied, but their patterns also differ from patient to patient (from mild, intermittent to very severe, persistent symptoms). Thus, asthma patients are classified from a variety of standpoints.¹

Patients with severe asthma, especially those with uncontrolled symptoms, are a noteworthy population, in consideration of the degree of the disease-related physical, social, and economic burdens they experience.^{3,4} Moreover, a population of severe asthma patients in whom disease control is difficult, even with the appropriate use of medication, is an ongoing medical issue of major concern. Although there is no universal definition of severe asthma,⁵ the task force of the European Respiratory Society (ERS)

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and the American Thoracic Society (ATS) has recently defined severe asthma as asthma that requires treatment with high-dosage inhaled corticosteroids (ICS) plus a second controller and/or systemic corticosteroids to prevent it from becoming “uncontrolled”, or which remains “uncontrolled” despite this therapy.⁶ This task force recently reported that the severe asthma population accounts for 5%–10% of the global asthma population.⁶ However, there are very few reports that focus on the concrete percentage of severe asthma patients in Japan. Moreover, global information on the percentage of uncontrolled patients of those with severe asthma is very limited.^{4,7–11} Several studies have reported on the patient characteristics and treatment patterns of uncontrolled asthma patients in actual clinical practice, but details are lacking.^{4,7,12} A better understanding of such issues and more detailed information regarding uncontrolled asthma will be instrumental in improving treatment regimens and outcomes for patients, particularly those with severe asthma. Therefore, we selected a large-scale, employee- and family-based health insurance claims database as a data source and assessed the percentages and the disease burden and treatment reality of severe asthma and severe, uncontrolled asthma (SUA) patients.

Methods

Patients

This study included patients who sought care for asthma and were prescribed ICS or ICS/long-acting β_2 -agonist (LABA) between 1 April 2014 and 31 March 2015. For each patient, the visit for asthma was confirmed based on ICD-10 codes (J45 and J46). The index date was defined as the date of the latest visit for asthma in which ICS or ICS/LABA was prescribed within the abovementioned period (Fig. 1). The study inclusion and exclusion criteria were established with the purpose of excluding seasonal impact on asthma status or influence of other diseases such as the common cold.

Patients who met all of the following criteria were defined as those with continuously treated asthma and were eligible for analysis: ≥ 17 years of age at the index date; at least one record of claims data within 12 months before the index date; diagnosis of

asthma at 12 months or more before the index date; and at least four visits for asthma with prescription of ICS or ICS/LABA within 12 months before the index date. Patients who met any of the following criteria were excluded: no prescription of asthma treatment with ICS or ICS/LABA within 6 months or during the period between 7 and 12 months before the index date, or a 6-month or greater interval between any two visits for asthma and prescription of ICS or ICS/LABA within 12 months before the index date.

Study design

This was a non-interventional study (KEIFU study) for which the data were obtained from a health insurance claims database. Using the index date (defined as the latest visit between April 2014 and March 2015 for asthma treatment) as the start date, the patient group was classified by severity and asthma control status, which were defined based on data of prescription for asthma treatment from the past year (Fig. 1). This study was also a historical prospective study as we used data collected on and after the index date up to 12 months to determine the medical resource utilization. The study protocol and its amendments were approved by the Takahashi Clinic Institutional Review Board. This study was conducted in accordance with the Ethical Guidelines for Biomedical Research Involving Human Subjects, the ethical principles of the Declaration of Helsinki, and all relevant regulations applicable to non-interventional studies. The need for informed consent was waived as data available in the database are standardized and anonymized. This study was registered in the UMIN Clinical Trials Registry: UMIN000027695.

The health insurance claims database used in this study is updated and managed by JMDC Inc. (Tokyo, Japan). The database contains health insurance claims (inpatient, outpatient, and pharmacy) and check-up data from over 90 health insurance unions. The database includes the employees (and their dependents) of relatively large corporations and does not include employees of small or medium-sized companies, civil servants, or those who are self-employed. The database includes longitudinal, anonymized data for all insured persons consisting of employees and their insurance-covered family members aged ≤ 74 years. The cumulative population since 2005 is approximately 3.7 million people, accounting for

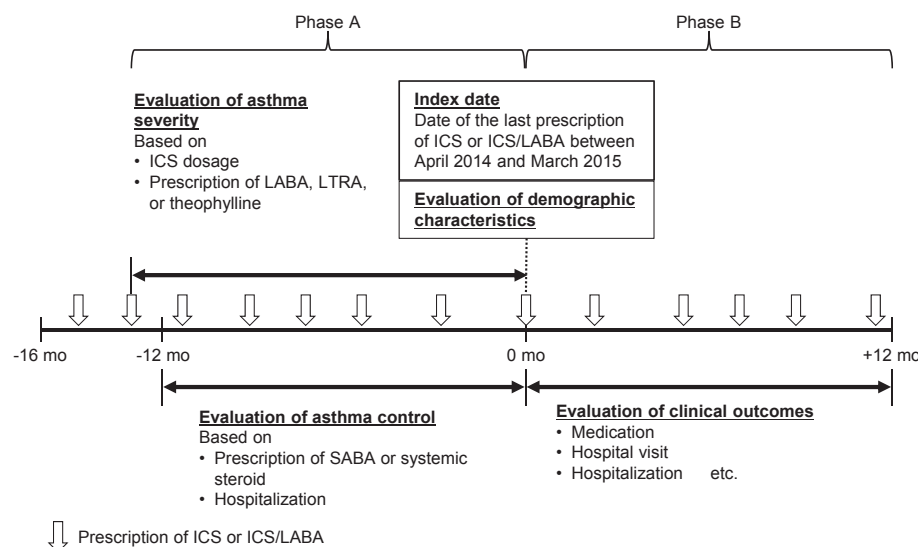


Fig. 1. Time points of study evaluations. Abbreviations: ICS, inhaled corticosteroids; LABA, long-acting β_2 -agonist; LTRA, leukotriene receptor antagonist; SABA, short-acting β_2 -agonist; mo, month.

2.5% of Japan's total population. Data for this study were retrieved from the database in July 2017. This database has served as a data source in several scientific studies.^{13–15}

Definitions of severity and control status of asthma

The definitions of severe asthma and uncontrolled asthma were those described in the International ERS/ATS guidelines on definition, evaluation, and treatment of severe asthma⁶ and adapted to the data available in the database (Supplementary Table 1). Patients with severe asthma were defined as patients prescribed 1600 µg per day budesonide equivalent dosage or a greater ICS dosage plus at least one controller (LABA, leukotriene receptor antagonist (LTRA), or theophylline) during 12 months before the index date. The budesonide equivalent dosage of ICS was calculated based on the prescriptions before the index date as described in Supplementary Figure 1 and Supplementary Table 2. Patients with 183 or more prescription days for systemic corticosteroids within 12 months before the index date were also defined as patients with severe asthma.

Patients were considered to have uncontrolled asthma if they met at least one of the following criteria during the 12 months before the index date: (1) prescription of short-acting β_2 -agonist (SABA) for more than 208 attacks; (2) two or more prescriptions of short-term-use oral corticosteroid (OCS) and/or injectable corticosteroids; and/or (3) hospitalization for asthma with at least one prescription of injectable corticosteroids. In this study, patients who did not meet any of the conditions of severe asthma were classified as having mild to moderate asthma. Having severe controlled asthma (SCA) did not necessarily mean that asthma symptoms were completely controlled but that patients did not fulfill the SUA criteria. Similarly, patients classified as having mild to moderate controlled asthma did not necessarily have completely controlled asthma symptoms, but such patients did not fulfill the “uncontrolled” asthma criteria.

Assessment of prevalence, disease burden, and treatment reality

We evaluated the percentages of patients with severe asthma and SUA among continuously treated asthma patients in this study population at the index date (Fig. 1; Phase A).

In addition, we evaluated the percentages of patients with SCA and mild to moderate asthma). Demographic characteristics and comorbidities (based on ICD-10 codes) were evaluated at the index date (Fig. 1).

For the historical prospective aspect of this study, we evaluated the following outcomes prospectively from the index date up to 12 months: asthma exacerbation-related items (length of hospitalization, number of short-term uses [oral or injectable] of systemic corticosteroids per year, number of patients prescribed short-term-use systemic corticosteroids, and total exposure to systemic corticosteroids per day), treatment reality items (number of outpatient visits per year, asthma medication prescription patterns and number of laboratory tests per year), and economic burden-related items (total medical expenses per year) (Fig. 1; Phase B).

Analysis

All eligible patients were included in the analysis. All outcomes and demographic characteristic data were summarized using descriptive statistics. Claims data without exact dates of prescriptions and tests were replaced with those for the first day of the prescription month or test month. Additional missing data were not replaced.

In addition to reporting descriptive data, we performed a post hoc statistical analysis to investigate possible relationships between demographic data/disease burden/treatment reality and patient subgroup. P-values for age were calculated using an F-test based on a one-way analysis of variance (ANOVA) model that included asthma severity. Fisher's exact test was used to calculate p-values for sex and asthma severity. For continuous outcomes, we estimated the difference between SUA and SCA groups and the difference between SUA and mild to moderate asthma groups using a linear model including patient subgroup and calculated p-values and 95% confidence intervals (CIs). For categorical outcomes, we estimated the odds ratio between SUA and SCA groups and between SUA and mild to moderate asthma groups, and calculated 95% CIs and p-values based on a logistic regression model including subgroup.

We used IBM Netezza analytics (IBM Netezza, Marlborough, MA, USA) and SAS version 9.3 (SAS Institute, Cary, NC, USA) for data analyses.

Results

Patients

Figure 2 shows that, of the 4,081,102 individuals included in the database between the years 2005 and 2016, 2,911,085 were policyholders during the study enrollment period (April 2014 to March 2015). Of these, 96,687 patients were diagnosed with asthma and were prescribed ICS or ICS/LABA. After applying the inclusion and exclusion criteria, 10,579 patients were identified as continuously treated asthma patients.

Prevalence of asthma by severity and control status

Of the 10,579 continuously treated asthma patients extracted from the database during the study period, 823 (7.8%) had severe asthma; 267 (2.5%) of whom had SUA and 556 (5.3%), SCA. There were 9756 (92.2%) patients with mild to moderate asthma; 1646 (15.6%) of whom had uncontrolled asthma and 8110 (76.7%), controlled asthma (Table 1).

Demographics at index date

Regarding the demographic characteristics at the index date (Table 2), mean (standard deviation) ages for SUA, SCA, and mild to moderate subgroups were 50.3 [10.6], 51.6 [12.2], and 47.7 [12.3] years, respectively. The most common comorbidities ($\geq 10\%$ in prevalence) in the SUA and SCA subgroups, respectively, were allergic rhinitis (65.2% and 58.1%), chronic obstructive pulmonary disease (COPD) (35.6% and 25.5%), gastroesophageal reflux disease (GERD) (34.5% and 34.9%), diabetes mellitus (27.7% and 20.5%), osteoporosis (21.7% and 18.3%), and chronic paranasal sinusitis (16.5% and 10.3%). In the mild to moderate asthma subgroup, the most common comorbidities included allergic rhinitis (52.8%), GERD (15.6%), COPD (13.7%), and diabetes mellitus (11.3%). Notably, in the mild to moderate asthma subgroup, osteoporosis (2.5%) was not a common comorbidity, unlike in the SUA and SCA subgroups.

Prospectively evaluated outcomes (disease burden, treatment reality, and economic burden)

The results of other outcomes evaluated prospectively using data from the index date to 12 months are summarized in Table 3–5. The mean dosage of regular-use OCS was greater for the SUA subgroup (2.99 [5.04] mg per day, prednisolone equivalent) compared with the SCA (1.56 [3.16] mg per day, p-value for the

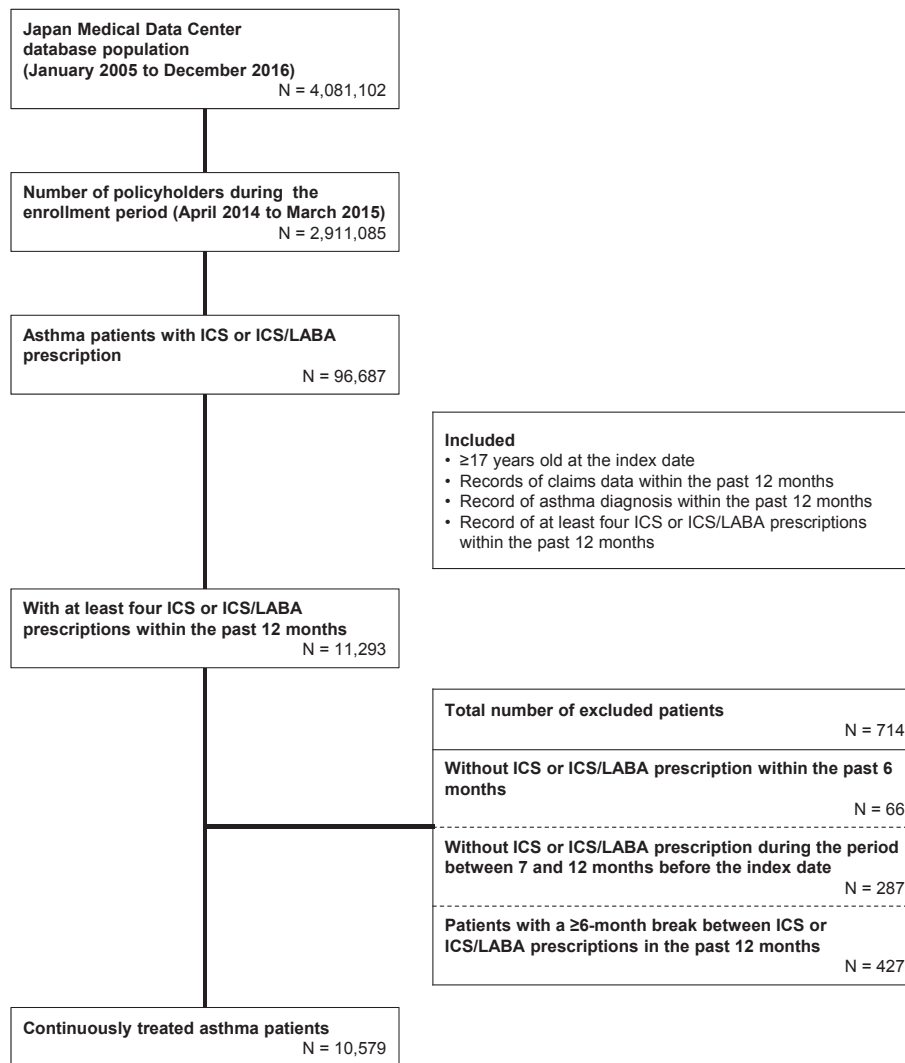


Fig. 2. Patient disposition. Abbreviations: ICS, inhaled corticosteroids; LABA, long-acting β_2 -agonist.

Table 1
Percentage of patients in each asthma severity subgroup.

Continuously treated asthma		Severe asthma			Mild to moderate asthma		
			Uncontrolled	Controlled		Uncontrolled	Controlled
N	10,579	823	267	556	9756	1646	8110
% (95% CI)	—	7.8 (7.3–8.3)	2.5 (2.2–2.8)	5.3 (4.8–5.7)	92.2 (91.7–92.7)	15.6 (14.9–16.3)	76.7 (75.8–77.5)

CI, confidence interval.

comparison vs SUA group<0.001) and mild to moderate asthma (0.14 [0.75] mg per day, p-value for the comparison vs SUA<0.001) subgroups (Table 3).

Regarding asthma exacerbation-related items, the mean number of short-term uses of systemic corticosteroids (2.29 [3.27] times per year) in the SUA subgroup was greater than that of the SCA (0.30 [0.92] times per year, p-value for the comparison vs SUA group<0.001) and mild to moderate asthma (0.41 [4.13] times per year, p-value for the comparison vs SUA group<0.001) subgroups (Table 4). Similarly, the percentage of patients prescribed short-term-use systemic corticosteroids was greater for the SUA subgroup (53.9%) compared with the SCA (14.9%, p-value for the comparison vs SUA group<0.001) and mild to moderate asthma (13.2%, p-value for the comparison vs SUA group<0.001) subgroups

(Table 4). The mean dosage of short-term-use OCS was greater for the SUA subgroup (0.28 [1.29] mg per day) compared with the SCA (0.02 [0.21] mg per day, p-value for the comparison vs SUA group<0.001) and mild to moderate asthma (0.02 [0.70] mg per day, p-value for the comparison vs SUA group<0.001) subgroups (Table 3). The mean dosage of injectable corticosteroids was at least 10-fold greater for the SUA subgroup (1.22 [4.01] mg per day) compared with the SCA (0.11 [0.66] mg per day, p-value for the comparison vs SUA group<0.001) and mild to moderate asthma (0.08 [0.61] mg per day, p-value for the comparison vs SUA group<0.001) subgroups (Table 3). The mean length of hospitalization (4.51 [19.50] and 1.78 [12.59] days per year, p-value for the comparison vs SUA group = 0.005) and the percentage of patients who required hospitalization (13.7% and 6.2%, p-value for the

Table 2
Demographic characteristics of patients.

	Continuously treated asthma	Severe asthma		Mild to moderate asthma	p-value [†]
		Uncontrolled	Controlled		
	N = 10,579	N = 267	N = 556	N = 9756	
Age, years, mean (SD)	48.0 (12.2)	50.3 (10.6)	51.6 (12.2)	47.7 (12.3)	<0.001
Female, n (%)	5302 (50.1)	135 (50.6)	316 (56.8)	4851 (49.7)	0.005
Comorbidity, n (%) [‡]					
Allergic rhinitis	5652 (53.4)	174 (65.2)	323 (58.1)	5155 (52.8)	<0.001
GERD	1806 (17.1)	92 (34.5)	194 (34.9)	1520 (15.6)	<0.001
COPD	1577 (14.9)	95 (35.6)	142 (25.5)	1340 (13.7)	<0.001
Diabetes mellitus	1286 (12.2)	74 (27.7)	114 (20.5)	1098 (11.3)	<0.001
Chronic paranasal sinusitis	879 (8.3)	44 (16.5)	57 (10.3)	778 (8.0)	<0.001
Atopic dermatitis	616 (5.8)	25 (9.4)	46 (8.3)	545 (5.6)	0.002
Osteoporosis	404 (3.8)	58 (21.7)	102 (18.3)	244 (2.5)	<0.001
Sleep apnea	195 (1.8)	14 (5.2)	13 (2.3)	168 (1.7)	0.001
Nasal polyp	61 (0.6)	4 (1.5)	3 (0.5)	54 (0.6)	0.135
Vocal cord dysfunction	16 (0.2)	3 (1.1)	0 (0.0)	13 (0.1)	0.012

ANOVA, analysis of variance; COPD, chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease; SD, standard deviation.

[†] p-values were calculated using the F-test (one-way ANOVA) for continuous variables and Fisher's exact test for categorical variables.

[‡] Comorbidities were identified using the assigned ICD-10 codes at the index date.

Table 3
Total exposure to systemic corticosteroids per asthma severity subgroup.

Statistics		Continuously treated asthma	Severe asthma		Mild to moderate asthma
			Uncontrolled	Controlled	
		N = 10,579	N = 267	N = 556	N = 9756
OCS, mg per day [†]	Mean (SD)	0.31 (1.57)	3.27 (5.09)	1.58 (3.17)	0.16 (1.03)
	Mean Diff vs SUA (95% CI) [‡]	—	—	−1.70 (−1.91, −1.48)	−3.12 (−3.29, −2.94)
	p-value [‡]	—	—	<0.001	<0.001
Regular-use OCS, mg per day [§]	Mean (SD)	0.28 (1.40)	2.99 (5.04)	1.56 (3.16)	0.14 (0.75)
	Mean Diff vs SUA (95% CI) [‡]	—	—	−1.43 (−1.62, −1.24)	−2.86 (−3.01, −2.70)
	p-value [‡]	—	—	<0.001	<0.001
Short-term-use OCS, mg per day [¶]	Mean (SD)	0.03 (0.70)	0.28 (1.29)	0.02 (0.21)	0.02 (0.70)
	Mean Diff vs SUA (95% CI) [‡]	—	—	−0.26 (−0.37, −0.16)	−0.26 (−0.35, −0.17)
	p-value [‡]	—	—	<0.001	<0.001
Injectable corticosteroids, mg per day [†]	Mean (SD)	0.11 (0.90)	1.22 (4.01)	0.11 (0.66)	0.08 (0.61)
	Mean Diff vs SUA (95% CI) [‡]	—	—	−1.11 (−1.23, −0.98)	−1.14 (−1.24, −1.03)
	p-value [‡]	—	—	<0.001	<0.001

CI, confidence interval; Diff, difference; OCS, oral corticosteroids; SD, standard deviation; SUA, severe uncontrolled asthma; SCA, severe controlled asthma.

[†] The dosage of OCS and injectable corticosteroids is indicated as prednisolone equivalent.

[‡] Based on a linear model including severity of asthma (SUA/SCA/mild to moderate) as a covariate.

[§] Regular-use OCS refers to OCS prescription data excluding short-term uses of OCS.

[¶] Short-term-use OCS refers to OCS prescription data with the record to use as needed.

comparison vs SUA group = 0.001) were greater for the SUA group than the SCA group (Table 4).

Asthma medication prescription patterns are provided in Supplementary Table 3. The most commonly prescribed asthma treatment drugs (prescribed in $\geq 10\%$ of patients) in the SUA and SCA subgroups, respectively, were ICS/LABA (87.6% and 80.6%), LTRA (73.0% and 66.9%), OCS (67.4% and 45.9%), SABA (59.6% and 21.4%), theophylline (53.2% and 36.2%), injectable corticosteroids (49.4% and 13.3%), single-agent ICS (23.2% and 26.3%), LABA (18.7% and 15.3%), and long-acting muscarinic antagonists (LAMAs) (15.0% and 10.4%). In the mild to moderate asthma subgroup, the most commonly prescribed asthma treatment drugs were ICS/LABA (77.7%), LTRA (46.3%), single-agent ICS (29.9%), SABA (24.0%), theophylline (21.6%), OCS (16.2%), LABA (12.8%), and injectable corticosteroids (11.9%).

The mean number of outpatient visits was greater for patients with SUA vs those with SCA (19.39 [18.84] and 13.53 [12.96] days per year, p-value for the comparison vs SUA group <0.001). Similarly, the mean number of eosinophil tests per year was greatest for SUA patients (1.54 [4.68]), followed by SCA (1.01 [4.74]) and mild to moderate (0.48 [2.63]) asthma patients. The mean number of spirometry tests per year among subgroups was similar; SUA (0.54

[2.64]), SCA (0.65 [1.87], p-value for the comparison vs SUA group = 0.711) and mild to moderate asthma (0.38 [4.33], p-value for the comparison vs SUA group = 0.548). In terms of economic burden-related items, the mean total medical expenses per year were greater for the SUA subgroup (8346 [12,280] USD) compared with the SCA (5989 [10,483] USD, p-value for the comparison vs SUA group = 0.001) and mild to moderate asthma (3422 [8800] USD, p-value for the comparison vs SUA group <0.001) subgroups (Table 5).

Discussion

This non-interventional/historical prospective study aimed to provide more substantial information regarding severe asthma and SUA. In this study, we evaluated the treatment reality in continuously treated patients in actual clinical practice using a health insurance claims database in Japan. Regarding the primary findings, our study revealed that, of continuously treated patients, the percentage of patients with severe asthma was 7.8%, which corresponds to the prevalence estimated globally.⁶ Of continuously treated patients, 2.5% had SUA and 5.3% had SCA; i.e., among severe asthma patients, approximately one third had SUA and two thirds

Table 4
Exacerbation-related items: Length of hospitalization, number of patients who required hospitalization, and short-term use of systemic corticosteroids by asthma severity subgroup.

Statistics	Continuously treated asthma	Severe asthma		Mild to moderate asthma
		Uncontrolled	Controlled	
Hospitalization [†]				
Length of hospitalization, days per year	N = 10,144	N = 249	N = 517	N = 9378
Mean (SD)	1.05 (12.66)	4.51 (19.50)	1.78 (12.59)	0.92 (12.42)
Mean Diff vs SUA (95% CI) [‡]	—	—	−2.72 (−4.64, −0.81)	−3.59 (−5.18, −2.00)
p-value [§]	—	—	0.005	<0.001
Patients who required hospitalization	n (%)	34 (13.7)	32 (6.2)	279 (3.0)
Odds ratio vs SUA (95% CI) [‡]	—	—	0.42 (0.25, 0.69)	0.19 (0.13, 0.28)
p-value [§]	—	—	0.001	<0.001
Short-term use of systemic corticosteroids [§]				
Times per year	N = 10,579	N = 267	N = 556	N = 9756
Mean (SD)	0.45 (4.01)	2.29 (3.27)	0.30 (0.92)	0.41 (4.13)
Mean Diff vs SUA (95% CI) [‡]	—	—	−2.00 (−2.58, −1.41)	−1.89 (−2.37, −1.40)
p-value [§]	—	—	<0.001	<0.001
Patients prescribed short-term systemic corticosteroids	n (%)	144 (53.9)	83 (14.9)	1288 (13.2)
Odds ratio vs SUA (95% CI) [‡]	—	—	0.15 (0.11, 0.21)	0.13 (0.10, 0.17)
p-value [§]	—	—	<0.001	<0.001

CI, confidence interval; Diff, difference; SD, standard deviation; SUA, severe uncontrolled asthma; SCA, severe controlled asthma.

[†] Patients whose last visit date after index date was at the same month as index date were excluded from the evaluation.

[‡] Based on a linear model for continuous variables and logistic regression model for dichotomous variables. Models included severity of asthma (SUA/SCA/mild to moderate) as the covariate.

[§] Short-term use of oral corticosteroids and injectable corticosteroids.

Table 5
Number of outpatient visits, laboratory tests and total medical expenses per year by asthma severity subgroup.

Statistics	Continuously treated asthma	Severe asthma		Mild to moderate asthma
		Uncontrolled	Controlled	
Number of outpatient visits (days) per year [†]				
Mean (SD)	N = 10,144 10.39 (10.07)	N = 249 19.39 (18.84)	N = 517 13.53 (12.96)	N = 9378 9.98 (9.39)
Mean Diff vs SUA (95% CI) [‡]	—	—	−5.86 (−7.36, −4.36)	−9.40 (−10.66, −8.15)
p-value [§]	—	—	<0.001	<0.001
Number of laboratory tests per year [§]				
Eosinophil count [†]	N = 10,579	N = 267	N = 556	N = 9756
Mean (SD)	0.54 (2.85)	1.54 (4.68)	1.01 (4.74)	0.48 (2.63)
Mean Diff vs SUA (95% CI) [‡]	—	—	−0.53 (−0.95, −0.12)	−1.06 (−1.40, −0.71)
p-value [§]	—	—	0.012	<0.001
Spirometry ^{††}	Mean (SD)	0.54 (2.64)	0.65 (1.87)	0.38 (4.33)
Mean Diff vs SUA (95% CI) [‡]	—	—	0.12 (−0.50, 0.73)	−0.16 (−0.67, 0.35)
p-value [§]	—	—	0.711	0.548
Total medical expenses per year ^{‡‡}				
USD	N = 10,144	N = 249	N = 517	N = 9378
Mean (SD)	3673 (9041)	8346 (12,280)	5989 (10,483)	3422 (8800)
Mean Diff vs SUA (95% CI) [‡]	—	—	−2357 (−3,717, −997)	−4924 (−6,056, −3792)
p-value [§]	—	—	0.001	<0.001

CI, confidence interval; Diff, difference; SD, standard deviation; SUA, severe uncontrolled asthma; SCA, severe controlled asthma; USD, United States Dollars.

[†] Patients whose last visit date after index date was at the same month as index date were excluded from the evaluation.

[‡] Based on a linear model including severity of asthma (SUA/SCA/mild to moderate) as a covariate.

[§] Laboratory tests are categorized based on database terms for “medical treatment classification” and “clinical practice”.

[†] Average number of complete blood count tests and eosinophil count tests (in sputum or nasal smears) per year.

^{††} Average number of spirometry examinations per year.

^{‡‡} Total medical expenses per year were calculated based on the total number of health insurance claim points obtained from visit records converted to yen. The resulting value was converted to USD (1 Yen = 0.0087846917 USD [27 October 2017]).

had SCA. These percentages of severe asthma and SUA among adult asthma patients who have been receiving continuous asthma treatment in Japan are an important finding. Although it is difficult to generalize due to the limitations discussed below, based on these results and data from the national patient survey of the Ministry of Health, Labour and Welfare,¹⁶ approximately 20,000 adult patients in Japan are estimated to have SUA at the time of this study.

The main strength of this study was the method used for analyzing data from Japan's national health insurance claims database. The database we used is especially suitable for large real-world epidemiological studies because it includes nationwide population data under the universal health coverage system in

Japan. The database includes information on consultations, hospitalizations, and treatments provided to patients for any medical condition, including asthma, accumulated not only from primary care centers but also secondary and tertiary care centers. Additionally, because the database accumulates information for all patients under the national insurance program (rather than by health care institution), if patients switch hospitals or care centers during treatment, there are no gaps in data collection. Therefore, using such data reduces the risk of selection bias. Another strength of this study is that we investigated only asthma patients receiving continuous treatment (i.e., patients who had four or more ICS prescriptions in a year and excluding patients who had no ICS

prescription in the last 6 months). We also evaluated asthma severity and control status based on data accumulated for a full year prior to the index date. This enabled us to evaluate asthma severity and control status more precisely. Notably, this approach is in line with the ERS/ATS guidelines, which define severe asthma according to treatment administered over the course of 1 year.⁶

By using the historical prospective study approach, in which outcomes were assessed from the index date up to 12 months, and considering the level of asthma control at the index date, we found that patients with severe asthma bear a heavy burden. This is in line with the higher rates of health care utilization reported for severe asthma patients in the TENOR¹⁷ and other studies.^{4,10} Our study also revealed that the mean length of hospitalization and the percentages of patients requiring hospitalization were higher in the SUA group compared with the other subgroups. Furthermore, the SUA subgroup had a higher prescription rate and required greater dosages of systemic corticosteroids compared with the other subgroups. Injectable corticosteroids were also prescribed in a higher percentage of SUA patients (49.4%) compared with SCA patients (13.3%). Furthermore, SUA patients also had a higher percentage of LAMA prescriptions compared to SCA (15.0 vs 10.4%). In some cases, LAMA agents are used off-label for asthma treatment before they are actually indicated for asthma, and although LAMA use and COPD comorbidity may be a confounding factor in this study, it is impossible to identify COPD patients based on LAMA prescription records, because the database does not necessarily record reasons for the prescription of each agent. These findings indicate that SUA patients experience more severe and more frequent exacerbations compared with other groups because injectable corticosteroids are mainly reserved for outpatients with symptom worsening at unscheduled visits or at the emergency room.

The medical expenses were higher in the SUA subgroup compared with other subgroups possibly because a higher percentage of patients in the SUA subgroup required hospitalization and a larger variety of drugs for asthma treatment than patients in the other subgroups. Patients in the SUA subgroup had a markedly higher frequency of non-allergic comorbidities, such as diabetes mellitus, osteoporosis, and GERD, compared with the SCA subgroup. It is possible that the greater expenditures for the SUA subgroup resulted not only from the treatment costs of severe asthma but also from the costs related to non-allergic comorbidities in addition to the costs resulting from comorbidities associated with the chronic use of systemic corticosteroids.

The mean dosage of regular-use OCS was greater for the SUA subgroup (2.99 [5.04] mg per day, prednisolone equivalent) compared with the SCA (1.56 [3.16] mg per day) and mild to moderate asthma (0.14 [0.75] mg per day) subgroups. In addition, the greater frequency of diabetes mellitus and osteoporosis in the SUA subgroup, compared with the other subgroups, may reflect the potential adverse effects of long-term use of systemic corticosteroids.¹⁸ Thus, SUA patients may be at an increased risk of various adverse effects associated with the chronic or frequent use of systemic corticosteroids.¹⁹

In consideration of patients whose symptoms are still uncontrolled despite adequate medication, there is a clear need for further treatment options. In cases where control is difficult with administration of medium/high dosages of ICS plus LABA, it is necessary to consider the needs of the patient on an individual basis and consider more appropriate treatment, such as treatment intensification or alternate options according to the treatment guidelines.^{1,6} Notably, during this study, only 3.0% of patients diagnosed with SUA received omalizumab. However, it is possible that some patients among the 97% who did not receive biologics during the study may have been previously treated with omalizumab, but discontinued treatment owing to a lack of efficacy or other reasons. Nevertheless, it is

possible that a considerable number of patients may have been treatment-naïve with respect to biologic therapies. As several biologics other than omalizumab have demonstrated efficacy,²⁰ a more proactive administration of biologics should be considered for patients with SUA in the future; although, all available options should be considered for each patient. At the time the present study was conducted, omalizumab was the only approved biologic drug for the treatment of SUA in Japan; thus, the database we used cannot provide information on use of newer biologics. As other biologics become available, these represent additional possible treatment options. The data obtained in the present study may provide important insights into the unmet needs of patients and the possibility of using newer medications, and therefore may be useful for future health care administration decision-making.

The main limitations of the study relate to the characteristics of the database used; namely, the database only includes employees (and their dependents) of large companies, which may have introduced bias to the sample population. Although the logical algorithm we developed confirmed treatment continuity and disease severity, the actual consumption of ICS and other drugs was not clear. Another shortcoming was the lack of patient-reported and medical record data; thus, the actual symptoms and control status may not be entirely accurate. Patients aged ≥ 75 years are not included in this database; therefore, our results cannot be assumed to reflect asthma status in the elderly population. In addition, the greater percentage of males vs females in the database may not be representative of the actual clinical sex ratio. Moreover, because no patients aged ≥ 75 years are included in this database, it is possible that the extrapolated number of each category of asthma patients among the total Japanese adult asthma population may be an over- or underestimate. In some cases, it was difficult to confirm the dosage prescribed based on the product name; thus, the ICS dosage used to estimate severity may not have been accurate. It is also possible that injectable corticosteroids were prescribed to treat conditions other than asthma. Despite these weaknesses, our study sheds light on the current status of patients with SUA and provides evidence of their treatment reality.

In conclusion, this large-scale health insurance claims database analysis revealed the percentages of patients with severe asthma and SUA among patients receiving continuous asthma treatment in Japan. The frequency of asthma exacerbations and direct health care costs were greater for SUA patients compared with both SCA and mild to moderate asthma patients. SUA patients required more medical resources seemingly due to asthma itself and non-allergic comorbidities. SUA patients had greater medical and economic burdens. On this basis, it is necessary to consider individual needs of the patient and more appropriate treatment approaches, such as intensification of current therapies or switching to other treatment options, which may be required according to the treatment guidelines.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.alit.2019.06.003>.

Conflict of interest

HN has received honoraria from AstraZeneca, Nippon Boehringer Ingelheim, and Kyorin Pharmaceutical. MA has received honoraria from AstraZeneca, Toa Pharmaceuticals, and Novartis Pharma. KM has received honoraria from AstraZeneca, Astellas Pharma, Nippon Boehringer Ingelheim, Kyorin Pharmaceutical, and Novartis Pharma. AY, TO, NH, and KE are all employees of AstraZeneca. YT has received honoraria from Boehringer Ingelheim and research funding from Kyorin Pharmaceutical and Meiji Seika Pharma.

Authors' contributions

HN, MA, KM, AY, TO, NH, KE, and YT designed the study, interpreted the data, and critically reviewed and approved the manuscript. AY, TO, NH, and KE developed the analysis plan. All authors read and approved the final manuscript.

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Supplementary Table 1. ERS/ATS criteria¹ applied in this study and conversions applied for the use of data available in the database

Category	ERS/ATS criteria	Items used for criteria of control in this study (by using data available in the database)	
		Use of ERS/ATS criteria without alteration	Conversion from ERS/ATS criteria
Severe asthma	GINA ² Step 4–5	×	Prescribed high-dosage ICS plus at least one other controller
	Use of systemic corticosteroids $\geq 50\%$	Number of days of prescriptions for systemic corticosteroids ≥ 183	—
Severe, uncontrolled asthma	ACQ >1.5 ACT <20	×	Number of SABA prescription records (≥ 208 attacks) [†]
	Short-term use of systemic corticosteroids ≥ 2 times (>3 times each)	×	At least two prescription records for short-term use of systemic corticosteroids or injectable corticosteroids [‡]
	Hospitalization admission to ICU mechanical ventilation ≥ 1 time	Number of hospitalizations for asthma [§] (emergency visits cannot be used)	—
	Airflow limitation	×	×

ERS/ATS, European Respiratory Society and American Thoracic Society; ICU, intensive care unit; ICS, inhaled corticosteroids; LABA, long-acting β_2 -agonist; SABA, short-acting β_2 -agonist; OCS, oral corticosteroids; GINA, Global Initiative for Asthma; ACQ, Asthma Control Questionnaire; ACT, Asthma control test

[†]Refers to a description of one criterion of level of asthma symptom control in GINA 2017 – “Reliever needed more than twice/week (in the past 4 weeks)” – and considering real-world usage of SABA as 50% of each formulation. The number of inhalations per attack depends on the formulation.

[‡]Refers to patients with at least two prescription records for short-term use of systemic corticosteroids or injectable corticosteroids ≤ 12 months prior to the index date. However, a minimum 14-day interval between the relevant record and the previous record was required.

§With at least one prescription of injectable corticosteroids.

×: data in the database could not be used as originally recorded. In these cases, criteria were altered so that data compiled in the database could be used (shown in the right column).

—: conversion of criteria was not necessary because data from the database could be used as originally recorded.

Note that the criterion for airflow limitation could not be appropriately converted and therefore was not used in this study.

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Supplementary Table 2. Conversion coefficients for conversion of inhaled corticosteroid dosage to budesonide dosage

Inhaled corticosteroids	Conversion to budesonide: Multiply the dosage (µg) by the following coefficients
Beclomethasone propionate ester/fluticasone propionate ester/ciclesonide/mometasone furoate ester	2.0
Fluticasone propionate ester/salmeterol–fluticasone propionate ester combination drug/formoterol fumarate hydrate combination drug	1.6
Fluticasone furoate ester/vilanterol trifenate combination drug	8.0
Budesonide/formoterol fumarate hydrate combination drug	1.25
Budesonide inhalation suspension	0.8

Supplementary Table 3. Prescription patterns of asthma treatment drugs stratified by asthma severity

Type of drug prescribed	Continuously treated asthma	Severe asthma		Mild to moderate asthma	p-value [†]
		Uncontrolled	Controlled		
	N = 10,579	N = 267	N = 556	N = 9,756	
ICS/LABA	8,265 (78.1)	234 (87.6)	448 (80.6)	7,583 (77.7)	<0.001
LTRA	5,086 (48.1)	195 (73.0)	372 (66.9)	4,519 (46.3)	<0.001
Single-agent ICS	3,128 (29.6)	62 (23.2)	146 (26.3)	2,920 (29.9)	0.012
SABA	2,621 (24.8)	159 (59.6)	119 (21.4)	2,343 (24.0)	<0.001
Theophylline	2,454 (23.2)	142 (53.2)	201 (36.2)	2,111 (21.6)	<0.001
OCS	2,020 (19.1)	180 (67.4)	255 (45.9)	1,585 (16.2)	<0.001
LABA	1,387 (13.1)	50 (18.7)	85 (15.3)	1,252 (12.8)	0.007
Injectable corticosteroids	1,363 (12.9)	132 (49.4)	74 (13.3)	1,157 (11.9)	<0.001
LAMA	318 (3.0)	40 (15.0)	58 (10.4)	220 (2.3)	<0.001
Biological preparation [‡]	25 (0.2)	8 (3.0)	5 (0.9)	12 (0.1)	<0.001

Data in the table are presented as number of patients (%). Prescription patterns refer to the prescription records of the drugs in the database.

[†]p-values were calculated using Fisher's exact test for categorical variables.

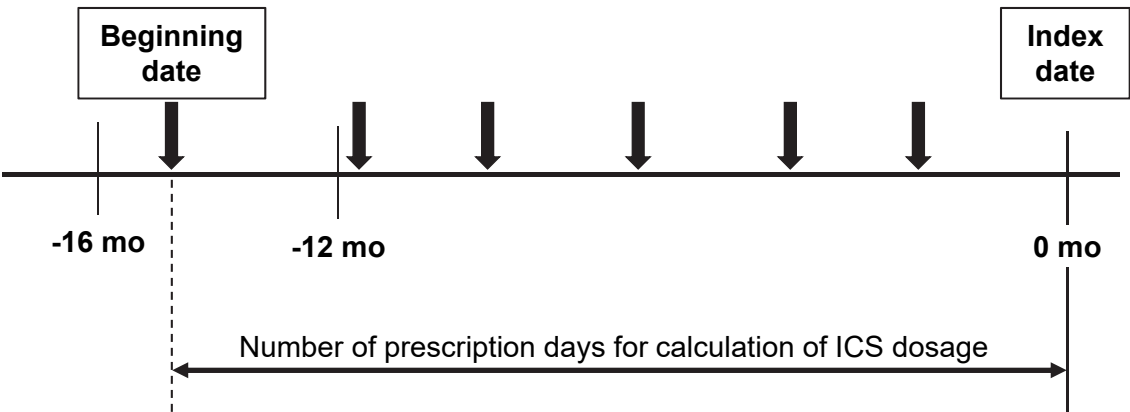
[‡]Only anti-IgE antibody is included during the period of this study.

ICS, inhaled corticosteroids; LABA, long-acting β_2 -agonist; LTRA, leukotriene receptor antagonist; SABA, short-acting β_2 -agonist; LAMA, long-acting muscarinic antagonist; OCS, oral corticosteroids

Supplementary Figure 1

Calculation of ICS dosage prescribed. The beginning date was defined as the date of the most recent asthma visit with ICS or ICS/LABA prescription between 12 and 16 months before the index date. If no such date existed, the beginning date was set as the oldest date of ICS or ICS/LABA prescription during 12 months before the index date. We then added the dosages of ICS or the ICS portion of ICS/LABA prescribed (equivalent dosage of budesonide) between the beginning date and the index date (excluding prescription on the index date). We multiplied the number of days in said period by 80% and then divided the sum of the dosages by the product (number of days) of the above multiplication.

ICS, inhaled corticosteroids; LABA, long-acting β_2 -agonist



↓ Prescription of ICS or ICS/LABA to calculate dosage prescribed

ICS dosage per day*	
High dosage	1,600 µg/day
Intermediate dosage	800 µg/day

*(Sum of the ICS dosage prescribed) ÷ (Number of prescription days × 0.8)