The Prevalence, Characteristics, and Patient Burden of Severe Asthma Determined by Using a Japan Health Care Claims Database

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ABSTRACT

Background: Recently, several new biological drugs targeting severe asthma are on the market, and various studies on severe asthma have been reported worldwide. However, in Japan, the data are still limited regarding epidemiology and burden of disease on severe asthma. This study determined the prevalence, characteristics, and burden of disease of patients with severe asthma.

Methods: : This retrospective study (HO-16-16484) used a nationwide health care claims database. Severity of asthma was defined according to the treatment during the baseline period (April 1, 2014−March 31, 2015). Eligible patients were >15−65 years of age with asthma during the 12-month baseline period and were followed up for 12 months. End points included the prevalence, characteristics, exacerbation frequency, and patient behavior in patients with severe, moderate, or mild asthma. Risk factors for exacerbations were explored in patients with all levels of asthma severity and in those with severe asthma.

Findings: Among the 16,107 patients with asthma, 2.4 (95% CI, 2.1−2.6) per 100 patients had severe asthma. During the baseline period, 130 (34.0%) of 382 patients with severe asthma had ≥1 asthma exacerbation. The exacerbation frequency was highest in patients with severe asthma, and most of the comorbidities increased in proportion to the asthma severity. During the follow-up period, exacerbation frequency increased with asthma severity. Approximately 70% of patients with severe asthma were treated at clinics, requiring outpatient visits ~10 times per year. Different exacerbation risk factors were identified between patients with all severity levels of asthma and those with severe asthma. With the severe asthma patients, experiencing exacerbations during the previous year was a risk factor for further exacerbations during the follow-up period.

Implications: In Japan, 2.4% of patients with asthma have severe asthma, and there is a significant burden of disease in patients with severe asthma undergoing high-intensity treatment. (*Clin Ther.* 2019;41:2239−2251)

Key words: burden of disease, claims database, prevalence, severe asthma.

INTRODUCTION

Asthma is a heterogeneous, chronic respiratory disease characterized by airway inflammation and recurrent attacks of breathlessness and wheezing that vary in severity and frequency from person to person.[1,2] The disease is recognized as a serious global health problem affecting all age groups, with World Health Organization estimates from 2015 suggesting that 235 million people have asthma and that 383,000 deaths due to asthma occurred worldwide.[1] In Japan, the Japanese Ministry of Health, Labour, and Welfare conducted a survey in October 2014, which revealed that 1,177,000 people (515,000 men and 662,000 women) were receiving asthma treatment.[3]

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Severe asthma has been the subject of a recent global focus due to emerging biological therapies that are expected to help control the disease. The global prevalence of severe asthma is estimated at ~5%–10% of the asthma population,[4,5] varying from 3.6% in the Netherlands to 8.1% in Denmark due to differences in definition of asthma and study design.[6,7] In Japan, there is scarce evidence regarding severe asthma in large-scale studies, and little is known about the disease, including disease burden to patients in daily practice settings.

Previous studies conducted in the United States and the United Kingdom have shown that severe asthma is associated with increased morbidity, treatment burden, and health care costs compared with mild or moderate asthma.[8–11] A cross-sectional survey conducted in northern California found that the total per-person costs for severe asthma are almost triple those for moderate asthma.[9] In Japan, although several studies[12,13] have been conducted to assess severe asthma subphenotypes in patients treated in a hospital-based setting, the clinical characteristics, disease burden, and patient behavior have not been well documented for severe asthma treated in various clinical settings, including local hospitals and clinics.

To better characterize severe asthma in Japan, we analyzed data from a nationwide health insurance claims database provided by JMDC Co, Ltd (Tokyo, Japan). The database includes longitudinal inpatient, outpatient, and pharmacy data from ~3 million (2%) people from the Japanese population as of November 2015. The goal of the present study was to determine the prevalence, characteristics, and patient burden of severe asthma by using data from JMDC.

PATIENTS AND METHODS

Study Design and Data Source

This retrospective study used a health insurance claims database provided by JMDC. One of the main advantages of using the JMDC claims database is that it contains nationwide hospital outpatient, hospital inpatient, and pharmacy data from >90 employee-based health insurance societies. Another advantage is that it provides patient-based longitudinal data; each patient can be tracked by using a consistent unique identifier as long as the patient does not leave the payer that he or she currently belongs to. These patient-based longitudinal data are key to understanding the overall clinical and economic burden to patients with severe asthma in a real-world setting. The database grants insured individuals a unique identifier, allowing patient movement and treatment across medical facilities to be tracked.

The study consisted of a 12-month baseline period (April 1, 2014–March 31, 2015) and a 12-month follow-up period (April 1, 2015–March 31, 2016), with April 1, 2015, defined as the common index date for all patients. During the baseline period, patients meeting the study definition of asthma were identified, and prevalence and characteristic-related data were collected. During the follow-up period, data on asthma-related burdens (including asthma exacerbations and risk factors for future asthma exacerbations) during the baseline period were collected and analyzed.

Study Population

Eligible patients were aged 15–65 years (on April 1, 2014), with a first diagnosis of asthma (*International Classification of Diseases, Tenth Revision* [ICD-10], code J45) at any time before the baseline period, with ≥1 claim with a diagnosis of asthma (ICD-10 code J45) during the baseline period, and continuous enrollment in a health insurance society during both the baseline and follow-up periods. To be enrolled in the study, all patients were required to meet the study definition of asthma: ≥2 prescriptions of an inhaled corticosteroid (ICS) or ICS/long-acting beta-agonist (LABA) during the 12-month baseline period. Patients were excluded from the study if they had a respiratory diagnosis (eg, chronic obstructive pulmonary disease [COPD], emphysema, chronic bronchitis, cystic fibrosis) or if they had an autoimmune diagnosis, multiple sclerosis, nephrotic syndrome, or cancer-related pain. Patients were excluded if they had missing JMDC data required to identify drug prescriptions, asthma exacerbations, asthma outpatient visits, and unscheduled asthma outpatient visits. All patients who satisfied the predefined inclusion and exclusion criteria were selected into the study population (defined as the asthma population).

Definitions of Asthma Severity and Asthma Exacerbations

Patients with asthma were categorized, based on according the intensity of asthma therapy provided

during the baseline period, into the following groups: severe, moderate, and mild asthma. Patients with severe asthma were defined as those who received a ≥240-day prescription of a high-dose ICS as defined by the Japanese guidelines for adult asthma (2014) plus a ≥90-day prescription of an additional controller (LABA, leukotriene receptor antagonist, theophylline, anti−immunoglobulin E monoclonal antibody, or oral corticosteroid) during the 12-month baseline period. In patients prescribed ICS/LABA therapy, the LABA medication counted as an additional controller medication. Patients with moderate asthma were defined as those who received a ≥240-day prescription of a high-/medium-dose ICS, with no prescription for any additional controller. Patients with mild asthma were defined as those not meeting the definition of either severe asthma or moderate asthma. A high-/medium-dose ICS was defined according to the Japanese Guideline for Adult Asthma 2014.[14]

Asthma exacerbations requiring hospitalization or emergency transportation (captured by code 113013810 or 114003010 provided by Health Insurance Claims Review & Reimbursement Services[15]) were identified by using a principal diagnosis of asthma (ICD-10 code J45) or status asthmaticus (ICD-10 code J46) without a nonasthma diagnosis. Asthma exacerbations requiring an outpatient visit with the use of a systemic corticosteroid (either IV or oral) were defined as an asthma outpatient visit accompanied by ≥3 days' administration of corticosteroids; for patients on maintenance systemic corticosteroid therapy, at least a doubling of the existing maintenance dose for ≥3 days was required. These events were identified on an individual patient basis by the JMDC based on the prescription period of each patient.

End Points Assessed During the Baseline Period

Study end points assessed during the baseline period included the prevalence and characteristics of patients with asthma, stratified according to severity. The characteristics assessed included age, sex, concomitant diseases, asthma exacerbation frequency, unscheduled outpatient visits, frequency of pulmonary function tests (vital capacity, flow volume testing, functional residual capacity, fractional exhaled nitric oxide, and multifrequency oscillation), and laboratory tests. To further describe the characteristics of patients with severe asthma, we examined the type of medical institutions they visited for routine asthma management and during asthma exacerbations. Institutions were categorized according to patient capacity (0−19 beds, 20−99 beds, 100−199 beds, and ≥200 beds).

End Points Assessed During the Follow-up Period

Study end points assessed during the follow-up period included asthma-related burdens (eg, asthma exacerbation frequency) stratified according to asthma severity during the baseline period. To explore risk factors associated with the occurrence of asthma exacerbations, the total number of asthma exacerbations during the follow-up period was used as the dependent variable. The characteristics collected during the baseline period were used as the explanatory variables.

Statistical Analysis

Descriptive statistics are provided to summarize the prevalence, characteristics, and burden of the disease on patients with asthma. The prevalence of asthma is shown as per 100 patients and 95% CIs. Categorical variables are presented as number (%), and the continuous variables are presented as mean (SD). The risk factors associated with the occurrence of asthma exacerbations were analyzed by using a logistic model.

The multivariate analyses were conducted as follows: (1) prognostic factors that were significant ($P < 0.1$) when assessed by the univariate analysis in patients with asthma or severe asthma were analyzed; (2) asthma control medications (ICS, ICS/LABA, LABA, leukotriene receptor antagonist, theophylline, anti−immunoglobulin E monoclonal antibody, and oral corticosteroids) were excluded because they were used to define asthma severity, which were included in the main multivariate model; (3) use of short-acting beta-agonists and an asthma management plan with peak flow meters were excluded because they were likely to be caused by the presence of an exacerbation in the previous year (baseline period); (4) osteoporosis was excluded due to the association between osteoporosis diagnosis and daily use of oral corticosteroids for ≥3 months; and (5) daily oral

corticosteroid use for ≥3 months was included only in patients with severe asthma to further examine the influence of oral corticosteroid maintenance therapy on asthma exacerbations.

Age was a categorical variable (<40 years and ≥40 years). Respiratory infections were treated as a single combined variable of any of the following: influenza, pneumonia, mycoplasma pneumonia, and bronchial pneumonia. Eosinophilic concomitant disease was treated as a single combined variable of any of the following: eosinophilic otitis media, eosinophilic rhinosinusitis, eosinophilic pneumonia, allergic bronchopulmonary aspergillosis, and eosinophilic granulomatosis with polyangiitis. References in categorical variables of binary data defined with "yes/no" responses were selected as "no." Other variables, including male sex, age <40 years, and mild severity, were defined as reference values. SAS version 9.3 (SAS Institute, Inc, Cary, North Carolina) was used for analyses.

RESULTS

Patient Population

A total of 16,107 patients with asthma were identified and included in the study analyses (mean age, 41.9 years; 50.6% female). Of these, 13,020 had mild asthma (mean age, 41.2 years; 51.5% female), 2705 had moderate asthma (mean age, 45.0 years; 46.2% female), and 382 had severe asthma (mean age, 45.4 years; 49.0% female). The numbers of patients excluded from the analysis per exclusion criteria are presented in Figure 1. The proportion of patients with a 4-year continuous enrollment was similar across all asthma severity groups (all severity levels of asthma, 81.3%; mild asthma, 81.5%; moderate asthma, 80.6%; and severe asthma, 79.4%).

Prevalence of Severe Asthma

Among the patients with asthma, 2.4 (95% CI, 2.1–2.6) per 100 patients had severe asthma

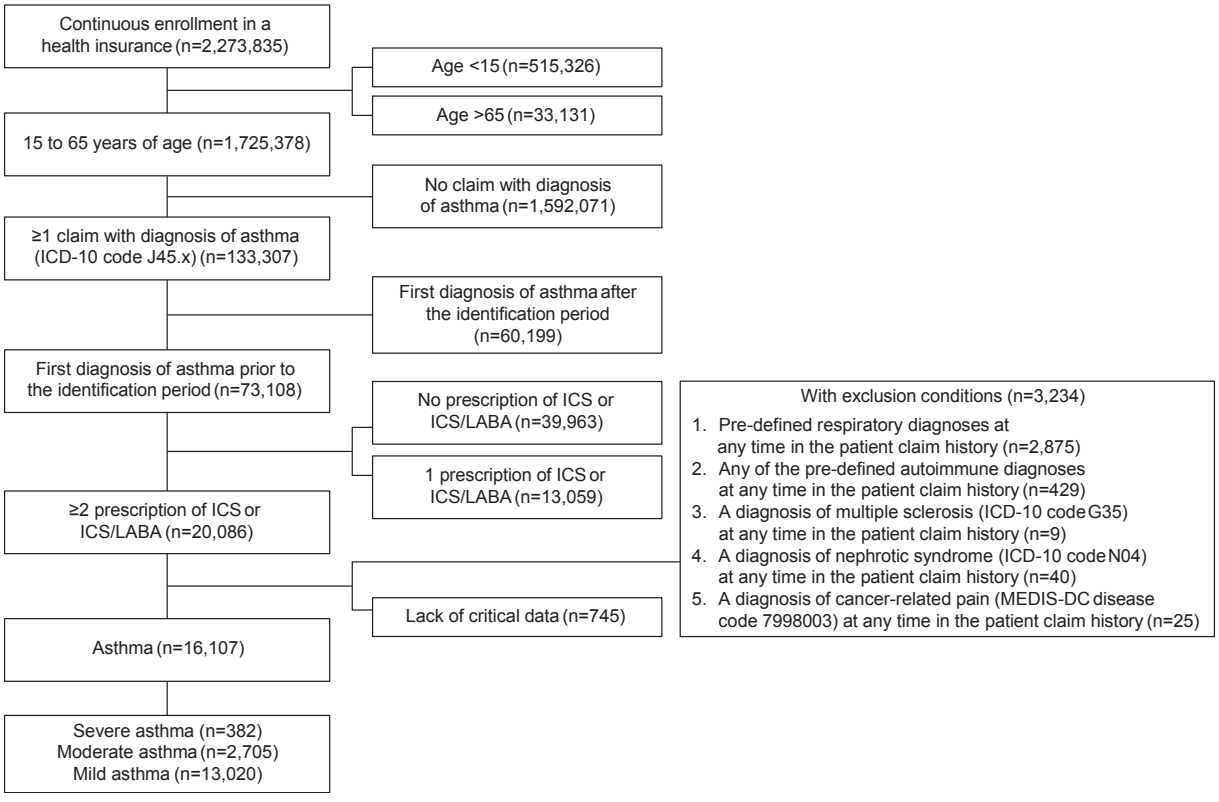

Figure 1. Patient flow diagram. ICD-10 = *International Classification of Diseases, Tenth Revision*; MEDIS-DC= Medical Information Systems Development Center.

(Table I). The prevalence of severe asthma among all asthma patients increased with increasing age. The prevalence per 100 patients among all asthma patients was 80.8 (95% CI, 80.2−81.4) for mild asthma and 16.8 (95% CI, 16.2−17.4) for moderate asthma.

Characteristics of Severe Asthma

In the patients with severe asthma, 130 (34.0%) of 382 had at least 1 asthma exacerbation and 71 (18.6%) patients had ≥2 exacerbations during the baseline period (Table II). Annual exacerbation rates (mean [SD]) increased with asthma severity, being highest in patients with severe asthma (0.7 [1.3]/year) compared with mild asthma (0.1 [0.6]/year) or moderate asthma (0.4 [1.1]/year). The most common concomitant diseases in patients with severe asthma were allergic rhinitis (70.2% of patients), gastroesophageal reflux disease (30.1%), hypertension (22.5%), and respiratory infection (22.0%). Patients with severe asthma tended to have more concomitant diseases compared with those with mild or moderate asthma.

Routine Asthma Management During the Baseline Period

To further describe the characteristics of patients with severe asthma, we examined the type of medical institutions they visited for routine asthma management during the 12-month baseline period. The proportion of patients with asthma visiting a hospital with ≥200 beds increased with asthma severity and was highest for patients with severe asthma (24.6%) compared with those with mild (7.6%) or moderate (18.0%) asthma (Table II).

Asthma Exacerbations During the Follow-up Period

Despite the high-intensity asthma treatment reported during the 12-month baseline period, 101 (26.4%) of 382 patients with severe asthma experienced ≥1 asthma exacerbation during the 12-month follow-up period. The proportion of patients with severe asthma who experienced ≥2 exacerbations was 14.9%. The proportion of patients who had exacerbations increased with increasing severity of asthma (Table III).

Asthma-Related Outpatient Visits During the Follow-up Period

During the follow-up period, the frequency of outpatient visits increased with increasing severity of asthma. The frequency of unscheduled outpatient visits for asthma (mean [SD]) was 0.3 (1.0) visit/year for mild asthma, rising to 1.0 (2.8) visit/year for severe asthma (Table IV). The numbers of

Table I. Prevalence and characteristics of mild, moderate, and severe asthma among asthma patients during the baseline period.

Variable	All Asthma	Mild Asthma		Moderate Asthma		Severe Asthma	
	N	n	Prevalence (95% CI)	n	Prevalence (95% CI)	n	Prevalence (95% CI)
All	16,107	13,020	80.8 (80.2−81.4)	2705	16.8 (16.2−17.4)	382	2.4 (2.1−2.6)
Sex							
Female	8148	6710	82.4 (81.5−83.2)	1251	15.4 (14.9−16.2)	195	2.3 (2.1−2.6)
Male	7959	6310	79.3 (78.4−80.2)	1454	18.3 (17.4−19.1)	187	2.5 (2.0−2.8)
Age, y							
15−19	799	733	91.7 (89.6−93.6)	61	7.6 (5.9−9.7)	5	0.6 (0.2−1.5)
20−39	5625	4825	85.8 (84.8−86.7)	700	12.4 (11.6−13.3)	100	1.8 (1.5−2.2)
40−59	8768	6792	77.5 (76.6−78.3)	1732	19.8 (18.9−20.6)	244	2.8 (2.5−3.2)
60−65	915	670	73.2 (70.2−76.1)	212	23.2 (20.5−26.0)	33	3.6 (2.5−5.0)

Prevalence was calculated as per 100 asthma patients. N, n = number of patients.
Note: These results were analyzed by using data from April 1, 2014, to March 31, 2015. The number of All Asthma patients is the sum total of patients with mild, moderate, and severe asthma.

Table II. Characteristics of asthma according to severity during baseline period. Values are given as number (%) unless otherwise indicated.

Variable	All Asthma (N = 16,107)	Mild Asthma (n = 13,020)	Moderate Asthma (n = 2705)	Severe Asthma (n = 382)
Concomitant diseases				
Atopic dermatitis	1492 (9.3)	1197 (9.2)	252 (9.3)	43 (11.3)
Allergic rhinitis	10,124 (62.9)	8157 (62.6)	1699 (62.8)	268 (70.2)
Nasal polyps	102 (0.6)	78 (0.6)	19 (0.7)	5 (1.3)
Otitis media	539 (3.3)	388 (3.0)	126 (4.7)	25 (6.5)
Acute sinusitis	2096 (13.0)	1798 (13.8)	254 (9.4)	44 (11.5)
Chronic sinusitis	2114 (13.1)	1679 (12.9)	376 (13.9)	59 (15.4)
Gastroesophageal reflux disease	2367 (14.7)	1750 (1.3)	502 (18.6)	115 (30.1)
Hypertension	2220 (13.8)	1627 (12.5)	507 (18.7)	86 (22.5)
Diabetes	1461 (9.1)	1056 (8.1)	332 (12.3)	73 (19.1)
Osteoporosis	266 (1.7)	174 (1.3)	77 (2.8)	15 (3.9)
Bone fracture	387 (2.4)	310 (2.4)	67 (2.5)	10 (2.6)
Anxiety	498 (3.1)	385 (3.0)	103 (3.8)	10 (2.6)
Depression	699 (4.3)	528 (4.1)	149 (5.5)	22 (5.8)
Cataract	274 (1.7)	194 (1.5)	66 (2.4)	14 (3.7)
Glaucoma	293 (1.8)	236 (1.8)	45 (1.7)	12 (3.1)
Chronic cardiac failure	100 (0.6)	68 (0.5)	31 (1.1)	1 (0.3)
Angina pectoris	284 (1.8)	201 (1.5)	67 (2.5)	16 (4.2)
Abnormal cardiac rhythm	249 (1.5)	202 (1.6)	42 (1.6)	5 (1.3)
Obesity	135 (0.8)	103 (0.8)	27 (1.0)	5 (1.3)
Sleep apnea syndrome	249 (1.5)	177 (1.4)	58 (2.1)	14 (3.7)
Respiratory infection*	2447 (15.2)	1977 (15.2)	386 (14.3)	84 (22.0)
Influenza	2041 (12.7)	1667 (12.8)	310 (11.5)	64 (16.8)
Pneumonia	349 (2.2)	254 (2.0)	73 (2.7)	22 (5.8)
Mycoplasma pneumonia	82 (0.5)	76 (0.6)	5 (0.2)	1 (0.3)
Bronchial pneumonia	84 (0.5)	64 (0.5)	16 (0.6)	4 (1.0)
Eosinophilic concomitant disease†	145 (0.9)	76 (0.6)	54 (2.0)	15 (3.9)
Eosinophilic otitis media	41 (0.3)	19 (0.1)	17 (0.6)	5 (1.3)
Eosinophilic rhinosinusitis	53 (0.3)	36 (0.3)	13 (0.5)	4 (1.0)
Eosinophilic pneumonia	40 (0.2)	20 (0.2)	17 (0.6)	3 (0.8)
Allergic bronchopulmonary aspergillosis	22 (0.1)	6 (0.0)	12 (0.4)	4 (1.0)
Eosinophilic granulomatosis with polyangiitis	2 (0.0)	2 (0.0)	0 (0.0)	0 (0.0)
Exacerbation frequency				
Times/year, mean (SD)	0.2 (0.7)	0.1 (0.6)	0.4 (1.1)	0.7 (1.3)
No. of exacerbations				
≥1 asthma exacerbation	1857 (11.5)	1252 (9.6)	475 (17.6)	130 (34.0)
≥2 asthma exacerbations	642 (4.0)	354 (2.7)	217 (8.0)	71 (18.6)
≥1 asthma exacerbation requiring hospitalization	65 (0.4)	32 (0.2)	19 (0.7)	14 (3.7)

Table II. (*Continued*)

Variable	All Asthma (N = 16,107)	Mild Asthma (n = 13,020)	Moderate Asthma (n = 2705)	Severe Asthma (n = 382)
Unscheduled outpatient visits[‡]				
Times/year, mean (SD)	0.5 (1.4)	0.4 (1.2)	0.7 (2.0)	1.0 (2.7)
≥1 Unscheduled outpatient visit	3248 (20.2)	2566 (19.7)	584 (21.6)	98 (25.7)
Daily use of oral corticosteroids (≥5 mg/d)				
Total	1882 (11.7)	1282 (9.8)	469 (17.3)	131 (34.3)
<1 month	1746 (10.8)	1223 (9.4)	419 (15.5)	104 (27.2)
≥1 month	136 (0.8)	59 (0.5)	50 (1.8)	27 (7.1)
≥3 month	70 (0.4)	23 (0.2)	27 (1.0)	20 (5.2)
≥6 month	43 (0.3)	15 (0.1)	13 (0.5)	15 (3.9)
≥9 month	27 (0.2)	9 (0.1)	7 (0.3)	11 (2.9)
Cumulative dose mg/y, mean (SD)	274.2 (552.3)	193.1 (359.5)	391.0 (673.1)	649.2 (1119.2)
Asthma-related management				
Asthma management planning with peak flow meters	783 (4.9)	462 (3.5)	258 (9.5)	63 (16.5)
Pulmonary function tests (outpatient visits)				
Times/year, mean (SD)	0.3 (1.0)	0.3 (0.8)	0.6 (1.6)	0.9 (2.0)
Any tests	2911 (18.1)	2077 (16.0)	707 (26.1)	127 (33.2)
≥1 Vital capacity	2144 (13.3)	1479 (11.4)	557 (20.6)	108 (28.3)
≥1 Flow volume testing	2338 (14.5)	1637 (12.6)	586 (21.7)	115 (30.1)
≥1 Functional residual capacity	53 (0.3)	30 (0.2)	20 (0.7)	3 (0.8)
≥1 FeNO	1024 (6.4)	718 (5.5)	263 (9.7)	43 (11.3)
≥1 Multifrequency oscillation	520 (3.2)	307 (2.4)	182 (6.7)	31 (8.1)
Laboratory tests				
≥1 Blood eosinophil count	2235 (13.9)	1668 (12.8)	455 (16.8)	112 (29.3)
≥1 Specific allergic test	955 (5.9)	755 (5.8)	165 (6.1)	35 (9.2)
≥1 IgE level	578 (3.6)	415 (3.2)	131 (4.8)	32 (8.4)
No. of beds of the facility for routine asthma management				
0—19	13,584 (84.3)	11,300 (86.8)	2201 (74.7)	263 (68.8)
20—99	309 (1.9)	239 (1.8)	61 (2.3)	9 (2.4)
100—199	460 (2.9)	327 (2.5)	119 (4.4)	14 (3.7)
≥200	1965 (9.7)	984 (7.6)	487 (18.0)	94 (24.6)

FeNO = fractional exhaled nitric oxide; IgE = immunoglobulin E.

Note: These results were analyzed by using data from April 1, 2014, to March 31, 2015. The number of All Asthma patients is the sum total of patients with mild, moderate, and severe asthma.

* Respiratory infections were treated as a single combined variable of any of the following: influenza, pneumonia, mycoplasma pneumonia, and bronchial pneumonia.

† Eosinophilic concomitant disease was treated as a single combined variable of any of the following: eosinophilic otitis media, eosinophilic rhinosinusitis, eosinophilic pneumonia, allergic bronchopulmonary aspergillosis, and eosinophilic granulomatosis with polyangiitis.

‡ Unscheduled visits defined as the visits during after-hours, late-night, or holiday.

Table III. Asthma exacerbation frequency during the 12-month follow-up period.

Variable	Exacerbation Frequency During 12-Month Follow-up Period					
	None	1	2	3	≥4	Times/Year
	n (%)*	n (%)	n (%)	n (%)	n (%)	Mean (SD)
All asthma (N= 16,107)						
Any asthma exacerbations	14,697 (91.2)	920 (5.7)	244 (1.5)	108 (0.7)	138 (0.9)	0.2 (0.7)
Hospitalization	16,056 (99.7)	46 (0.3)	5 (0.0)	0 (0.0)	0 (0.0)	0.0 (0.1)
Emergency transport	16,103 (100.0)	4 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.0 (0.0)
Asthma outpatient with IV/oral corticosteroids use	14,738 (91.5)	890 (5.5)	236 (1.5)	106 (0.7)	137 (0.9)	0.2 (0.7)
Mild asthma (n = 13,020)						
Any asthma exacerbations	12,120 (93.1)	637 (4.9)	152 (1.2)	59 (0.5)	52 (0.4)	0.1 (0.5)
Hospitalization	12,987 (99.7)	32 (0.2)	1 (0.0)	0 (0.0)	0 (0.0)	0.0 (0.1)
Emergency transport	13,017 (100.0)	3 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.0 (0.0)
Asthma outpatient with IV/oral corticosteroids use	12,150 (93.3)	613 (4.7)	147 (1.1)	58 (0.4)	52 (0.4)	0.1 (0.5)
Moderate asthma (n = 2705)						
Any asthma exacerbations	2296 (84.9)	239 (8.8)	66 (2.4)	35 (1.3)	69 (2.6)	0.3 (1.1)
Hospitalization	2693 (99.6)	9 (0.3)	3 (0.1)	0 (0.0)	0 (0.0)	0.0 (0.1)
Emergency transport	2704 (100.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.0 (0.0)
Asthma outpatient with IV/oral corticosteroids use	2304 (85.2)	234 (8.7)	65 (2.4)	33 (1.2)	69 (2.6)	0.3 (1.1)
Severe asthma (n = 382)						
Any asthma exacerbations	281 (73.6)	44 (11.5)	26 (6.8)	14 (3.7)	17 (4.5)	0.6 (1.2)
Hospitalization	376 (98.4)	5 (1.3)	1 (0.3)	0 (0.0)	0 (0.0)	0.0 (0.2)
Emergency transport	382 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.0 (0.0)
Asthma outpatient with IV/oral corticosteroids use	284 (74.3)	43 (11.3)	24 (6.3)	15 (3.9)	16 (4.2)	0.6 (1.2)

n = number of patients.

Note: These results were analyzed by using data from April 1, 2015, to March 31, 2016 (follow-up period). The number of All Asthma patients is the sum total of patients with mild, moderate, and severe asthma. The number of asthma exacerbations was tabulated as follows, and the number of any asthma is not sum of Hospitalization, Emergency transport, and Asthma outpatient with IV/oral corticosteroids use.

In instances of an exacerbation meeting the requirement for multiple exacerbation definitions, events were counted in the following order of preference: (1) asthma-related hospital admission; (2) asthma emergency transportation; and (3) asthma-related outpatient visit with systemic corticosteroids use. Patients were not counted in duplicate.

* Percentage among each severe category.

Table IV. Number of asthma-related outpatient visits during follow-up period.

Variable	No. of Patients	Outpatient Visits (Office Hours)	Unscheduled Outpatient Visits*
		Mean (SD)	Mean (SD)
All asthma	16,107	4.4 (4.8)	0.3 (1.3)
Mild asthma	13,020	3.6 (4.2)	0.3 (1.0)
Moderate asthma	2705	7.7 (5.0)	0.6 (1.8)
Severe asthma			
Total	382	10.2 (6.0)	1.0 (2.8)
Managed by single site with 0–19 beds	217	10.4 (5.5)	NC
Managed by single site with ≥20 beds	91	8.7 (6.1)	NC
Managed by 2 s ites with 0–19 beds	20	11.9 (4.5)	NC
Managed by 2 sites with ≥20 beds	3	19.7 (8.5)	NC
Managed by 2 sites with 0–19 beds, and ≥20 beds	38	12.0 (6.5)	NC
Managed by 3 sites with 0–19 beds	3	17.7 (3.1)	NC
Managed by 3 sites with 0–19 beds, and ≥20 beds	3	10.3 (4.0)	NC
Managed by 4 sites with 0–19 beds	1	26.0 (NC)	NC

These results were analyzed by using data from April 1, 2015 to March 31, 2016.
NC = Not calculated.
* Defined as the visits during after-hours, late-night, or holiday.

facilities and outpatient visits in office hours were calculated. A total of 308 patients with severe asthma were visiting a single site for their asthma management. Among them, 70% were treated at sites with 0–19 beds. Sixty-eight patients were treated at ≥2 facilities.

Risk Factors Associated With Asthma Exacerbations

In all patients with asthma, factors associated with increased risk of exacerbations during the follow-up period were female sex, moderate or severe asthma, otitis media, gastroesophageal reflux disease, chronic cardiac failure, eosinophilic concomitant disease (eosinophilic otitis media, eosinophilic rhinosinusitis, eosinophilic pneumonia, allergic bronchopulmonary aspergillosis, or eosinophilic granulomatosis with polyangiitis), and an exacerbation in the previous year (Figure 2). In patients with severe asthma, the risk of having any exacerbation during the follow-up period increased in patients who had experienced an exacerbation in the previous year or had used oral corticosteroids daily for ≥3 months (Figure 3).

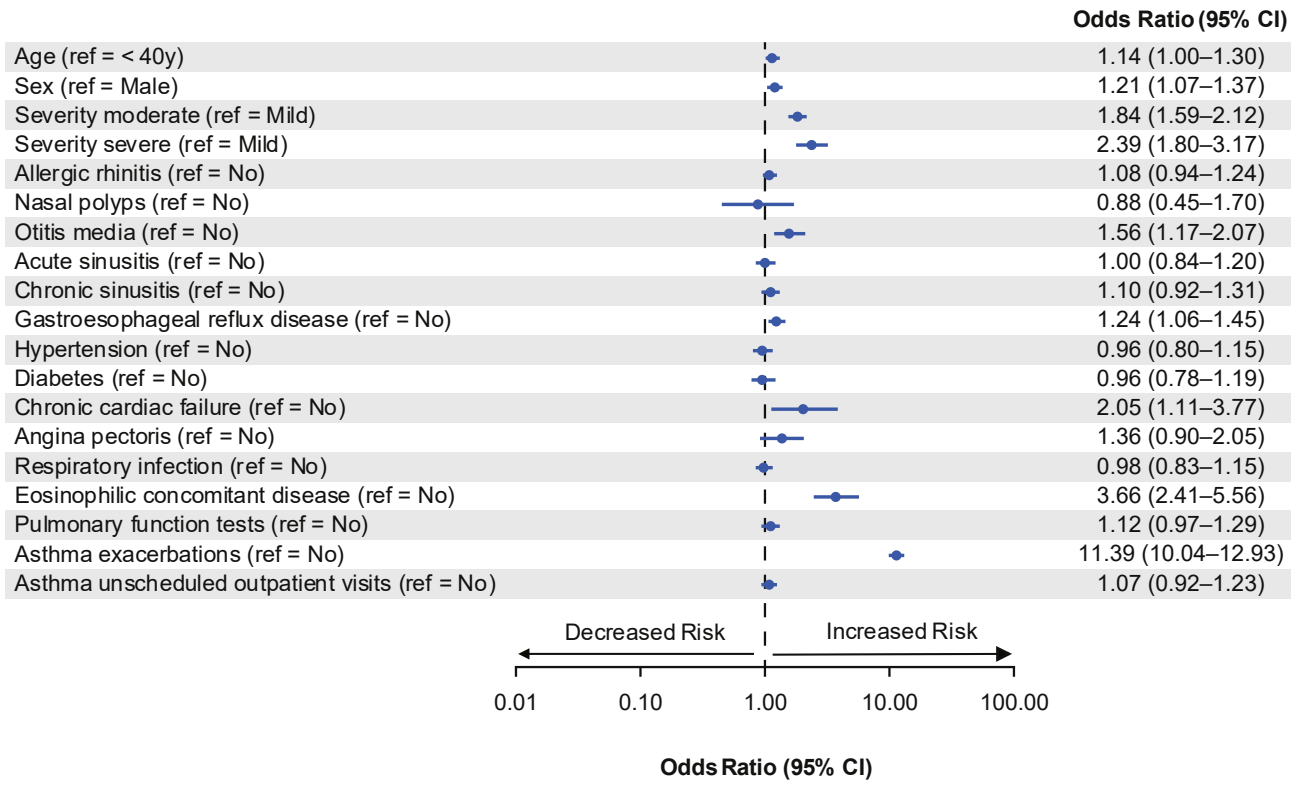

Figure 2. Risk factors associated with asthma exacerbations in patients with asthma according to multivariate analyses. The asthma group was the sum total of patients with mild, moderate, and severe asthma. Respiratory infections were treated as a single combined variable of any of the following: influenza, pneumonia, mycoplasma pneumonia, and bronchial pneumonia. Eosinophilic concomitant disease was treated as a single combined variable of any of the following: eosinophilic otitis media, eosinophilic rhinosinusitis, eosinophilic pneumonia, allergic bronchopulmonary aspergillosis, and eosinophilic granulomatosis with polyangiitis.

DISCUSSION

To our knowledge, this study is the first to determine the characteristics and clinical burden of severe asthma in Japan by using a nationwide health care claims database, providing a detailed description and identifying risk factors for exacerbation in these patients in Japan. Compared with milder forms of the disease, severe asthma in Japan was found to be associated with more frequent exacerbations, a higher prevalence of comorbidities, and more frequent outpatient visits. Overall, these results suggest that a significant disease burden exists in patients with severe asthma in Japan.

In this study, the prevalence of severe asthma within the working-age population (15–65 years of age) with asthma was 2.4%. Our study results also showed that patients with severe asthma were older than patients with less severe forms of asthma, which was consistent with previous findings in the United States and the United Kingdom.[16] The results of this study also describe the reality of severe asthma management in Japan. Our study found that ~70% of patients with severe asthma visited clinics or small hospitals (0–19 beds) an average of 10 times per year. Approximately 20% of the patients with severe asthma were visiting multiple sites for asthma management. Of these patients with severe asthma, 6 patients experienced exacerbations requiring hospitalization during the follow-up period. All 6 patients were admitted to the hospitals where they

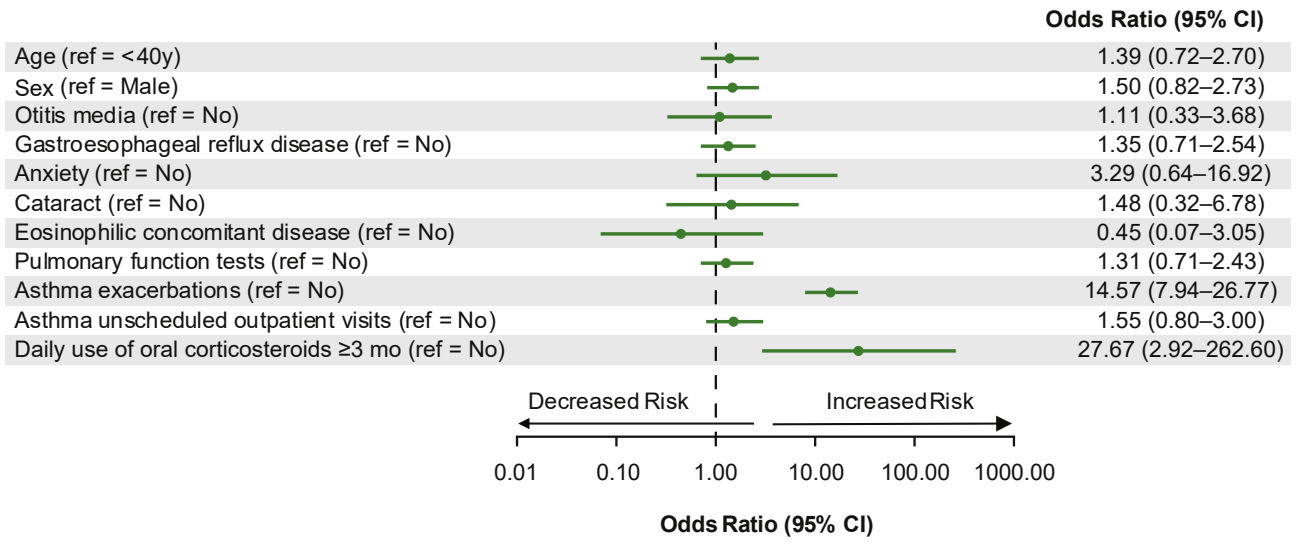

Figure 3. Risk factors associated with asthma exacerbations in patients with severe asthma according to multivariate analyses. Respiratory infections were treated as a single combined variable of any of the following: influenza, pneumonia, mycoplasma pneumonia, and bronchial pneumonia. Eosinophilic concomitant disease was treated as a single combined variable of any of the following: eosinophilic otitis media, eosinophilic rhinosinusitis, eosinophilic pneumonia, allergic bronchopulmonary aspergillosis, and eosinophilic granulomatosis with polyangiitis.

were receiving routine asthma care. No patients were treated at clinics. These results have 2 implications. Among patients with severe asthma, those with more severe disease might be treated at hospitals rather than at clinics; a hospital-based study could capture exacerbations requiring hospitalization for patients with severe asthma.

Regarding management of asthma, the proportion of patients who were planning asthma management using a peak flow meter was 16.5%. The pulmonary function test was conducted in only one third of patients with severe asthma during the 12-month baseline period despite the Japanese guidelines recommending check of pulmonary functions once a year.

Previous research studies have reported several factors that are likely to be associated with future asthma exacerbations. In database studies conducted in the United States and the United Kingdom, the frequency of exacerbations increased with asthma severity.[10] In related studies, the risk of two or more future exacerbations increased ~1.4-fold or more in patients with blood eosinophil counts ≥400 cells/μL.[17,18] In several studies, including TENOR (Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens), patients experiencing a recent exacerbation were 6- to 8-fold more likely to experience a future exacerbation than those without a recent exacerbation.[13,19,20] Consistent with this finding, the present study's multivariate analysis showed that the risk of exacerbations during the follow-up period increased in patients who currently had severe asthma or eosinophilic disease or who had experienced asthma exacerbations in the previous year. Among patients with severe asthma, the risk of a subsequent exacerbation increased in patients who experienced an exacerbation in the previous year and in patients who used daily oral corticosteroids for ≥3 months. In patients with severe asthma, especially in those with frequent exacerbations, current treatment strategies need to be carefully reviewed to achieve effective exacerbation management.

There are both strengths and weaknesses of using the JMDC claims database. One of the main

advantages is that, as a nationwide database, it provides health care claims data from a large number of people. Another advantage is that all outpatient visits or hospitalizations can be identified by JMDC. Most retrospective studies are hospital based and thus often have difficulty in following up patients who visit several different clinics or hospitals. In contrast, the JMDC, a patient-based database collecting patient information from employee-based health insurance societies, allows tracking of patient movement and treatment across medical facilities. These advantages enabled the study to determine the reality of asthma management and complemented the limitations of studies with a hospital-based setting.

The present study also has several limitations. First, because the JMDC collects patient data from employee-based health insurance societies, little information is available for older patients. In Japan, most company employees retire at ~60−65 years of age, and consequently these people may drop out from the database. To address this limitation, we excluded those aged >65 years because their sociodemographic characteristics were not fully reflective of the Japanese general population for this age range. This exclusion of patients >65 years of age in this study may have underestimated the prevalence of severe asthma in patients with asthma. Second, it should be noted that the study classified asthma severity according to the ICS prescription claims, not using any clinical information. Because the study did not assess adherence, not all patients may have taken all medications prescribed. As a result, some patients who should have been categorized as having mild or moderate asthma may have been misclassified as having severe asthma, leading to disease prevalence overestimation. Third, the study analyzed patients with asthma who had an asthma-related diagnosis code and medication identified by using the claims data. In the reality of daily practice, patients sometimes might be prescribed asthma-related medicines for other reasons such as prolonged cough and bronchitis. The study defined asthma by using 1 diagnosis code of asthma and 2 prescriptions of an ICS or ICS/LABA during the 12-month baseline period. This definition might lead to a large population of asthma and then a low prevalence of severe asthma. Fourth, concomitant diseases were identified with diagnosis codes, and their treatments were not assessed in this study. Therefore, the prevalence of concomitant diseases might have been overestimated, and impacts of treatments for concomitant diseases on the burden of asthma were not assessed. Finally, because patients who had COPD were excluded, the severity and burden of asthma-COPD overlap were not evaluated in this study. Given that the COPD population is more elderly than those with asthma, and patients with asthma-COPD overlap have a poorer prognosis than patients without COPD, further research with a different data source and an elderly population are needed to describe more complete and detailed characteristics and burden of severe asthma.

CONCLUSIONS

In Japan, severe asthma represents a significant burden on patients and health care providers.

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Drs. Sato, Ohno, and Kaise contributed to the study concept and design, interpretation, and manuscript preparation. Dr. Ishii contributed to the study concept and design, and interpretation. Dr. Ito contributed to data analysis and interpretation. All authors were involved in the preparation and review of the manuscript and approved the final version to be submitted.

DISCLOSURES

Keiko Sato, Tomoya Ohno, Takeo Ishii and Toshihiko Kaise are employees of GSK and hold stock/shares in GSK. GSK supported the study design, interpretation of results, and review of the manuscript. The decision to submit the final manuscript was made by the authors, the sponsor did not place any restrictions on access to the data or on the statements made in the manuscript.

Note: These results were analyzed by using data from April 1, 2014, to March 31, 2015. The number

of All Asthma patients is the sum total of patients with mild, moderate, and severe asthma.

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