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ORIGINAL RESEARCH

A Retrospective Claims Database Study to Clarify Disease Burden of Severe Asthma Patients with Type 2 High or Low Inflammation

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Purpose: The disease burden of severe asthma patients stratified by type 2 (T2) biomarkers is not well studied in large patient samples, especially for T2-low severe asthma patients. Using a Japanese medical record database, we investigated disease and economic burdens in T2-high and T2-low severe asthma patients.

Patients and Methods: Data of severe asthma patients (receiving high-dose inhaled corticosteroids and additional asthma-related controller medications or oral corticosteroids [OCS] prescription [≥183 days] during the 1-year baseline period) were analyzed in the Real World Data database, comprising electronic medical records from Japanese medical institutions. Severe asthma patients were stratified into a T2-high population with higher eosinophils (≥150 cells/μL) and/or higher total immunoglobulin E (IgE, ≥75 IU/mL) or a T2-low population with lower eosinophils (<150 cells/μL) and lower total IgE (<75 IU/mL). The incidence of asthma exacerbation events and drug costs were analyzed for each population. Different T2 thresholds were explored, including eosinophil count 300 cells/μL and/or IgE 150 IU/mL.

Results: Of the 732 severe asthma patients, 599 (81.8%) patients had T2-high type, and 133 (18.2%) had T2-low type. Proportions of the T2-high patients (30.6%) with asthma exacerbations, defined as a composite outcome, including OCS burst, injectable steroid use, and hospitalization, were similar to those of T2-low type (34.6%). The annual drug cost was similar between T2-high (175,487 JPY) and T2-low (165,322 JPY) populations.

Conclusion: In this large-scale study, both T2-high and T2-low severe asthma patients in Japan were shown to have a high disease burden and high economic burden, suggesting an unmet treatment need.

Keywords: phenotype, disease exacerbation, treatment, Japan

Introduction

Asthma is a heterogeneous chronic inflammatory disease characterized by airway constriction and hyperresponsiveness that causes wheezing, coughing, and exacerbations. The reported prevalence of asthma patients in Japan ranges from 6% to 10%.[1] The prevalence of severe asthma, defined as asthma that requires treatment with high-dose inhaled corticosteroids (ICS) and additional treatment,[1] ranges from 2.4% to 12.7% of patients with asthma in Japan.[2–4] Severe asthma patients have a higher risk of exacerbations than non-severe asthma patients.[2] Therefore, appropriate treatment for severe asthma is required.

Severe asthma patients are classified into two major phenotypes: type 2 (T2)-high and T2-low.[5] T2-high eosinophilic and/or allergic asthma is defined by eosinophil counts and total serum immunoglobulin E (IgE) levels.[6] Phenotyping, primarily based on T2 inflammatory biomarkers, such as serum IgE, peripheral blood eosinophils, and fractional exhaled nitric oxide (FeNO), is conducted to determine active inflammatory pathways and inform the selection of the most appropriate biologics (eg, omalizumab, mepolizumab, benralizumab, and dupilumab) for the treatment of severe asthma.[7]

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Previously, several studies have investigated patients with severe asthma based on their phenotype, particularly T2 inflammatory biomarkers.[8] The exacerbation risk was found to be higher in severe asthma patients with T2-high features than in those with severe asthma and without any T2-high features.[9] Conversely, other studies did not show a higher exacerbation rate in severe asthma patients with T2-high features.[6,10] The discrepancy in the results was attributed to the small samples of T2-low severe asthma patients and the inclusion of severe asthma patients treated with biologics which affected the T2 biomarkers value.[11] Therefore, it is essential to clarify the disease burden and real-world treatment patterns of severe asthma patients with or without T2 inflammation in a large sample of patients, particularly one including a sufficient number of T2-low severe asthma patients before initiating treatment with biologics.

This study aimed to investigate the characteristics and disease burden among severe asthma patients with T2-high or T2-low type asthma, stratified by peripheral eosinophil and serum IgE levels from a medical record database, including biomarker data.

Materials and Methods

Study Design

This retrospective cohort study analyzed data from the Real World Data database (RWD; Real World Data, Co., Ltd.), a medical record database. As of 2020, this database contained the records of 20 million patients from 160 medical institutions across Japan. The stored information includes demographic data, diagnoses according to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) classification, prescriptions coded according to the Anatomical Therapeutic Chemical classification, procedures, and laboratory results from both outpatient and inpatient services. The data were automatically extracted from electronic medical records at each medical institution. Patient records are maintained by allocating unique identifiers for each individual, which are valid within the same institution.

The data of severe asthma patients with available laboratory results, including eosinophil counts and total IgE concentrations, recorded between January 2004 and December 2019 were analyzed. The index date was defined as the latest date of the eosinophil count assessed at least 1 year before the last visit in the database. The baseline period was defined as 1 year before the index date, and the follow-up period as 1 year after the index date (Figure 1). Asthma exacerbation events and drug costs were investigated in the follow-up period. Other patient background factors (eg, prescription of asthma-related medications and asthma-related laboratory tests) were analyzed in the pre-index period.

The research was led by AstraZeneca K.K. Because the company does not have an institutional review board, we sought independent ethical review by the NPO-MINS Institutional Review Board (Approval No. 210214 in 2021). The 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. Informed consent was waived because the available data in the RWD database were standardized and anonymized.

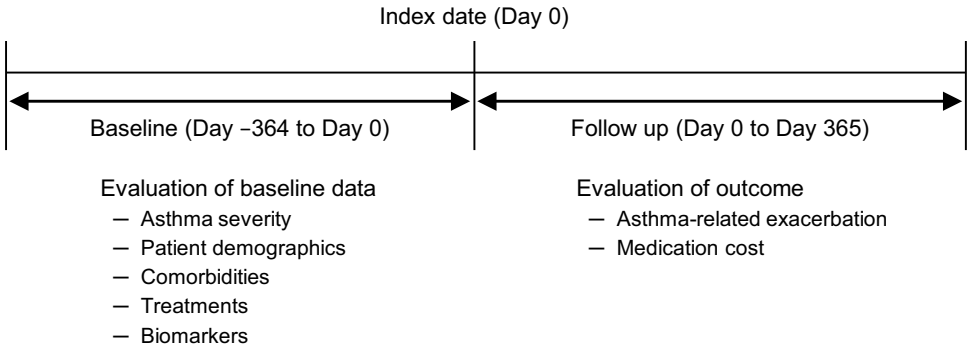

Figure 1 Study design. Index date: latest date of the eosinophil count assessed at least 1 year prior to the last visit. Baseline period: 1 year before the index date. Follow-up period: 1 year after the index date.

Patients

This study included adult asthma patients (aged ≥17 years at the index date) who had been diagnosed with asthma (ICD-10 code: J45 or J46) and had received an ICS or ICS/long-acting beta agonist (LABA) prescription at least twice during the baseline period, and who had available data on eosinophil counts at the index date and total IgE concentration at any time before the index date. Additionally, patients were required to have been enrolled continuously in the database for a minimum of 1 year before and 1 year after the index date. Further, severe asthma patients were required to have >2 high-dose ICS or ICS/LABA prescriptions and additional asthma-related prescriptions or total days of oral corticosteroid (OCS) prescription ≥183 days during the baseline period.

Furthermore, to exclude the use of OCS treatment for other diseases during the study period, patients diagnosed with an autoimmune disease (ICD-10 codes: D51.0, D59.1, D69.3, E05.0, E06.3, E10, E27.1, G35, G61.0, H20, K50-K51, K73, K74.3, K90.0, L10, L12, L40 [excluding L40.4], L63, L80.9, M05-M06, M08, M31.3, M33, M31.5-M31.6, M35.3, G70.0, M34, M32.1, M32.9, M35.0, M45.9 [13], and N04) were excluded from the study. In the baseline period, patients treated with biologics (ie, omalizumab, mepolizumab, benralizumab, and dupilumab) were also excluded because T2 biomarkers are strongly affected by the use of biologics.[11]

Definition of T2-High and T2-Low Populations

In the primary analysis, severe asthma patients were divided into two populations using blood eosinophil counts and total IgE amount, as previously described by Denton et al.[6] The T2-high population was characterized by a high eosinophil count (≥150 cells/μL) at the index date and/or high total IgE (≥75 IU/mL) at the latest date before the index date. The T2-low population was characterized by a low eosinophil count (<150 cells/μL) at the index date and low total IgE (<75 IU/mL) on the latest date before the index date. In the exploratory analysis, severe asthma patients were divided into T2-high and T2-low populations using different eosinophil (150 or 300 cells/μL) and IgE level cutoffs (30, 75, or 150 IU/mL).

Definitions of Asthma Exacerbation-Related Events

An asthma exacerbation-related hospitalization event was defined as any hospitalization with asthma as the primary disease or causative disease or any hospitalization with a systemic corticosteroid prescription. An asthma exacerbation-related injectable corticosteroid event was defined as a record of an injectable corticosteroid prescription with the coexistence of an asthma diagnosis. An asthma exacerbation-related OCS burst event was defined as a record of an OCS prescription with a dosage of 20 mg/day or an OCS prescription 10 mg/day higher compared with the previous OCS prescription with the coexistence of an asthma diagnosis. A composite outcome of asthma exacerbation was defined as a record of any of these events during the follow-up period. If the interval between the end of the previous event and the start of the next event was 14 days, the two events were counted as one.

Patient Demographics and Clinical Variables

The prevalence and characteristics of severe asthma patients were assessed. The demographic characteristics included sex, age, comorbidities, asthma-related prescriptions, asthma-related laboratory tests (eg, eosinophil count and total IgE), asthma exacerbation history (ie, asthma exacerbations with hospitalization, systemic corticosteroid prescription, and OCS burst), total drug cost, and asthma-related drug costs.

Statistical Analysis

Baseline characteristics and outcomes were summarized using descriptive statistics; for continuous variables, data were shown as number of patients, mean (standard deviation), median, interquartile range, and minimum and maximum values. For categorical variables, data were shown as number and percentage of patients. The annual medicine costs according to the National Health Insurance drug price lists were summarized. No statistical model or hypothesis test was applied. As the study focused on the distribution of patients, only 95% confidence intervals (CIs) were provided. Data analyses were performed using SAS Viya 3.5 (SAS Institute Inc., Cary, NC, USA).

Results

Patient Characteristics and Asthma Treatment

Overall, 1,022,447 patients with asthma diagnoses were identified between January 2004 and December 2019 in the RWD database (Figure 2). After applying the inclusion and exclusion criteria, 732 patients were identified as having severe asthma.

Severe asthma patients were divided into two populations: T2-high severe asthma (n = 599, 81.8%) and T2-low severe asthma (n = 133, 18.2%). T2-high severe asthma patients were subcategorized into eosinophil low-IgE high (n = 158, 21.6%), eosinophil high-IgE low (n = 107, 14.6%), and eosinophil high-IgE high (n = 334, 45.6%) (Figure 3).

Patient demographics, baseline characteristics, laboratory tests, and medications are shown in Table 1. The mean (standard deviation) of age of T2-high severe asthma patients was 64.6 (18.6) years and that of T2-low severe asthma patients, 65.5 (18.8) years. The proportions of female patients were 54.9% and 75.9% in the T2-high and T2-low severe asthma populations, respectively. Comorbidities related to allergy were allergic rhinitis (27.2%, 24.8%), chronic

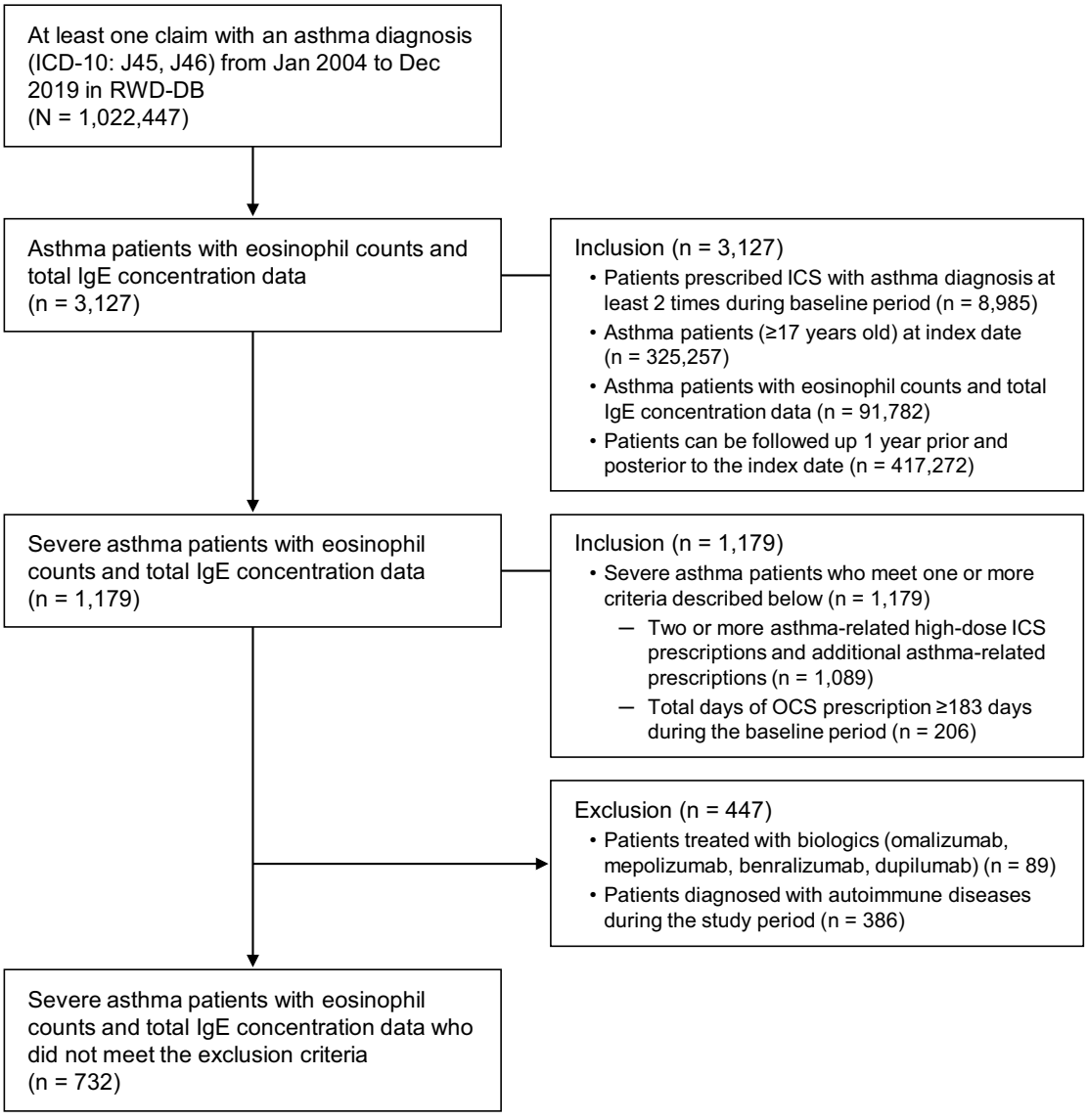

Figure 2 Analysis population.

Abbreviations: ICD-10, International Statistical Classification of Diseases and Related Health Problems, 10th Revision; ICS, inhaled corticosteroids; IgE, immunoglobulin E; OCS, oral corticosteroids; RWD-DB, Real World Data database.

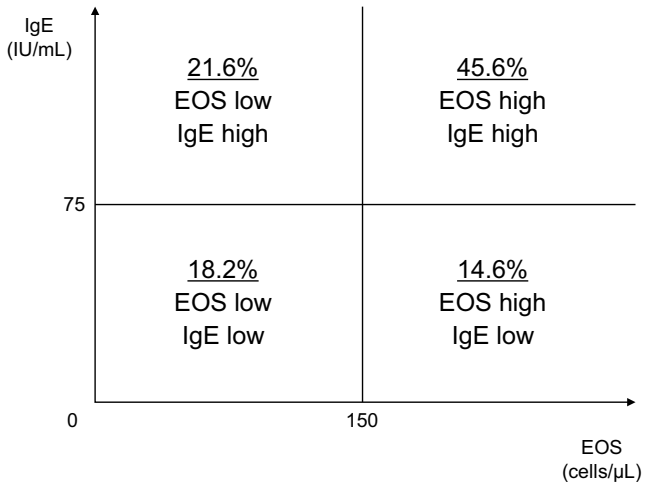

Figure 3 Proportion of severe asthma patients classified by eosinophil counts and total IgE.
Abbreviations: EOS, eosinophil; IgE, immunoglobulin E.

paranasal sinusitis (8.2%, 4.5%), and atopic dermatitis (2.5%, 0.8%) in the T2-high and T2-low severe asthma populations, respectively. T2-related factors had higher values in T2-high severe asthma patients than in T2-low severe asthma patients (eosinophil counts: 248.2 and 70.0 cells/μL; total IgE: 300.0 and 29.6 IU/mL; and positive for specific IgE for perennial antigen: 50.8% and 20.0% in T2-high and T2-low severe asthma populations, respectively). Similar treatments were prescribed in T2-high and T2-low severe asthma patients (ICS/LABA, 88.5% and 82.7%; short-acting beta agonist, 52.8% and 48.1%; long-acting muscarinic antagonists, 25.2% and 26.3%; and OCS, 46.4% and 51.9%, respectively).

Table 1 Patients' Demographics and Baseline Characteristics in T2-High and T2-Low Populations

	T2-High	**T2-Low**
Total number of patients	599 (81.8)	133 (18.2)
Age, years, mean (SD)	64.6 (18.6)	65.5 (18.8)
Sex, female	329 (54.9)	101 (75.9)
BMI, kg/m^2, n = 283	n = 231	n = 52
Mean (SD)	23.5 (4.2)	23.2 (4.8)
Quan-Charlson comorbidity index score, mean (SD)	2.1 (1.8)	2.2 (1.7)
Comorbidities		
Respiratory infection	36 (6.0)	4 (3.0)
Allergic rhinitis	163 (27.2)	33 (24.8)
Gastroesophageal reflux disease	142 (23.7)	33 (24.8)
Chronic obstructive pulmonary disease	143 (23.9)	40 (30.1)
Chronic paranasal sinusitis	49 (8.2)	6 (4.5)
Atopic dermatitis	15 (2.5)	1 (0.8)
Nasal polyp	5 (0.8)	0
Psychiatric disorder/anxiety/depression	36 (6.0)	15 (11.3)
Treatments		
SABA	316 (52.8)	64 (48.1)
ICS	135 (22.5)	42 (31.6)
LABA	28 (4.7)	8 (6.0)
LAMA	151 (25.2)	35 (26.3)

(*Continued*)

Table 1 (Continued).

	T2-High	T2-Low
ICS/LABA	530 (88.5)	110 (82.7)
ICS/LABA/LAMA	2 (0.3)	1 (0.8)
LTRA	409 (68.3)	79 (59.4)
Theophylline	267 (44.6)	49 (36.8)
OCS	278 (46.4)	69 (51.9)
Maintenance OCS	60 (10.0)	13 (9.8)
Injectable steroid	321 (53.6)	73 (54.9)
Biomarkers		
Eosinophils, cells/μL, median (IQR)	248.2 (356.2)	70.0 (73.5)
Neutrophils, cells/μL, n = 616	n = 503	n = 113
Median (IQR)	4150 (2970)	4700 (3460)
Basophils, cells/μL, n = 726	n = 594	n = 132
Median (IQR)	33 (41)	21 (25)
Monocytes, cells/μL, median (IQR)	424 (235)	357 (230)
Lymphocytes, cells/μL, median (IQR)	1710 (974)	1558 (898)
Total IgE, IU/mL, median (IQR)	300.0 (649.1)	29.6 (34.3)
Specific IgE for perennial antigen		
Tested	179 (29.9)	35 (26.3)
Positive in tested patients	91 (50.8)	7 (20.0)
CRP, mg/dL, n = 665	n = 545	n = 120
Median (IQR)	0.21 (0.56)	0.22 (0.77)

Note: Data are n (%) unless otherwise indicated.
Abbreviations: BMI, body mass index; CRP, C-reactive protein; ICS, inhaled corticosteroid; IgE, immunoglobulin E; IQR, interquartile range; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid; SABA, short-acting beta agonist; SD, standard deviation; T2, type 2.

Asthma Exacerbations and Drug Costs in the T2-High and T2-Low Populations

The clinical burden of severe asthma, including asthma exacerbations in both populations, was assessed. The proportions of patients with asthma-related exacerbations, including hospitalization, injectable steroid use, or OCS burst, were 30.6% (95% CI: 26.9–34.4) in the T2-high and 34.6% (95% CI: 26.6–43.3) in the T2-low populations (Table 2). Each component of the asthma exacerbations was assessed in the T2-high and T2-low populations: hospitalization, 9.7% (95% CI: 7.4–12.3) and 14.3% (95% CI: 8.8–21.4); injectable steroid use, 21.9% (95% CI: 18.6–25.4) and 26.3% (95% CI: 19.1–34.7); and OCS burst, 18.4% (95% CI: 15.3–21.7) and 21.1% (95% CI: 14.5–29.0) (Figure 4).

Table 2 Asthma-Related Exacerbation Events and Medicine Cost During the Follow-Up Period in the T2-High and T2-Low Populations

	T2-High	T2-Low
Patients with asthma-related exacerbation, % (95% CI)		
Composite outcome	30.6 (26.9–34.4)	34.6 (26.6–43.3)
OCS burst	18.4 (15.3–21.7)	21.1 (14.5–29.0)
Injectable steroid	21.9 (18.6–25.4)	26.3 (19.1–34.7)
Hospitalization	9.7 (7.4–12.3)	14.3 (8.8–21.4)
Medicine cost, JPY/patient-year		
Total cost, median (IQR)	175,487 (298,926)	165,322 (334,775)
Asthma-related cost, median (IQR)	76,961 (127,287)	75,061 (123,764)

Abbreviations: CI, confidence interval; IQR, interquartile range; JPY, Japanese Yen; OCS, oral corticosteroids; T2, type 2.

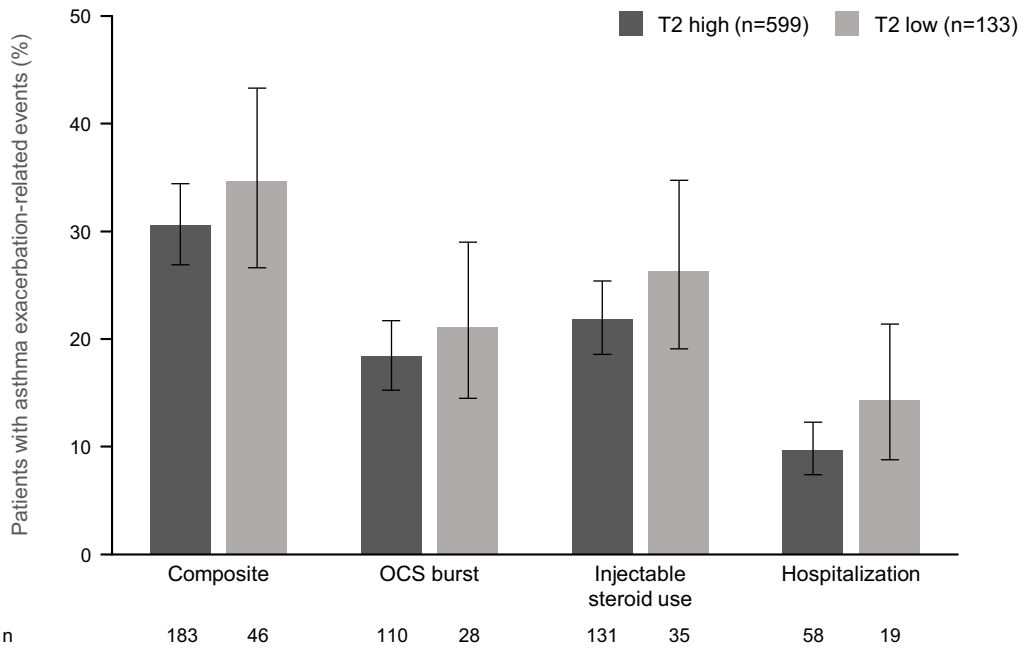

Figure 4 Proportion of patients with asthma exacerbation in the T2-high population and T2-low population.
Abbreviations: OCS, oral corticosteroids; T2, type 2 phenotype.

Median total drug costs were assessed between the T2-high and T2-low populations (175,487 and 165,322 JPY/patient-year, respectively). Median asthma drug costs were also assessed (T2-high, 76,961 and T2-low, 75,061 JPY/patient-year) (Table 2).

Asthma Exacerbations and Drug Costs in the T2-High Population

In the T2-high severe asthma population, the clinical burden was assessed for eosinophil low-IgE high, eosinophil high-IgE low, and eosinophil high-IgE high (Table 3). The proportions of patients with asthma-related exacerbations were 34.8% (95% CI: 27.4–42.8) in the eosinophil low-IgE high population, 25.2% (95% CI: 17.3–34.6) in the eosinophil high-IgE low population, and 30.2% (95% CI: 25.4–35.5) in the eosinophil high-IgE high population. Other components of asthma exacerbations were assessed among the eosinophil low-IgE high, eosinophil high-IgE low, and eosinophil high-IgE high populations: hospitalization, 13.3% (95% CI: 8.4–19.6), 8.4% (95% CI: 3.9–15.4), and 8.4% (95% CI: 5.6–11.9); injectable steroid use, 28.5% (95% CI: 21.6–36.2), 17.8% (95% CI: 11.0–26.3), and 20.1% (95% CI: 15.9–

Table 3 Asthma-Related Exacerbation Events and Medicine Cost During the Follow-Up Period in the T2-High Subpopulation

	Eosinophil Low-IgE High	Eosinophil High-IgE Low	Eosinophil High-IgE High
Patients (n)	158	107	334
Patients with asthma-related exacerbation, % (95% CI)			
Composite outcome	34.8 (27.4–42.8)	25.2 (17.3–34.6)	30.2 (25.4–35.5)
OCS burst	19.6 (13.7–26.7)	13.1 (7.3–21.0)	19.5 (15.4–24.1)
Injectable steroid	28.5 (21.6–36.2)	17.8 (11.0–26.3)	20.1 (15.9–24.8)
Hospitalization	13.3 (8.4–19.6)	8.4 (3.9–15.4)	8.4 (5.6–11.9)
Medicine cost, JPY/patient-year			
Total cost, median (IQR)	173,298 (360,285)	172,012 (307,078)	175,565 (260,316)
Asthma-related cost, median (IQR)	74,978 (126,719)	53,400 (118,125)	80,461 (130,966)

Abbreviations: CI, confidence interval; IgE, immunoglobulin E; IQR, interquartile range; JPY, Japanese Yen; OCS, oral corticosteroids; T2, type 2.

24.8); and OCS burst, 19.6% (95% CI: 13.7–26.7), 13.1% (95% CI: 7.3–21.0), and 19.5% (95% CI: 15.4–24.1), respectively.

Median total drug cost was assessed in the eosinophil high-IgE high, eosinophil high-IgE low, and eosinophil high-IgE high population (173,298, 172,012, and 175,565 JPY/patient-year, respectively). The median asthma drug cost was also assessed between the populations (74,978, 53,400, and 80,461 JPY/patient-year, respectively) (Table 3).

Asthma Exacerbations and Drug Costs in the T2-High and T2-Low Populations by Different Criteria

Severe asthma patients were also divided according to different thresholds, such as eosinophil count 150 or 300 cells/μL and total IgE 30, 75, or 150 IU/mL. In this subpopulation, the proportions of T2-high severe asthma patients were 74.0%–90.8%, and the proportions of T2-low severe asthma patients were 9.2–26.0% (Table 4).

The proportions of patients with asthma-related exacerbations between the T2-high and T2-low populations by the different T2 criteria were 30.0% (95% CI: 26.3–34.0) and 31.2% (95% CI: 27.3–35.3) in the T2-high population and 31.6% (95% CI: 25.0–38.7) and 40.3% (95% CI: 28.5–53.0) in the T2-low population (Table 4).

Discussion

To the best of our knowledge, this is the largest-scale study to clarify the disease burden in T2-high and T2-low severe asthma patients in Japan, including 732 severe asthma patients. The total severe asthma population consisted of 81.8% of T2-high severe asthma patients and 18.2% of T2-low severe asthma patients. The proportion of patients with asthma exacerbations as a composite outcome, including OCS burst, injectable steroid use, and hospitalization, was relatively similar between the T2-high (30.6%, 95% CI: 26.9–34.4) and the T2-low (34.6%, 95% CI: 26.6–43.3) populations. Moreover, annual drug costs were also similar between the T2-high (175,487 JPY) and the T2-low (165,322 JPY) populations. Therefore, this study showed no marked differences in the disease and economic burdens of patients with T2-high and T2-low severe asthma. Among patients with T2-high severe asthma, the breakdown of clinical burden by eosinophil low-IgE high, eosinophil high-IgE low, and eosinophil high-IgE high also revealed relative similarities in terms of disease burden.

The patient characteristics, such as age, sex, and medical treatment, in our target population were similar to those in previous studies.[9,10] However, the proportion of patients with comorbidities was lower than the proportion reported in previous research.[10] The reason for this might be that patients with comorbidities were treated in other hospitals or by

Table 4 Proportions of Patients and Asthma-Related Exacerbation Events During the Follow-Up Period in T2-High and T2-Low Populations Stratified by Different T2 Criteria

Cutoff Values for T2 Criteria[a]			Patients With T2-High or T2-Low, %	Patients With Asthma Exacerbations, % (95% CI)
Eosinophil, Cells/μL	IgE, IU/mL			
150	75	T2-high T2-low	81.8 18.2	30.6 (26.9–34.4) 34.6 (26.6–43.3)
150	30	T2-high T2-low	90.8 9.2	30.4 (26.9–34.0) 40.3 (28.5–53.0)
150	150	T2-high T2-low	76.9 23.1	30.0 (26.3–34.0) 35.5 (28.3–43.2)
300	75	T2-high T2-low	74.0 26.0	31.2 (27.3–35.3) 31.6 (25.0–38.7)

Note: [a]T2-high was defined as an eosinophil count ≥ cutoff value and/or an IgE level ≥ cutoff value; T2-low was defined as an eosinophil count < cutoff value and an IgE level < cutoff value.
Abbreviations: CI, confidence interval; IgE, immunoglobulin E; T2, type 2.

self-medication, which is not included in the RWD database. The proportion of female patients in the T2-low severe asthma population was higher than that of male patients in this study. This finding was consistent with previous studies.[6,12] Differences were not observed in the medical treatment prescribed between the T2-high and T2-low populations. One of the reasons is that, in this study, patients treated with biologics during the baseline period were excluded to prevent changes in T2 biomarkers due to treatment with biologics. For T2-high severe asthma patients with allergic and/or eosinophilic phenotypes without previous biologics treatment, the following treatment option consists of biologics treatments, such as omalizumab, mepolizumab, benralizumab, and dupilumab, which have shown efficacy in achieving asthma control.[13–16]

The higher proportion of patients with COPD in the T2-high (23.9%) and T2-low (30.1%) populations with asthma in this study compared with that in other countries where overlap occurs in approximately 20% of asthma patients[17] may be attributed to the higher age in the present study population.[18] Previous research in Japan has found that COPD is associated with higher age;[19] furthermore, our data are consistent with those reported in a previous study in Japan in which COPD was reported in 27.1% of patients with asthma.[20]

In this study, the proportions of patients with asthma exacerbation were similar between the T2-high population (30.6%, 95% CI: 26.9–34.4) and T2-low population (34.6%, 95% CI: 26.6–43.3). However, the results of the studies by Kimura et al[9] and Denton et al[6] were inconsistent in terms of asthma exacerbations in T2-high and T2-low severe asthma patients. In the study by Denton et al,[6] a large cohort of severe asthma patients from the International Severe Asthma Registry (ISAR) study had a similar incidence of asthma exacerbations between T2-high and T2-low patients. Conversely, the incidence of asthma exacerbations in T2-high severe asthma patients was higher than in T2-low patients in the Kimura et al[9] and Haughney et al[21] studies. These differences may derive from the differences in biomarkers, the criteria used to categorize severe asthma patients as T2-high or T2-low, and general patient characteristics in each study (eg, Haughney et al used a cutoff point of 400 cells/μL to categorize patients as being in the high eosinophil or low eosinophil groups, and had a younger patient population).[21] In our study, the incidence of asthma exacerbations using different cutoffs for eosinophil count (150 or 300 cells/μL) and IgE (30, 75, and 150 IU/mL) showed consistent results. The finding of similarly high exacerbation rates in both the T2-high and T2-low populations may be the result of the exclusion of patients treated with biologics from the present analysis. If patients with T2-high severe asthma who require treatment with biologics actually undergo treatment with biologics, a lower exacerbation rate may be expected for this population. However, biologics have been shown to have a lower efficacy in T2-low severe asthma patients, based on subgroup analyses of Phase 3 studies;[13–16] thus, in some countries, biologics are not approved for use in this specific population. Macrolides were reported to be effective for treating patients with persistent asthma.[22,23] However, macrolide use as maintenance treatment was not observed in this study (data not shown), possibly because low-dose and long-term macrolide treatment is not covered by public health insurance in Japan. Thus, treatment options specific to T2-low severe asthma patients have been very limited, emphasizing the unmet treatment needs for T2-low severe asthma patients.[12]

The median of total drug costs and asthma-related drug costs for the T2-high population (175,487 and 76,961 JPY, respectively) and T2-low population (165,322 and 75,061 JPY, respectively) were similar to the total and asthma-related drug costs (208,000 and 63,000 JPY, respectively) of severe asthma patients in the Japanese database study by To et al.[24] Of note, the study by To et al showed costs in overall severe asthma patients without stratification by T2 biomarkers. Therefore, the similarity of annual drug cost among T2-high and T2-low severe asthma patients in Japan is a novel finding.

The proportions of patients with asthma exacerbations were similar between the T2-high subpopulations (eosinophil low-IgE high, eosinophil high-IgE low, and eosinophil high-IgE high) in this study. Previous studies showed inconsistent results regarding asthma exacerbations in T2-high overlap severe asthma patients. In the ISAR study, a large cohort of severe asthma patients showed similar asthma exacerbation incidence among these subpopulations.[6] Conversely, the incidence of asthma exacerbations in severe asthma patients with several T2-high features was higher than in patients without T2-high features or with a single T2-high feature in a previous study.[9] Regarding the economic burden, similarities between the T2-high subpopulation in Japan were also observed in this study. Further, all four subpopulations (eosinophil low-IgE high, eosinophil high-IgE low, eosinophil high-IgE high, and eosinophil low-IgE low) were found to have similar disease burden and economic burden, showing similarities between the T2-high and T2-low populations.

One of the strengths of this study was the inclusion of a substantial number of severe asthma patients with available data on T2 biomarkers, including eosinophil counts and amount of total IgE. It is challenging to enroll a sufficient number of severe asthma patients in a prospective observational study, especially T2-low severe asthma patients.[9,10] In contrast, previous claim database studies included many patients but lacked biomarker data.[2–4]

Nonetheless, some limitations of this study should be noted. The data included in the database did not include all clinical information, such as clinical signs and symptoms that are related to asthma evaluation. Although some studies evaluated severe asthma patients with/without T2 inflammation based on neutrophils and eosinophils in sputum and FeNO, the RWD database does not include sufficient data on parameters such as sputum and FeNO.[25,26] Sputum eosinophil count is not evaluated in routine clinical practice in Japan. Therefore, we did not evaluate sputum eosinophil count data. T2 status was defined using a single time point measure of blood eosinophil count in this study. As previously shown by Azim et al, the blood eosinophil count can fluctuate over time.[27] That study notably defined eosinophilic asthma using other factors in addition to blood eosinophil data, including treatment (oral corticosteroids and anti-IL 5) and phenotype (FeNO, nasal polyps, and adult onset).[28] These differences in eosinophilic asthma might affect the definition of the T2-high and T2-low populations. Additionally, severe asthma patients treated with biologics were not included in this study's analysis population because T2 biomarkers are strongly affected by biologics.[11] This might affect the disease burden of T2-high populations eligible for biologics. Finally, in this study, we used total IgE for T2 status classification. Although previous studies have used total IgE to classify patients as having severe asthma,[6] it is considered that total IgE could potentially overestimate T2 status. Specific IgE data may have yielded more accurate estimates of T2 status; however, the RWD database lacked sufficient data on these parameters.

Conclusion

In this study, which is the largest-scale study of this nature conducted in Japan thus far, we showed that T2-high and T2-low severe asthma patients in Japan had a high disease burden and a high economic burden. These results suggest an unmet treatment need for T2-high and T2-low severe asthma patients.

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