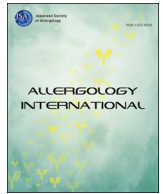




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Invited Review Article

Severe asthma in Japan

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ABSTRACT

The characteristic phenotype of severe asthma in Japan seems to be distilled into the following two features: low incidence of obesity and high prevalence of patients with type 2 inflammation. Only 5–7% of Japanese severe asthma patients had a body mass index (BMI) ≥ 30 kg/m², and more than 80% of patients with severe asthma exhibited type 2 inflammation. Although the relationship between obesity and non-type 2 inflammation is complex, the low incidence of obesity might explain the prevalence of type 2 inflammation.

Some asthma cohorts in Japan have investigated the roles of type 2 biomarkers extensively, including periostin, to identify a severe phenotype, suggesting the utility of combining biomarkers to identify an exacerbation-prone subgroup.

Although the prevalence of severe asthma is comparable to Western countries, the rate of asthma death and disease burden seems to be lower in Japan. These trends might be due to the system of public health insurance for the whole nation, leading to good access to hospital and asthma specialists due to the geographically narrow country.

In this review article, we will discuss the definition, epidemiology, comorbidities, biomarkers, specific phenotype, and current treatment for severe asthma in Japan.

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Definition of severe asthma in Japanese guideline

In the Japanese guidelines for adult asthma,¹ treatment steps are divided into four steps, and step 4 treatment consists of high dose inhaled corticosteroids (ICS) plus long-acting β_2 -agonists (LABA) with additional controllers, including long-acting muscarinic receptor antagonist, leukotriene receptor antagonists, sustained-release theophylline, anti-IgE antibody, IL-5-targeted biologics, and oral corticosteroids. Severe asthma is defined as asthma that requires step 4 treatments to prevent the disease from becoming “uncontrolled” or that remains “uncontrolled” despite those therapies.¹

The Global Initiative for Asthma (GINA) defines severe asthma in an identical manner to the Japanese guidelines, based on GINA treatment step 4 or 5 consisting of medium or high dose ICS with a second controller.² In the international ERS/ATS guidelines for severe asthma,³ the required treatment to fulfill the definition of severe asthma is high dose ICS with a second controller. The

Japanese guidelines are stricter than the international guidelines are, citing the criteria of high dose ICS plus two or more controllers for definition of severe asthma.

Epidemiology of severe asthma in Japan

The European Community Respiratory Health Survey has been used to perform the surveys of asthma prevalence in various countries. Although those surveys were conducted in different years, the prevalence of wheeze among people aged 20–44 years in Japan was 9.3% in 2006,⁴ which is suggested to be lower European countries and the United States (8.5%–32.0%).⁵

International experts estimate the prevalence of severe asthma to be approximately 5–10% of the entire asthma population. The reported proportion of severe asthma among all asthma patients was 3.6% from Dutch pharmacy databases⁶ and 8.1% in Danish adult asthma patients aged 18–44 years using their nationwide prescription database.⁷ Concerning the prevalence of severe asthma in Japanese patients, the proportion of adult patients in step 4 treatment of the Japanese guideline was 10.6% in a cross-sectional study administered by postal mail.⁸ Recently, the prevalence of severe asthma among patients aged 17–75 years treated by ICS or ICS/LABA was investigated by using a Japanese health insurance claims database between 2014 and 2015 (n = 10,579) (manuscript in

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revision),⁹ with 823 (7.8%) patients having severe asthma and 267 (2.5%) having severe uncontrolled asthma.

In the last 20 years, the number of patients who die from asthma has markedly decreased.¹ According to the Vital Statistics of the Japanese Ministry of Health, Labour, and Welfare, the rate of death was 4.5–5.0 per 100,000 persons before 1994, and decreased after 1997,¹⁰ reaching its lowest point of 1.2 per 100,000 persons (1454 deaths) in 2016. Although the asthma mortality rate in the 5–34 year age group in Japan was higher than the global average until 2000, the rate has since improved to below global average levels.¹¹ Thus, the number of deaths from asthma in Japan at an early age has markedly decreased; approximately 90% of asthma deaths occur in patients aged 65 years or older.¹

Compared to various countries, the burden of disease by asthma in Japan as assessed by years lived with disability and years of life lost by asthma are among the lowest.¹² However, health care costs for asthma treatment were greater for severe uncontrolled asthma compared to mild-to-moderate asthma (\$8,346 vs \$3,422 USD/year) from the Japanese health insurance claims database.⁹

In summary, the rate of asthma death and disease burden appears to be lower in Japan although the prevalence of severe asthma is comparable to Western countries. These trends may be due to the system of public health insurance for the whole nation and good access to hospital and asthma specialists due to the fact that, geographically, the country is narrow. In addition, the publication of Asthma Prevention and Management Guidelines since 1998 in Japanese¹³ and the asthma death zero campaign from 2004 aimed to standardize therapy based on guidelines might help to improve asthma prognosis.

Comorbidities of asthma patients in Japan

Obesity

In patients with severe asthma, obesity is a common comorbidity. Approximately 30%–50% of severe asthma patients in Western countries are obese and the association between obesity and asthma incidence has been investigated extensively.¹⁴ In addition, in Japanese severe asthma populations, a body mass index (BMI) of $>30 \text{ kg/m}^2$ is a significant risk factor for uncontrolled asthma in women and non-atopics.¹⁵

Regarding a threshold value of BMI to diagnose increased risk of asthma, previous studies from Western countries have shown an increased prevalence of asthma with a BMI higher than 25 kg/m^2 or 30 kg/m^2 .¹⁶ However, even at the same BMI, the accumulation of body fat in Asian populations is higher than in Western populations.¹⁷ Also, Asian patients are more susceptible to type 2 diabetes than Western populations.^{13,18} The threshold of BMI for an increase in type 2 diabetes in Japanese populations is between 23 and 24 kg/m^2 , although this threshold is 25 kg/m^2 in European populations.¹⁸ Likewise, regarding Japanese asthma populations, there is a significant association of BMI $\geq 25 \text{ kg/m}^2$ in both genders, and BMI of $\geq 23 \text{ kg/m}^2$ in females with an increased risk of asthma was observed using the data from a nationwide survey.¹⁹ In addition, obesity, but not metabolic syndrome, was a significant risk factor for the incidence of asthma, suggesting the specific importance of obesity in asthma pathogenesis.²⁰ The mechanism for sex differences has yet not been elucidated fully; however, the effect of estrogen^{21,22} or difference in adiponectin profile due to different fat distributions²³ has been suggested previously.

In addition to the above discussed relationship between BMI and asthma incidence, the impact of obesity on asthma exacerbation in patients with severe asthma was investigated in Japan.²⁴ The ratio of annual exacerbations and the proportion of frequent exacerbators were significantly higher in patients with BMI $\geq 25 \text{ kg/}$

m^2 ; however, this relationship was observed only in female cohorts. In addition, levels of malondialdehyde, a serum oxidative stress marker, are significantly higher in obese patients and positively correlated with the frequency of severe exacerbations only in obese patients; this suggests that oxidative stress in obese patients is a facilitator of acute asthma exacerbations.²⁵

As the mean BMI is lower in the Japanese population compared to Western populations,¹⁸ only 5–7% of Japanese severe asthma patients had a BMI of $\geq 30 \text{ kg/m}^2$.^{15, 26} In contrast, in the United States, 37% of patients with severe asthma patients enrolled in the Severe Asthma Research Program had a BMI of $\geq 30 \text{ kg/m}^2$.²⁷

Taken together, although the proportion of obese patients is lower in Japan, the incidence of asthma and exacerbations in Japanese asthma patients, especially in females, are likely to be affected with a lesser degree of obesity than Western populations.

Sensitization to fungus and *Staphylococcus aureus* enterotoxin

The pathogenic significance of *Alternaria*, *Cladosporium*, *Penicillium*, and *Aspergillus* has been well described.²⁸ *Alternaria* and *Cladosporium* are two major outdoor airborne fungi found worldwide.²⁸ The most common indoor environmental fungi in Japan are *Cladosporium*, *Penicillium*, and *Aspergillus*, with frequencies of isolates reported to be 100%, 78%, and 84%, respectively.²⁸

The major sensitized fungal allergens in adult Japanese patients were *Candida* (45%), *Aspergillus* (10%), *Alternaria* (10%), *Penicillium* (10%), *Trichophyton* (7%), and *Cladosporium* (5%) species.²⁸ The profile is identical in severe asthma: the species for positive specific serum IgE was *Candida* (16%), *Aspergillus* (11%), and *Trichophyton* (11%).²⁹ The prevalence of fungal sensitization varies with geography.³⁰ Due to high temperature and humidity, the feature of fungal sensitization might affect the pathology of asthma in Japan. The proportion of sensitized patients for *Alternaria* in Japan is approximately 10%, generally lower than in European countries; however, it is comparable to the United States and Australia.³⁰ Sensitization to *Alternaria*, and *Cladosporium* tends to decrease with age, but the frequency of *Aspergillus fumigatus* does not decrease with age³¹; this suggests that sensitization to *Aspergillus* might be related to severe persistent asthma. In fact, patients sensitized to *Aspergillus* and *Penicillium* had a significantly increased risk of poor asthma control in Japan.³²

Among severe asthma patients, the rate of early-onset asthma and serum interleukin-33 was found to be higher in patients with fungal sensitization than in patients without sensitization, and multiple fungal sensitizations are associated with poor asthma control.²⁹ Apart from severe asthma with fungal sensitization (SAFS), a nationwide survey for allergic bronchopulmonary mycosis in Japan was also conducted recently.³³ *Aspergillus* species were most frequently isolated from sputum in 59% of cases and *Schizophyllum commune* was identified in 6% of patients. The survey identified that late-onset, relatively low serum IgE levels, and frequent recurrences were unique characteristics of allergic bronchopulmonary aspergillosis in Japan.

S. aureus is an opportunistic human pathogen and sensitization to *S. aureus* enterotoxin (SE) has been reported to be associated with asthma susceptibility and severity. The prevalence of positive SE-IgE was higher in asthma,³⁴ and the proportion of sensitized patients to SE in allergic diseases was 25.7% in Taiwan.³⁵ The proportion of sensitization to SEs is known to be higher in smokers, and, thus, an association between sensitization to SEs and feature of asthma was investigated in patients with smoking history.³⁶ The frequency of sensitization to SEs in asthma patients was significantly higher in current smokers (48%) compared to never smokers (18%). In addition, SEs-sensitized patients exhibited greater airflow limitation, more severe disease, and higher levels of serum IgE and

blood eosinophil counts. Taken together, this suggests that sensitization to SEs in asthma with smoking history may contribute to the pathogenesis of severe eosinophilic asthma in smokers.

SEs are subdivided into different groups, and SEA and SEB were the first reported SEs. An association between poor asthma control and SEA-IgE positivity has been reported^{36,37} and fractional exhaled nitric oxide (FeNO) levels were significantly higher in SEA-IgE positive patients than in negative patients.³⁷ The sensitization to SEA rather than SEB was associated with poor asthma control in adult asthma.

Rhinosinusitis

Rhinitis is the most prevalent comorbidity in asthma, and 70%–80% of asthma patients in Western countries are reported to have rhinitis.^{38,39} Based on physician-administered questionnaires of allergic rhinitis and its impact on asthma (ARIA) criteria, among the Japanese general asthma population, the prevalence of rhinitis was 66.2%; asthma control was also significantly impaired in patients with rhinitis.⁴⁰ Among severe uncontrolled asthma patients, prevalence of allergic rhinitis was the most common comorbidity (65.2%) (manuscript in revision),⁹ and it has been reported that 20%–40% of asthma patients have rhinosinusitis.^{38,39} The Hokkaido-based Investigative Cohort Analysis for Refractory Asthma (Hi-CARAT) study identified that 41.3% of severe asthma patients had abnormal sinus findings on computed tomography imaging.⁴¹ In addition, the cohort showed a positive correlation between severity of sinusitis and severity of asthma on spirometry in nonsmoking adults.

Japanese cedar pollen is the most common seasonal allergen in Japan and causes seasonal allergic rhinitis in the spring season. Cedar pollinosis is termed as “a folk disease” in Japan. The prevalence of Japanese cedar pollinosis among adult asthma patients was reported to be 34.8%.⁴² Although, 30%–60% of adult asthma patients with concomitant pollinosis experience asthma exacerbations during the Japanese cedar pollen season, previous reports do not suggest that concomitant pollinosis is related to chronic severity of asthma.⁴²

Biomarker studies for severe asthma in Japan

There has been significant effort to develop non-invasive biomarkers to detect type 2 airway inflammation because type 2 inflammation plays an important role in asthma. Currently, FeNO and peripheral blood eosinophil counts are clinically available biomarkers for type 2 inflammation. In addition, Izuhara and colleagues demonstrated that an extracellular matrix protein periostin is one of the highly expressed IL-13-inducible genes by DNA microarray⁴³; in addition, they showed that periostin is a type 2 inflammation marker, which is related to airway remodeling.⁴⁴ Since then, some Japanese asthma cohorts have intensively investigated the role of periostin in asthma. The Kinki Hokuriku Airway disease Conference (KiHAC) cohort clarified the role of periostin in the accelerated decline of pulmonary function.⁴⁵ In addition, the Keio research program for severe asthma in Japanese population (Keio-SARP) cohort showed that high serum periostin levels are related to late-onset asthma, aspirin intolerance, lower pulmonary function, and complications from chronic rhinosinusitis with nasal polyps.⁴⁶

In addition to periostin, tenascin-C (TNC) is also a type 2 cytokine-induced extracellular matrix protein. Recently, serum TNC level has been shown to be significantly higher in severe asthma, and patients with both high serum TNC and periostin levels presented with higher disease severity and severe airflow limitation; this suggests that serum TNC can serve as a novel biomarker.⁴⁷

As a single-marker approach potentially limits the ability to accurately diagnose and predict outcomes of severe type 2 asthma, the utility of classification by combining type 2 biomarkers has been investigated. The KiHAC cohort reported the utility of the combination of serum periostin and FeNO in the management of asthma,⁴⁸ and showed positive correlations between FeNO and serum periostin levels, especially in severe asthma. However, among patients with high FeNO levels, patients with high serum periostin level showed an accelerated decline in FEV₁ and higher risk of exacerbation.

Although the levels of FeNO and blood eosinophil count have been reported previously as independent risk factors for severe asthma exacerbation, patients with both high FeNO and eosinophils showed the highest incidence for asthma diagnosis and exacerbations.⁴⁹ Consistent with that report, a cohort of severe asthma patients in Saitama prefecture showed that the largest proportion of patients experiencing frequent severe exacerbations had high FeNO and blood eosinophils.⁵⁰

The Keio-SARP cohort investigated clinical characteristics of subgroups divided by serum periostin and blood eosinophils.²⁶ Although the ratio of patients with olfactory dysfunction was highest in the subgroup with high periostin and eosinophils, there were no differences in asthma control status, or asthma-related quality of life among the four categories.

Taken together, the combination of FeNO and blood markers (blood eosinophil count or serum periostin) seems to have value in identifying an exacerbation-prone subgroup. While the precise underlying mechanism remains unclear, one potential explanation might be that FeNO signals come from local IL-4/IL-13-mediated mechanisms in the airway and blood eosinophil counts and serum periostin levels may reflect the systemic effect of IL-5 or IL-13.

Phenotypes of severe asthma in Japan

Asthma phenotypes are fundamentally divided into two subsets, type 2 inflammation dominant asthma and non-type 2 asthma.⁵¹ Even when smoking asthmatics were included in cluster analysis, the Hi-CARAT cohort identified both type 2 and non-type 2 clusters composed of smokers.⁵²

As a characteristic feature of phenotype in severe asthma in Japan, more than 80% of patients with severe asthma fulfilled some subphenotypes of type 2 asthma: eosinophilic, periostin-high, or atopic asthma.²⁶ In contrast, in the Belgian Severe Asthma Registry, 39% of severe asthma patients were categorized into non-eosinophilic asthma by sputum analysis, and 43% of severe asthma patients were classified as non-type 2 phenotype.⁵³ Because many studies have indicated that sputum eosinophils are reduced in obese severe asthmatics,¹⁴ one plausible explanation for high prevalence of type 2 asthma in Japan might include a low incidence of obesity. However, the relationships between obesity and eosinophilic inflammation seem to be complex; adding to the complication is the reported heterogeneity in inflammatory biomarkers across obese individuals.⁵⁴ It has also been reported that sputum IL-5 and submucosal eosinophils, but not sputum eosinophils, are elevated in obese asthmatics⁵⁵ and the Hi-CARAT cohort identified an obese type 2 dominant cluster.⁵² To understand the physiological mechanism better, the inflammatory background of severe Japanese patients with obesity should be investigated in future studies.

Treatment for severe asthma in Japan

Novel therapeutic strategies with type 2 inflammation-targeted biologics have been developed for severe asthma, with omalizumab, mepolizumab, and benralizumab having been approved in

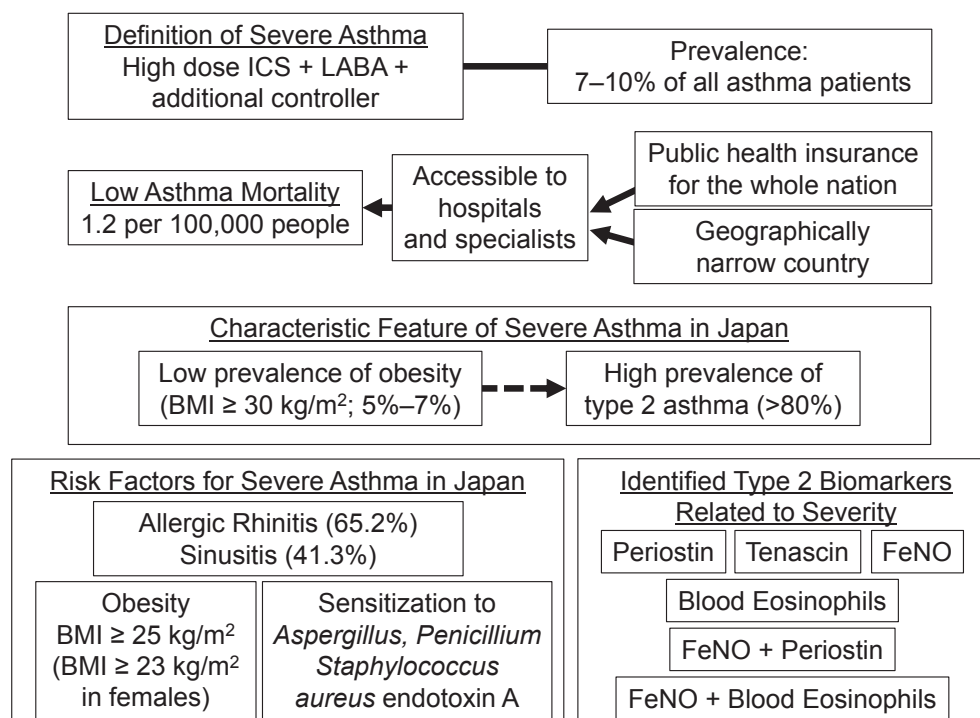


Fig. 1. Severe asthma is defined as asthma that requires high dose ICS and LABA plus additional controller in Japan. The asthma mortality seems to be lower in Japan, possibly due to the system of public health insurance for the whole nation, leading to good access to hospital and asthma specialists in the geographically narrow country. The characteristic phenotype of severe asthma in Japan is low incidence of obesity and this might partly explain the high prevalence of type 2 inflammation. Some asthma cohorts in Japan have investigated the roles of type 2 biomarkers extensively, including periostin, to identify a severe phenotype.

Japan. As discussed previously, the majority of severe asthma patients in Japan exhibit type 2 inflammation, and so a large proportion of patients can potentially be treated by these biologics. Only 17% of the severe asthma had no indications for any of the type 2 inflammation-targeted biologics.²⁶ In addition, the costs of biologics are covered by public health insurance and, thus, the use for treatment of severe asthma is prevailing in Japan as thousands of patients are currently treated by those biologics.

The effect and safety profile of biologics in Japanese patients appears to be fundamentally the same as global studies. Subgroup post-hoc analyses of global studies for biologics have been performed in Japan, finding that the effect on asthma exacerbations appear to be more prominent in the Japanese subgroup. Mepolizumab reduced the annual exacerbation rate by 62% [rate ratio (RR), 0.38; 95% CI, 0.06–1.29] in Japanese patients and 53% (0.36–0.65) in patients overall.^{56,57} The reduction in the annual exacerbation rate with benralizumab was also more pronounced in Japanese patients compared to the overall analysis [83% (0.05–0.60) vs 28% (0.54–0.95)].^{58,59} These differences may be attributed to different baseline blood eosinophil counts and rate of exacerbation. Japanese patients had greater baseline blood eosinophil counts compared with the overall group in both studies (420 vs 290 cells/mL for mepolizumab and 550 vs 500 cells/mL for benralizumab) as well as greater annual rate of exacerbation (4.6 vs 3.6 for mepolizumab and 3.2 vs 2.7 for benralizumab).

Conclusion

In this review, we discussed the current status of the definition, epidemiology, comorbidities, biomarkers, specific phenotype, and treatment for severe asthma in Japan and these features are summarized in Fig. 1. The characteristic phenotype of severe asthma in Japan can be summarized into the following two features: low

incidence of obesity and high prevalence of patients with type 2 inflammation. These findings suggest that the proportion of treatable patients by type 2 inflammation-targeted biologics might differ among ethnicities.

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Conflict of interest

The author has no conflict of interest to declare.

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