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Original Article

Predicting future risk of exacerbations in Japanese patients with adult asthma: A prospective 1-year follow up study

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ACT, Asthma Control Test; BMI, body mass index; COPD, chronic obstructive pulmonary disease; FeNO, fraction of exhaled nitric oxide; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroids; JGL, Asthma Prevention and Management Guidelines; OCS, oral corticosteroids; NAEPP, National Asthma Education and Prevention Program; SD, standard deviation; TENOR, The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens

ABSTRACT

Background: To avoid future risk is a definitive goal of long-term asthma management. Exacerbations are considered to be the most relevant future risk in real life asthma management. Few comparative studies have evaluated the risk factors associated with exacerbations in Japanese patients with asthma.

Methods: We performed the prospective 1-year follow up study in Japanese patients with adult asthma. A total of 189 patients with asthma were enrolled and followed up for 1 year. Finally, 181 patients completed the study protocol.

Results: Of 181 patients, 43 patients (23.8%) had exacerbations during the follow-up period. Among the 45 patients who had exacerbations during the preceding year, 32 patients (71.1%) had exacerbations. Prevalence of patients with previous exacerbations and those with previous admissions were significantly higher in patients with exacerbations than those with no exacerbation. Logistic regression analysis also identified a significant association between exacerbations during the follow-up period and exacerbations during the preceding year, admissions during the preceding 3 years, ACT score below 20, low % FVC (<80%), or low FEV₁ (<70%), respectively. Of the 55 patients with severe asthma, 29 patients (52.7%) had exacerbations. Among the 36 patients with severe asthma with previous exacerbations, 26 patients (72.2%) had exacerbations. The history of exacerbations during the preceding year was associated with a significantly increased risk of exacerbations both among the patients with severe asthma and those with non-severe asthma.

Conclusions: This study implicated that exacerbations during the preceding year reliably predict future risk of exacerbations in Japanese patients with asthma.

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Introduction

Asthma is a chronic airway inflammatory disease and is clinically characterized by variable episodes of shortness of breath, chest tightness, wheezing and cough. With improvements in controller therapy, such as inhaled corticosteroids (ICS) and long-

acting bronchodilators, it is now recognized that highly satisfactory levels of asthma control can be achieved and maintained for long periods.¹ However, certain triggers, such as virus infection and the changing of the season, cause exacerbations in patients with asthma. In addition, patients with severe asthma may require frequent bursts of oral corticosteroids (OCS) or even depend on daily OCS despite adequate treatments.^{2,3}

The goals of asthma treatment in current guidelines, such as National Asthma Education and Prevention Program (NAEPP),⁴ and Global Initiative for Asthma (GINA) guideline⁵ have two points of view: one is to achieve current asthma control, and the other is to reduce asthma-associated future risk. Current asthma control was

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assessed by asthma symptoms, pulmonary function, and frequency of short-acting beta agonist use. Asthma-associated future risk involves exacerbations, admission, asthma death, fixed airflow limitation, and side-effects. During the past decade, admissions and death due to asthma have been dramatically decreased. Currently, exacerbations would be the most relevant future risk in long-term asthma management. Therefore, identification of risk factors associated with future exacerbations is of considerable importance to physicians, public health officials, and patients.

It is recognized that poor asthma control is a predictor of future instability in asthma control and asthma exacerbations.^{6,7} Previous exacerbations,⁸ low forced expiratory volume in 1 s (FEV₁) predicted,^{9,10} a requirement for a short course of OCS,¹¹ hospitalization, or an emergency room visit¹² are also known to be major predictors for future exacerbations of asthma. Osborne *et al.* demonstrated that FEV₁ predicted <60% was the better predictor than histories of hospitalization, urgent care use or breathing problems in the past year.¹³ Regarding Japanese patients with asthma, Sato *et al.* showed a combined analysis of patients-based questionnaire and FEV₁ could predict the risk for future asthma exacerbation.¹⁴ However, the A comparison of risk factors associated with future exacerbations in Japanese patients with asthma has not been fully investigated. We therefore designed this prospective trial to assess the risk factors associated with future exacerbations in Japanese patients with adult asthma, following up for 1 year in clinical setting.

Methods

Study design

This study was prospectively carried out in the pulmonary and allergy units of the Showa University Hospital, Tokyo, Japan, between July 2012 and December 2013. Study protocol was reviewed and approved by the Showa University ethics committee and written informed consent was obtained.

Participants were followed up by the same physician for 1 year to determine whether they had exacerbations. Exacerbations were defined as an episode of worsening asthma requiring intravenous corticosteroid, 3 or more consecutive days of OCS use, an increase in systemic corticosteroids from an individual maintenance dose, or a visit to the emergency room. Treatments for asthma were adjusted in accordance with the Asthma Prevention and Management Guidelines, referred to the Japanese guideline (JGL),¹⁵ during the study period. Briefly, if asthma was controlled for 3–6 months, step-down of the treatment was considered. If the patients were in poorly controlled or in uncontrolled, 1 step-up or 2 step-up of the treatment were considered, respectively. Asthma control was also assessed in accordance with JGL.¹⁵ To identify potential factors associated with the development of exacerbations, the associations between the future risk of exacerbation and clinical parameters, including pulmonary function and fraction of exhaled nitric oxide (FeNO), were analyzed.

Study subjects

A hundred eighty-nine patients, regularly followed up at Showa University Hospital for at least 2 years and aged 20–80, were randomly enrolled. Patients who had exacerbations more than 6 times the preceding year, no exacerbation within the preceding 3 years, or a regular treatment with oral corticosteroid above 10 mg/day, were excluded. Patients with chronic obstructive pulmonary disease (COPD) or other lung disease, poor adherence to treatment (<80%), smoking history >20 pack-years, vocal cord dysfunction, or neurological disease were also excluded. The diagnostic criteria of asthma were mostly based on the GINA guideline. Briefly, asthma was diagnosed in patients who had a reversible airflow limitation

that represented an increase of 12% and 200 ml in FEV₁ after the inhalation of salbutamol or the clinical treatment targeting asthma. Diagnoses of perennial allergic rhinitis and seasonal cedar pollinosis were based on clinical history and a positive serum allergen-specific IgE. The diagnosis of chronic rhinosinusitis was based on the standard criteria issued in the European Position Paper on Rhinosinusitis and Nasal Polyps guidelines.¹⁶

Assessments

Patients underwent extensive characterization and investigations, including medical history, severity, spirometry, fraction of exhaled nitric oxide (FeNO), blood tests for peripheral eosinophil count and IgE. Body mass index (BMI) was based on measured weight and height, and calculated as weight in kilograms divided by the square of the height in meters. Asthma control was assessed by using the validated Japanese version of the Asthma Control Test (ACT). Patients were subjectively evaluated for the degree of impairment caused by their asthma during the preceding 4 weeks by responding to five questions; activity limitation, shortness of breath, nighttime symptoms, use of rescue medication, and the patient's overall rating of asthma control. Treatment steps and asthma severity were classified according to the JGL.¹⁵ Asthma severity was assessed on the basis of asthma control level and treatment step of JGL.¹⁵ For descriptive purposes, mild intermittent, mild persistent, and moderate stage of severity were regarded as non-severe.

Spirometry was performed using a AS-302 spirometer (MINATO MEDICAL SCIENCE CO., LTD, Osaka, Japan) in accordance with American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines^{17,18} to determine FEV₁, forced vital capacity (FVC), FEV₁/FVC. The highest value from three technically satisfactory attempts was recorded. FEV₁ and FVC values are expressed as measured value, and predicted values of FEV₁ and FVC were obtained from the Japanese Respiratory Society guideline.¹⁹

FeNO was measured by a portable device (NIOX MINO; Aero-crone AB, Solna, Sweden) at an expiratory flow rate of 50 mL/s for 10 s. The sensor on the device was changed periodically, in line with the manufacturer's guidance. Measurements of FeNO were performed before spirometry.

Statistical analyses

To identify the factors associated with the development of exacerbations, variables were compared between the patients who had exacerbations and those who had no exacerbation during the 1-year follow-up period. The results are expressed as mean $\pm$ SD for continuous variables. All analyses were performed using JMP system version 12 (SAS Institute Inc., Cary, NC, USA). The differences in the continuous variables were analyzed using Mann–Whitney U test, and the differences in the categorical variables were analyzed using Pearson χ^2 tests. Values that were not normally distributed, such as IgE, were log-transformed to obtain normal distribution for regression analysis. In order to examine the association between exacerbations and each parameter, logistic regression analyses were performed using exacerbations as the outcome variable. These models were adjusted for age and sex. A value of $p < 0.05$ was considered significant for all statistical assessments.

Results

Baseline characteristics of the study subjects

One hundred eighty-nine patients were recruited and signed informed consents. Of these, 8 patients discontinued the study protocol (1 had pulmonary tuberculosis, 1 withdrew the consent

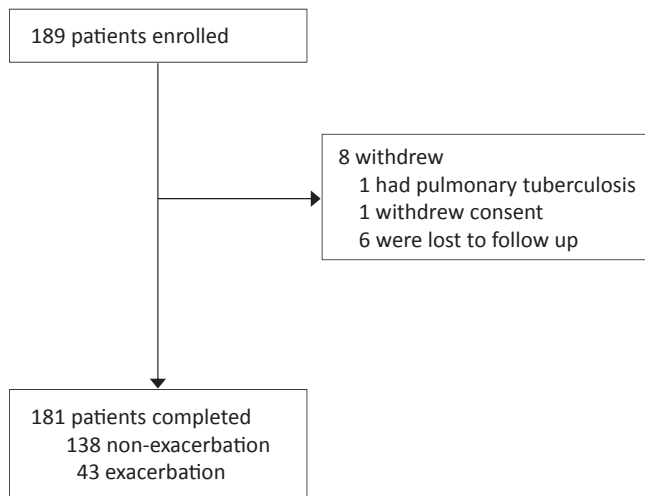


Fig. 1. Enrollment and follow-up of participants.

due to a pregnancy, and 6 were lost to follow up) (Fig. 1). Finally, 181 patients were followed up for 1 year. All patients received at least ICS. At the time of enrollment, 46 patients were treated with STEP 1, 68 patients with STEP 2, 38 patients with STEP 3, and 29 patients with STEP 4.

Table 1 shows the demographic characteristics of 181 patients who completed the study protocol. The mean age of the patients was 57.3 ± 16.1 years with a range of 20–80, and the mean onset age was 31.2 ± 21.2 years. Mean BMI was 21.9 ± 3.5 , and 100 patients (55.2%) were women. Fifteen patients (8.3%) were current smokers, and 49 patients (27.1%) were ex-smokers at the time of enrollment. Mean ACT score was 21.8 ± 3.0 and FeNO was 46.3 ± 36.8 ppb (log-FeNO was 1.56 ± 0.30). In pulmonary function test, FVC was 2.82 ± 0.92 L (%FVC: $93.5 \pm 17.9\%$); FEV₁ was 2.11 ± 0.83 L (%FEV₁: $80.8 \pm 21.8\%$); and FEV_{1%} was 73.9 ± 12.8 .

Differential characteristics of the study subjects between patients with exacerbations and patients without exacerbations

We compared the baseline characteristics between the patients with exacerbations and patients without exacerbations during the

Table 1
Demographic characteristics of 181 patients who completed the study.

	N = 181
Age, yr	57.3 ± 16.1
Gender (Female), n (%)	100 (55.2)
BMI	21.9 ± 3.5
Smoking: current/ex/never, n	15:49:117
Pet owner, n (%)	46 (25.4)
Exacerbation during a previous year, n (%)	45 (24.9)
Admission during previous 3 years, n (%)	9 (5.0)
Perennial allergic rhinitis, n (%)	75 (41.4)
Seasonal cedar pollinosis, n (%)	81 (44.7)
Chronic sinusitis, n (%)	36 (19.9)
Severity (MI, MP, Mod, Sev), n	41:41:44:54
ACT	21.8 ± 3.0
Treatment (>STEP3), n (%)	67 (37.0)
Peripheral eosinophils (%)	5.47 ± 4.63
Total IgE (log)	2.35 ± 0.71
Atopic type, n (%)	113 (62.4)
FVC, L (%predicted)	2.82 ± 0.92 (93.5 ± 17.9)
FEV ₁ , L (%predicted)	2.11 ± 0.83 (80.8 ± 21.8)
FEV _{1.0%} , %	73.9 ± 12.8
FeNO (log)	1.56 ± 0.30

Abbreviations: BMI, body mass index; MI, mild intermittent; MP, mild persistent; Mod, moderate persistent; Sev, severe; ACT, asthma control test; FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 s; FeNO, fractional exhaled nitric oxide.

Table 2

Comparison of baseline clinical characteristics of the patients who had or had no exacerbation.

	Exacerbation (–) (N = 138)	Exacerbation (+) (N = 43)	P value
Age, yr	57.8 ± 15.9	57.3 ± 16.1	0.584
Gender (Female), n (%)	73 (52.9)	27 (62.9)	0.254
BMI	23.2 ± 3.5	21.91 ± 3.54	0.281
Smoking: current/ex/never, n	11: 35: 92	4: 14: 25	0.586
Pet owner, n (%)	36 (26.1)	10 (23.3)	0.780
Exacerbation during a previous year, n (%)	13 (9.4)	32 (74.4)	<0.001
Admission during previous 3 years, n (%)	3 (2.2)	6 (14.0)	0.002
Perennial allergic rhinitis, n (%)	59 (42.8)	16 (37.2)	0.519
Seasonal cedar pollinosis, n (%)	63 (45.7)	18 (41.9)	0.662
Chronic sinusitis, n (%)	24 (17.4)	12 (27.9)	0.131
ACT	22.8 ± 2.2	18.9 ± 3.5	<0.001
Treatment (>STEP3), n (%)	33 (24.6)	34 (76.7)	<0.001
Peripheral eosinophils (%)	5.42 ± 3.93	6.42 ± 6.43	0.218
Total IgE (log)	2.35 ± 0.71	2.35 ± 0.75	0.956
Atopic type, n (%)	88 (63.8)	25 (59.5)	0.619
FVC, L (%predicted)	2.9 ± 0.9	2.5 ± 0.8	0.023
FEV ₁ , L (%predicted)	95.3 ± 16.9	87.5 ± 19.6	(0.011)
	2.2 ± 0.8	1.8 ± 0.8	0.005
	83.4 ± 20.1	72.4 ± 24.9	(0.004)
FEV _{1.0%} , %	75.2 ± 11.6	69.7 ± 15.5	0.013
FeNO (log)	1.56 ± 0.32	1.56 ± 0.29	0.988

Abbreviations: BMI, body mass index; ACT, asthma control test; FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 s; FeNO, fractional exhaled nitric oxide; The differences in the continuous variables were analyzed using Mann–Whitney U test, and the differences in the categorical variables were analyzed using Pearson χ^2 tests.

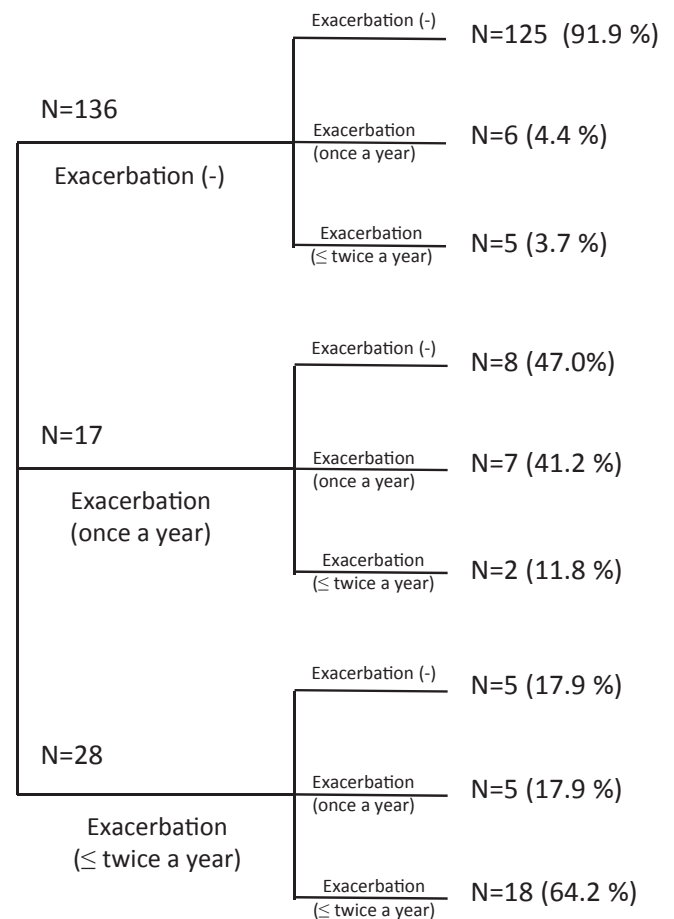


Fig. 2. Distribution of the number of patients classified by exacerbation frequency.

follow-up period (Table 2). More patients with exacerbations during the follow-up period had exacerbations during the preceding year and admission during the preceding 3 years than patients without exacerbation during the follow-up period (74.4% vs 9.4%, $P < 0.001$ and 14.0% vs 2.2%, $P = 0.002$; respectively). Mean ACT score, mean FVC, mean FEV₁, and mean FEV₁% were significantly lower in patients with exacerbations than in those without exacerbation during the follow-up period (18.9 ± 3.5 vs 22.8 ± 2.2 , $P < .001$; 2.5 ± 0.8 vs 2.9 ± 0.9 , $P = 0.023$, 1.8 ± 0.8 vs 2.2 ± 0.8 , $P = 0.005$; and 69.7 ± 15.5 vs 75.2 ± 11.6 , $P = 0.013$; respectively). Meanwhile, no significant differences were observed in percentage of peripheral eosinophils, serum total IgE, and log-FeNO between the two groups.

Time course of the study subjects

During the follow-up period, 43 patients had exacerbations (23.8%) (Fig. 2). Among the 45 patients who had exacerbations during the preceding year, 32 patients (71.1%) had exacerbations (Fig. 2). Moreover, among the 28 patients who had frequent exacerbations (twice or more) during the preceding year, 23 patients (82.1%) had exacerbations and 18 patients (64.3%) had frequent exacerbations (Fig. 2). Meanwhile, among the 136 patients who had no exacerbation during the preceding year, 11 patients (8.1%) had exacerbations (Fig. 2).

Association between variables and exacerbations

We used multivariate logistic regression analysis to examine the association between variables of baseline patients' characteristics and exacerbations. The exacerbations during the preceding year showed the highest OR (OR 27.97, 95% CI 11.46–68.24, $P < .001$; Fig. 3), indicating the best predictor for exacerbations. The OR was

still high after adjustment for BMI, treatment step, smoking history, severity, ACT score, and a history of admission in addition to age and sex (OR 21.39, 95% CI 5.93–92.79, $P < .001$). Similarly, admissions during the preceding 3 years were independent predictors of higher risk of exacerbations (OR 7.29, 95% CI 1.74–30.57, $P = .002$; Fig. 3). Severe stage of the disease, assessed by composition of asthma control and treatment step, and ACT score below 20 were significantly associated with an increased risk of exacerbations (OR 9.36, 95% CI 4.41–20.78, $P < .001$; OR 6.04, 95% CI 2.72–13.38, $P < .001$; respectively; Fig. 3). Regarding pulmonary function test, %FVC (<80%) and %FEV₁ (<70%) were also associated with a significantly increased risk of exacerbations (OR 2.41, 95% CI 1.11–5.26, $P = .024$; OR 2.06, 95% CI 1.02–4.15, $P = .041$; respectively; Fig. 3). Meanwhile, the presence of sinusitis, being female, older age (over 65 years), high BMI, owning pets, cedar pollinosis, perennial allergic rhinitis, and current smoking were not associated with higher risk of exacerbations (Fig. 3).

Relationship between asthma severity and susceptibility to exacerbations

The number of patients with exacerbations and those with no exacerbation during the follow-up period were shown by differential asthma severity (Fig. 4A), assessed by treatment step and asthma control. As the severity increased, the number of patients with exacerbations increased. Of the 55 patients with severe asthma, 29 patients (52.7%) had exacerbations. Among the 36 patients with severe asthma who had exacerbations during the preceding year, 26 patients (72.2%) had exacerbations (Fig. 4B). Meanwhile, among the 19 patients with severe asthma who had no exacerbation during the preceding year, 3 patients (15.8%) had exacerbations (Fig. 4B). The history of exacerbations during the preceding year was associated with a significantly increased risk of

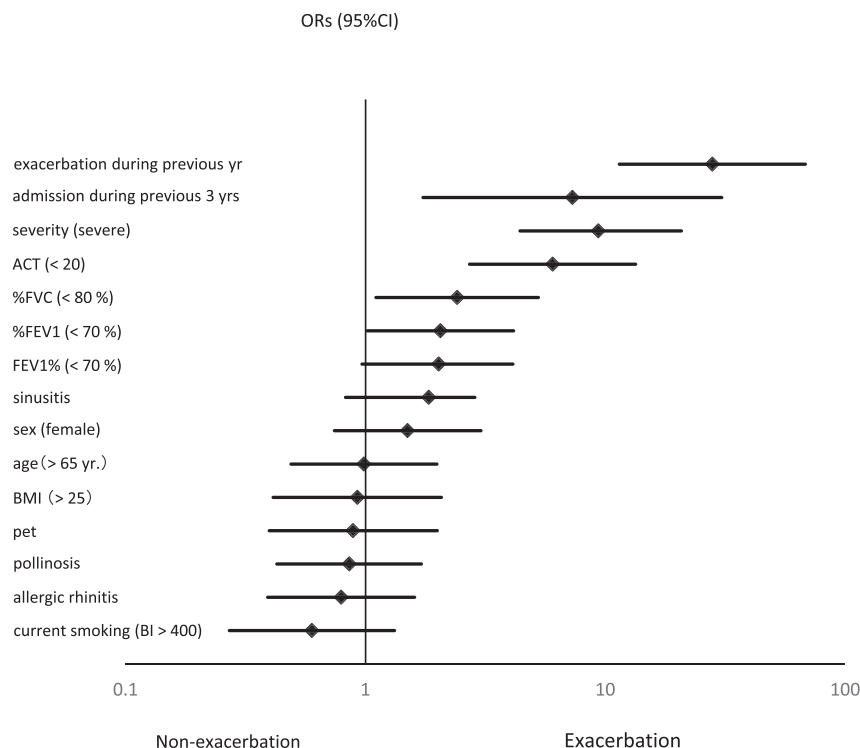


Fig. 3. Logistic regression models for the prediction of exacerbation during the follow-up period. ORs and 95% CIs are represented for the different comparisons. These models were adjusted for age and sex. Exacerbation during the preceding year, admission during the preceding 3 years, severe stage of the disease, ACT score lower than 20, %FVC lower than 80%, or %FEV₁ lower than 70% were associated with exacerbations during the follow-up period.

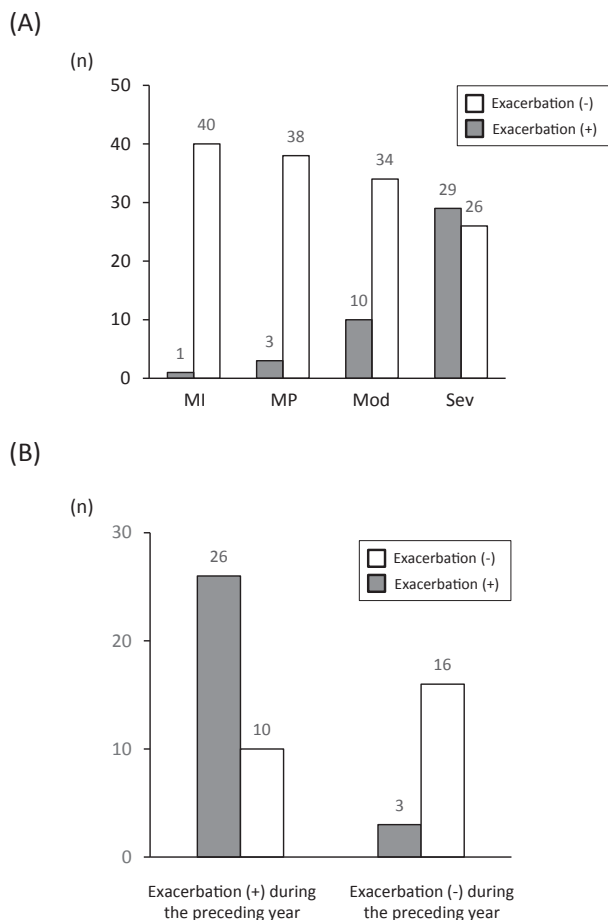


Fig. 4. (A) Distribution of the numbers of patients classified by differential stage of severity among total patients. (B) Distribution of the numbers of patients classified by the exacerbation during the preceding year among the severe patients. MI, mild intermittent; MP, mild persistent; Mod, moderate persistent; Sev, severe.

exacerbations during the follow-up period both among the patients with severe asthma and those with non-severe asthma (OR 19.88, 95% CI 3.89–169.52, $P < .001$, OR 41.01, 95% CI 7.76–317.88, $P < .001$, respectively).

Discussion

We performed a prospective 1-year follow up study to assess the risk factors for exacerbations in Japanese patients with asthma. Our results showed that a history of exacerbations during the preceding year, a history of admission due to asthma during the preceding 3 years, low ACT score, and low pulmonary function indicate the increased risk of the exacerbations in a follow-up period. In particular, a history of exacerbations during the preceding year was likely the most reliable indicator for future exacerbations. This result confirms the previous result derived from The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study,¹² showing that previous exacerbations are the strongest predictor for future exacerbations and steroid bursts. In the present study, 82.1% of the patients, who had experienced frequent exacerbations (two or more) in the preceding year, had exacerbations in the follow-up period, indicating that more frequent patients experience exacerbations, further the risk of exacerbations increase, and that there is a frequent-exacerbation phenotype of asthma.

In the present study, the prevalence of patients with exacerbations increased as the severity increased, and a half of the patients

with severe asthma had exacerbations during the follow-up period. Taking these findings into consideration, identification of patients who are susceptible to exacerbation among the patients with severe asthma is of importance. Our study showed that patients with previous exacerbations were susceptible to exacerbations even among the patients with severe asthma. These results indicate that phenotype of susceptibility to exacerbations can be identified even among the patients with severe asthma by asking previous exacerbations.

One possible reason why patients with asthma who experienced exacerbations in the preceding year tend to repeat exacerbations may be the increased susceptibility to virus infection. Previous studies showed that patients with asthma having frequent exacerbations are vulnerable to virus infection.^{20,21} Hurst *et al.* showed that self-reported exacerbations during a preceding year were the best predictor of future exacerbations among all variables they examined in patients with COPD in Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study.²² Intriguingly, patients with COPD who have frequent exacerbations are also reported to be vulnerable to virus infection.^{23,24}

Most of the previous studies regarding the risk factors for asthma exacerbation have evaluated the association between exacerbations and single clinical variables such as pulmonary function or asthma control score.^{7–10} There were a few studies which evaluated the association between exacerbations and multiple clinical variables in patients with asthma.^{12,13} Our study design was the latter type. TENOR study showed the proportion of the patients with BMI greater than 30 was higher in patients who experienced severe asthma exacerbations within 1.5 preceding years than those who did not experienced.¹² Our data showed no differences in mean BMI level between patients with exacerbations and those with no exacerbation. In addition, BMI greater than 25 had no association with increased risk of exacerbation. This inconsistency of BMI may be derived from racial difference. There are not so many Japanese whose BMI is greater than 30. A large-scale Japanese study investigating epidemiology of severe asthma showed 4.9% of the patients were BMI greater than 30 among 1107 patients.²⁵ Same study showed obesity is a risk factor for difficult-to-treat asthma only in non-atopic women. Another previous study revealed less association of obesity with asthma control in Japanese patients.²⁶ Further study is needed to investigate the substantial association between obesity and exacerbations in Japanese patients with asthma. The prospective study conducted by Osborne *et al.* showed that airflow limitation defined by FEV₁ was the most significant predictor of subsequent acute care utilization.¹³ They also showed, in contrast to our results, that cigarette smoke exposure and ownership of cat or dog were high risk factors for acute care utilization. Cigarette smoke exposure and ownership of cat or dog are regarded as deteriorating factors for asthma control, therefore we instruct the patients with asthma, in particular poor controlled asthmatics, to inhibit them as much as possible in the clinical setting. We speculate these instructions might bring the differences.

A considerable proportion of patients with asthma cannot receive pulmonary function test in out-patient clinics. In addition, it relatively takes longer to perform pulmonary function test than to check asthma control levels such as ACT. The utility of ACT to assess asthma control level was reported in many previous studies.^{27,28} This study clearly showed that low ACT score predicts a future risk of exacerbations. Moreover, low ACT level is more likely to predict exacerbations than low pulmonary function, shown by high ORs. These results suggest the time-efficient utility of ACT to predict future exacerbations in clinical setting.

One of the novel points of this study was the treatment-unfixed design. Treatments for asthma were adjusted in accordance with JGL. After all, 34 patients' treatment steps were decreased and 16

patients' treatment steps were increased during the follow-up period. We confirmed, in this study, that step-up and step-down of the treatment were not associated with the increase in exacerbations, indicating that there were few inappropriate step-down which influenced the results in this study.

This study contains several limitations that need to be acknowledged. First, the assessment of asthma severity and treatment step were in accordance with JGL, but not with GINA. In addition, step-down of asthma treatment was in accordance with JGL. Strategy of step-down was similar between JGL¹⁴ and GINA,⁵ indicating that step-down should be considered when asthma symptoms are well controlled for 3 or more months. However, assessment of asthma control was slightly different between JGL and GINA. Any daytime symptoms and reliever use were not permitted for achieving well control in JGL, indicating that JGL is more difficult to achieve well control than GINA. If GINA guideline were used as assessment of asthma control, the same results were not necessarily obtained. Second, this study involved relatively a small sample size, compared to the previous prospective studies which evaluate the future risks of asthma exacerbations.^{7–9,12,13} It is likely that prevalence of female and chronic sinusitis, and peripheral eosinophil counts were higher in patients with exacerbations than those with no exacerbation, despite no statistical difference. These factors are considered to be associated with poor asthma control. Thus, if sample size was much larger, there might be statistical differences in these factors between patients with exacerbations and those with no exacerbation. Third, all participants were regularly followed up at Showa University Hospital for at least 2 years, and patients with poor adherence to treatment (<80%) were excluded. In real life, no treatment and poor adherence to treatment can be a risk factor for future exacerbations. In fact, van der Merwe *et al.* showed an association between no use of ICS and severe life threatening asthma exacerbations.²⁹

In conclusion, the present study indicates that the most reliable determinant predicting future exacerbation is a history of exacerbations in Japanese patients with asthma. It should be realized that increase in severity, poor asthma control assessed by ACT, and lower pulmonary function were also associated with future risk of exacerbations from our results. These results suggest that when considering step-down of asthma treatment, exacerbations during the preceding year should be taken into account in order to avoid the future exacerbations.

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Conflict of interest

The authors have no conflict of interest to declare.

Authors' contributions

AT performed the major part of the data collection and analysis, contributed to the interpretation of the results and drafted the manuscript. TU, HaS, MJ, KH, YM, MuY, SO, TH, MaY, SS, and TY contributed to the analysis of the study, and supported the development of the manuscript. His conceived the outline of the current analysis, and supervised its completion. All authors agreed with the final draft of the manuscript.

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