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A study of factors related to asthma exacerbation using a questionnaire survey in Niigata Prefecture, Japan

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Abstract

Background: As indices of asthma control, exacerbations are equally important with symptoms and respiratory function. Thus, it is critical to recognize the risk factors of exacerbation.

Objective: We conducted a questionnaire survey of asthma patients in Niigata Prefecture to clarify the factors involved in asthma exacerbation.

Methods: The questionnaire survey was carried out in patients and their physicians from September to October 2014. In 2015, the same sample population also received a questionnaire about current asthma control and exacerbation.

Results: One hundred patients experienced asthma exacerbation during the 1-year period. There were significant differences in age, sex, history of hospitalization due to asthma, smoking history, Asthma Control Test, treatment step, and transient steroid treatment history in the previous year between the exacerbation group and non-exacerbation group. On multivariate analysis, there was a significant difference in history of transient steroid therapy, history of hospitalization associated with asthma attacks, and nonsmoking history. Cluster analysis of cases with exacerbation was classified into three clusters. Cluster 1 comprised slightly older cases with smoking history, Cluster 2 had more females, non-smoking and nonatopic cases with uncontrolled symptoms, and Cluster 3 had more females, non-smoking and mild atopic cases.

Conclusions: Our findings suggest that patients with asthma exacerbation in the previous year and nonsmoking females are important targets for the study of asthma exacerbation. The adequate treatment of women patients might be important for the prevention of asthma exacerbation.

Key words: Bronchial asthma, exacerbation, questionnaire survey, nonsmoking, menopause

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Introduction

Bronchial asthma is characterized by symptoms such as wheezing, chest discomfort, shortness of breath, and cough based on chronic airway inflammation and reversible airway obstruction.[1] In guidelines such as the Global Initiative for Asthma (GINA) and the National Asthma Education and Prevention Program (NAEPP), two asthma treatment goals are proposed,[2,3] to achieve asthma control and to reduce future risk of asthma. Reduction of future risk includes the maintenance of respiratory function and prevention of acute exacerbation and asthma death. Acute exacerbations are a major cause of asthma death, and the American Thoracic Society and European Respiratory Society have reported that acute exacerbations are related to severe stress and anxiety and higher medical expenses.[4] Therefore, the prevention of asthma exacerbation is an important goal for asthma treatment.

Medical circumstances such as national public medical insurance and the unique culture of Japan may influence asthma treatment. For example, rather than monotherapy with inhaled corticosteroid (ICS), a combination therapy of ICS and long-acting beta-agonist is mainly used for asthma control.

Other circumstances include unique lifestyle such as using futons that allow mites to thrive easily and humid climate. Based on these, it is difficult to compare the risk factors of asthma exacerbation in Japan with those of other countries. In the analysis of risk of acute exacerbation in the Japanese population, Sato et al. reported that patient-based questionnaires and forced expiratory volume in 1 second (FEV_1) are indicators for risk of future exacerbation.[5] Meanwhile, Tanaka et al. reported that the worsening of symptoms in the previous year is a predictor of future exacerbation,[6] consistent with previous reports.[7] However, the samples were collected from limited facilities, and overall, both findings are inconsistent.

The Niigata Asthma Treatment Study Group (NATSG) was established in 1997 and is engaged in exchanging asthma treatment information, improving asthma control, and preventing asthma deaths in Niigata Prefecture. The main activities of the NATSG include conducting questionnaire surveys of asthma cases in the prefecture; these were started in 1998 and are conducted every year or every alternate year. Based on this questionnaire survey data, many studies have been conducted on the situation and features of asthma patients in Niigata prefecture, Japan.[8-11]

In this study, we conducted a questionnaire survey between 2014 and 2015 in Niigata Prefecture and analyzed the factors involved in asthma exacerbation in the Japanese population.

Methods

Subjects

The questionnaire survey was performed from September to October both in 2014 and 2015, in accordance with the ethical principles for medical research involving human subjects and the Declaration of Helsinki and with approval from the ethics committee of Niigata University (approval no. 1231). The subjects included patients who were diagnosed with asthma according to the guidelines of the Japanese Society of Allergology. The institutions involved were 28 large hospitals (≥ 200 beds), 15 small hospitals (< 200 beds), and 69 clinics (no beds). Among the patients who participated in both the 2014 and 2015 questionnaire surveys, we enrolled patients who reported the latest data for respiratory function test in the 2014 questionnaire and a description of asthma exacerbation in the 2015 questionnaire. A total of 552 patients were therefore enrolled in this study.

Protocol

After providing informed consent, the patients completed a questionnaire on age, sex, smoking status, disease duration, Adherence Starts with Knowledge-12 (ASK-12), and Asthma Control Test (ACT). Their physicians also provided data on the contents of therapy, recent pulmonary function test, and existence of exacerbation. Asthma exacerbation was defined as systemic steroid use (or increased use) for ≥ 3 days due to asthma exacerbation, hospitalization due to worsening of asthma, emergency outpatient visit for asthma exacerbation, or unscheduled consultation due to asthma exacerbation.

Statistical analysis

The results were expressed as medians (25^{th}-75^{th} interquartile range), because the data for continuous variables were mainly distributed non-normally. To compare differences among the groups, one-way analysis of variance and Bonferroni's multiple comparison tests were used. The in-group comparisons were performed using Wilcoxon's signed-rank test. Comparisons for all pairs were performed using the Kruskal-Wallis test. Multivariate analysis was used to identify the variables that influenced asthma control. Variables that were statistically significant in the dichotomous analysis were applied in the multivariable logistic regression analysis. We performed a hierarchical cluster analysis on the exacerbation group using Ward's method, as reported previously.[12,13] In brief, we chose important variables for cluster establishment, including disease duration, sex, age, disease type, smoking status, ACT score, medication content, and $\%FEV_1$. Decision tree analysis was conducted to retrieve methods of clinical categorization for ease of usage. All of these factors were modified to the nominal scale and input. Most statistical analyses were performed using JMP software version 11 (SAS Institute, Inc., Tokyo, Japan). Decision tree analysis was performed using CAnalysis ver. 4.0 software. For the adjustment of age and sex, optimal matching using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan) was performed. For all statistical analyses, $p < 0.05$ was considered significant.

Results

A total of 100 patients were included in the group that experienced at least one episode of exacerbation during the 1-year period (exacerbation group). Compared with the non-exacerbation group, the exacerbation group were younger, women-dominant, and nonsmoker-dominant. Regarding treatment step defined by the Japanese Society of Allergology, the prevalence of patients with step 4 (i.e., most intensive treatment) was significantly higher in the exacerbation group. Moreover, administration of other maintenance therapies such as leukotriene receptor antagonist, long-acting muscarinic receptor antagonist, oral sustained-release theophylline, and oral corticosteroid (OCS) was significantly higher in the exacerbation group. Furthermore, ACT score was significantly lower in the exacerbation group. In terms of comorbidity, the prevalence of allergic rhinitis and osteoporosis was higher in the exacerbation group (**Table 1**).

The exacerbation group had higher prevalence with regard to history of hospitalization than the exacerbation group. The prevalence of attack episodes and OCS burst episodes in the previous year was also significantly higher in the exacerbation group (**Table 2**).

To determine the factors associated with asthma exacerbation, multivariate analysis was conducted. Based on data from the comparison test between the exacerbation and non-exacerbation groups, age, OCS burst, smoking history, sex, ACT score, allergic rhinitis, treatment step, and osteoporosis were applied as variables. In the multivariate analysis, significant differences were observed in OCS burst in the previous year, history of hospitalization, and smoking history. Interestingly, a nonsmoking history was more likely to cause exacerbation (**Table 3**).

Table 1. Comparison of clinical characteristics between subjects with and without exacerbation

	Exacerbation (+)	Exacerbation (-)	p-value
No. of cases (n)	100	452	
Age (years), median (IQR)	57 [43-71]	63 [50-72]	0.04
Female, n (%)	70 (70)	255 (56.4)	0.01
BMI (kg/m^2), median (IQR)	23.2 [20.2-25.5]	23.0 [20.7-25.3]	0.72
Duration of disease (years)	10 [4-20]	9 [4-28]	0.62
Age of onset (years), median (IQR)	43 [31-57]	59 [35-63]	0.03
Smoking history (non/ex/cur), n (%)	68/27/5 (68/27/5)	230/185/36 (51/41/8)	0.009
Atopic disease type, n (%)	60 (60)	286 (63.2)	0.57
Immunoglobulin E (IU/ml), median (IQR)	167 [50-620]	158 [52-442]	0.44
%FEV$_1$ (%), median (IQR)	93 [76-110]	95 [83-108]	0.50
Treatment step 4, n (%)	32 (32)	53 (12)	< 0.0001
Asthma Control Test, median (IQR)	22 [19-24]	24 [21-24]	< 0.0001
LTRA use, n (%)	68 (68)	209 (46)	< 0.0001
LAMA use, n (%)	11 (11)	21 (4.6)	0.0003
OSRT use, n (%)	40 (40)	99 (22)	0.0003
OCS use, n (%)	12 (12)	17 (3.8)	0.002
Allergic rhinitis, n (%)	43 (43)	45 (34.4)	0.039
GERD, n (%)	11 (11)	43 (9.9)	0.65
Osteoporosis, n (%)	7 (7)	9 (2)	0.001

BMI: body mass index, IQR: interquartile range, LTRA: leukotriene receptor antagonist, LAMA: long-acting muscarinic receptor antagonist, non/ex/cur: nonsmoker/ex-smoker/current smoker, OSRT: oral sustained-release theophylline, OCS: oral corticosteroid, GERD: gastroesophageal reflux disease. Data expressed in medians (IQR).

Table 2. Comparison of past episodes related with exacerbation between subjects with and without exacerbation

	Exacerbation (+)	Exacerbation (-)	p-value
History of hospitalization, n (%)	39 (39)	93 (21)	0.0002
Attack episodes in the previous year, n (%)	56 (56)	118 (26)	< 0.0001
OCS burst episode in the previous year, n (%)	50 (50)	45 (10)	< 0.0001
Emergency department use, n (%)	32 (32)	102 (22.6)	0.0519

OCS: oral corticosteroid.

Table 3. Multiple regression analysis of factors related to asthma exacerbation

Factor	Hazard ratio	95% CI	p-value
Age (≤ 64 years)	1.36	0.78-2.39	0.268
OCS burst (yes)	6.01	3.28-11.1	< 0.001
Smoking history (never)	2.57	1.39-4.90	0.003
History of hospitalization (yes)	2.31	1.32-4.02	0.002
Female	0.97	0.52-1.82	0.93
Asthma Control Test score (< 22)	1.46	0.86-2.47	0.15
Allergic rhinitis (yes)	1.26	0.92-2.17	0.40
Treatment step (4)	1.82	0.93-3.51	0.07
Osteoporosis (yes)	1.10	0.29-3.98	0.87

OCS: oral corticosteroid.

Table 4. Demographic features of the groups by cluster analysis.

	Cluster 1	Cluster 2	Cluster 3	p value
Sample	40	41	17	
Sex (M/F)	19/21	8/33	1/16	0.0015
Age	60.0 [55.34-64.5]	58.7 [54.2-63.3]	49.9 [42.9-57.0]	0.055
Onset of Disease	39.2 [33.7-44.6]	50.1 [44.7-55.6]	41.9 [33.5-50.3]	0.018
BMI	23.2 [21.9-24.7]	23.9 [22.5-25.2]	23.4 [21.3-25.5]	0.82
Duration of disease	20.8 [17.5-24.1]	8.6 [5.4-11.9]	8.0 [2.9-13.0]	< 0.001
Atopic (+/-)	33/7	13/28	14/3	< 0.001
Smoking history (current or past/never)	24/16	4/37	3/14	< 0.001
Attack in previous year (+/-)	26/13	22/14	7/10	0.19
ACT	21.6 [20.7-22.5]	19.5 [18.56-20.4]	24.0 [22.6-25.4]	< 0.001
Treatment step (1-2/3-4)	7/33	10/31	14/3	< 0.001
%FEV$_1$	73.9 [67.8-80.1]	103.6 [97.6-109.2]	99.5 [90.0-108.9]	< 0.001

OCS: oral corticosteroid.

Based on the multivariate analysis, cluster analysis was performed to further analyze the cause of exacerbation (**Table 4**). The subjects were classified into three groups: male-dominant group with slightly older age, smoking history, and poor respiratory function and asthma control (Cluster 1); female-dominant group with nonatopic disease type with relatively poor asthma

control (Cluster 2); female-dominant group with better asthma control and mild atopic disease type (Cluster 3). Both Clusters 2 and 3 were mainly nonsmokers with good respiratory function.

From the valuable parameters, we further retrieved 4 parameters including %FEV_1, ACT score, disease type (atopic or non-atopic), and disease duration to establish an easily used method of clinical categorization using discriminant analysis and decision tree analysis. The clusters were differentiated using these 4 parameters with a sensitivity of 95.0%, 92.7%, and 58.8% and a specificity of 87.9%, 88.1%, and 100% in cluster 1, 2, and 3, respectively (**Figure 1 and Table 5**).

Table 5. Sensitivity and specificity of categorization in different clusters

	Cluster 1	Cluster 2	Cluster 3
Sensitivity	95.0%	92.7%	58.8%
Specificity	87.9%	88.1%	100.0%

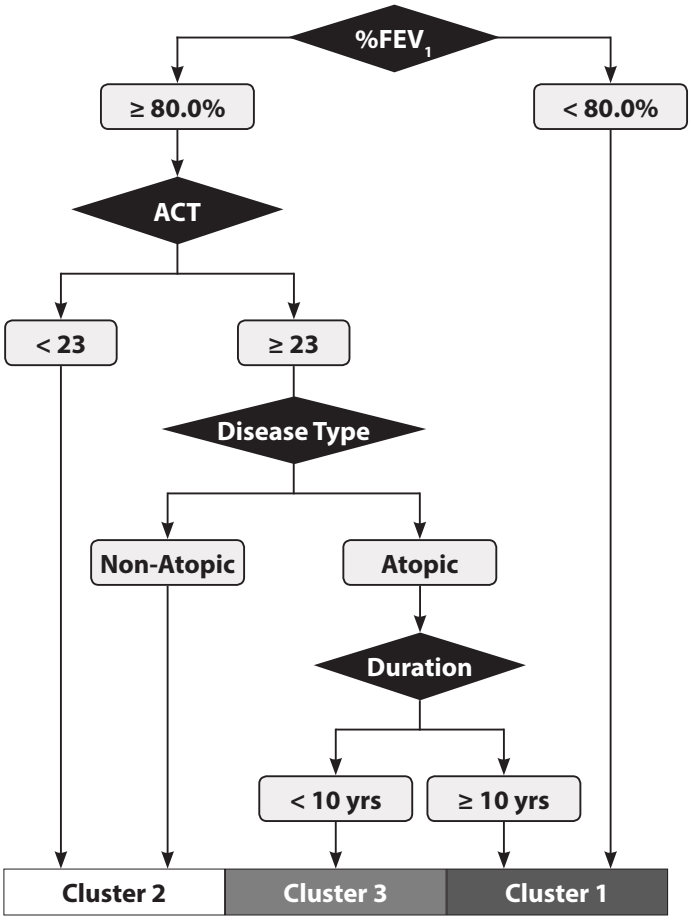

Figure 1. Decision tree analysis. The patients are classified into three clusters based on %FEV_1, ACT score, disease type, and disease duration.
%FEV_1, percent predicted forced expiratory volume in 1 second; ACT, Asthma Control Test

Discussion

Asthma exacerbation causes aggravation of acute/subacute symptoms and a decline in respiratory function, impairing the patient's quality of life and being a major cause of burden on treatment costs. Although its prevention is important, patients with good current control do not necessarily escape exacerbation. A previous report described that the risk of future exacerbation is caused by a mechanism different from the current control state.[14] To elucidate factors related to asthma exacerbation in the Japanese population, we analyzed factors of the same patients who underwent a questionnaire survey for 2 consecutive years.

To determine the classification of patients who had exacerbation, we performed a cluster analysis dividing the patients into three clusters. Cluster 1 included patients with smoking history, higher treatment steps, and lower respiratory function. Kupczyk M et al. reported that smoking history and a high fraction of exhaled nitric oxide (FeNO) are risk factors of asthma exacerbation,[15] consistent with the results of our study. The other two clusters were women-dominant and nonsmoker-dominant. Cluster 2 comprised nonatopic cases with poor asthma control despite higher treatment steps, while Cluster 3 included atopic cases with good asthma control and lower treatment steps. FEV_1 values were good in both clusters. However, it has been often reported that women have a higher prevalence of hospitalizations, rescue consultations, and unscheduled consultations despite their good respiratory function and oxygenation.[16,17] Thus, adequate asthma management is required for female patients to prevent exacerbation despite treatment.

Cluster 2 comprised many patients with poor control of asthma symptoms despite higher treatment. Compared with Cluster 3, Cluster 2 showed a significantly higher age of onset and a tendency of higher overall age. Although both clusters were female-dominant, we focused on menopausal age as a difference in the pathogenesis among both clusters. The average menopausal age of Japanese females is around 50 years (data from the Japan Society of Obstetrics and Gynecology), and several studies have reported on the risk of developing asthma and occurrence of respiratory symptoms after menopause.[18] Triebner et al. reported that menopause is a risk factor for the development of asthma and respiratory symptoms, independent of body mass index and age, which could be attributed to reduced estrogen levels and decreased anti-inflammatory effects inhibiting protective effects in the lungs.[19] In addition, the effect of menopause on systemic inflammation has also been noted; in one study, airway inflammation in asthma patients with postmenopausal onset was significantly different from that in asthma patients with juvenile onset.[20] Asthma patients with postmenopausal onset were less responsive to anti-inflammatory therapy and experienced the exacerbation more frequently.[20] Based on these findings, Cluster 2 might include many postmenopausal onset cases as this group was characterized by less atopic disease type and relatively uncontrolled cases. In contrast, patients in Cluster 3 showed good symptom control and mild treatment intensity; however, they experienced exacerbations. This cluster might have experienced undertreatment, or the results might have been underestimated.

Almqvist et al.[21] reported on undertreatment among females, suggesting that appropriate treatment is essential for this subgroup.

In this study, non-smoking was an independent risk factor of asthma exacerbation in multivariate analysis. Although it is widely known that smoking is a risk factor for asthma exacerbation, the interpretation of this result is difficult. This study included many female patients; thus, female bias was observed in the exacerbation group. Therefore, non-smoking might have been extracted as an independent risk factor. After adjustment for sex and age, the data showed that the correlation between nonsmoking and exacerbation disappeared (supplemental table).

Our study has some limitations. Firstly, chronic obstructive pulmonary disease (COPD) was not excluded in this study. Therefore, COPD exacerbation might have also been included in addition to asthma exacerbation. Secondly, the physicians were mainly respiratory physicians, and it is possible that the diagnosis was biased toward severe or refractory asthma. Lastly, approximately 60% of the participants in this study were women, which could be associated with the greater possibility of nonsmokers.

In summary, we examined the factors involved in asthma exacerbation using two consecutive questionnaires for 2014 and 2015. In the multivariate analysis, there was a significant difference in transient OCS administration in the previous year, hospitalization due to asthma in the past, and smoking history, especially a nonsmoking history. Through cluster analysis, exacerbation cases were classified into three clusters: Cluster 1, slightly older cases with smoking history; Cluster 2, female-dominant, non-smoking and nonatopic cases with uncontrolled symptoms; and Cluster 3, female-dominant and non-smoking group with mild atopic cases. These results suggest the presence of several phenotypes in female patients that easily exacerbate their asthma despite a nonsmoking history and good pulmonary function. Therefore, sufficient control of symptoms is important for asthma management among female patients.

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Declaration of interest

The authors declare no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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