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Original Article

Asthma exacerbations in patients with asthma and rhinitis: Factors associated with asthma exacerbation and its effect on QOL in patients with asthma and rhinitis

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ABSTRACT

Background: The comorbidity of asthma and allergic rhinitis is remarkably high, but not much is known about the effects of this combined condition on the quality of life. We aimed to evaluate the factors associated with asthma exacerbations and the effect of the exacerbations on the quality of life (QOL) through a one-year, large-scale, observational study in Japanese patients with asthma and rhinitis.

Methods: A case survey by attending physicians and a patient survey was conducted at each assessment timepoint over a period of one year. Patients were divided into two groups according to the presence or absence of asthmatic attacks after enrollment and were matched using propensity scores to evaluate the factors associated with asthma exacerbations and the effect of the exacerbation on QOL.

Results: Potential factors associated with asthma exacerbations included high body mass index value, low forced expiratory flow 75% of forced vital capacity (FEF75%), severe rhinitis as determined based on ARIA (Allergic Rhinitis and its Impact on Asthma). Although patients with asthma exacerbations had significantly impaired quality of life at baseline as evidenced by the economic aspects, in addition to physical, mental, and social activities, no further reduction with the attacks was observed.

Conclusions: This study suggested that higher body mass index (BMI) and severe asthma as well as severe rhinitis were factors associated with asthma exacerbations. Although patients with asthma exacerbations had impaired QOL, attacks caused no further reduction.

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Introduction

Asthma and allergic rhinitis are strongly related, sharing allergens and inflammatory processes. Thus, the frequency of asthma combined with allergic rhinitis is high, and their comorbidity is associated with significant increases in the number of

emergency room visits or the frequency of asthmatic attacks.¹ Furthermore, there is an associated increase in the severity of each comorbid condition.² Asthmatic attacks not only reduce physical activity in patients but also adversely affect their mental and/or social activities. However, there are no reports from large-scale, long-term, observational studies in patients with both asthma and allergic rhinitis that have evaluated the effects of this condition on the quality of life (QOL). Thus, we conducted a one-year observational study on patients with both asthma and allergic rhinitis who visited medical institutions across Japan and their attending physicians to evaluate changes in asthmatic symptoms, treatment patterns and QOL by using questionnaires

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designed for patients and physicians. In particular, we explored factors associated with asthma exacerbations by comparing “the group without exacerbations” (i.e. patients who had no asthmatic attacks) and “the group with exacerbations” (i.e. patients who had at least one asthmatic attack). This study also evaluated the effects of asthmatic exacerbations on QOL.

Methods

Patients

This study enrolled 7882 patients with asthma and rhinitis between December 1, 2010 and November 30, 2012. Out of these patients, after the completion of the one-year observation period, a total of 4918 patients had all case surveys and patient surveys available at all time points. Patients from 421 participating sites across Japan were considered eligible for this study when all of the following criteria were met: (1) Japanese residents aged 18 years or higher, (2) diagnosed with asthma and allergic rhinitis within the last three years, and (3) capable of filling out the patient questionnaires adequately after granting informed consent. Patients were excluded from the study if they met any of the following criteria: (1) under 18

years of age, (2) had complications of respiratory diseases (except asthma) such as chronic obstructive pulmonary disease, or (3) had already participated in other clinical trials for the purpose of regulatory approval at the time of enrollment.

Prior to the enrollment in the study, all patients were fully informed in writing of this study and provided informed consent before the beginning of the study.

After providing informed consent, patients were withdrawn from participation in this study when any of the following criteria was met: (1) loss to follow-up, (2) patient's withdrawal of consent, or (3) investigator's decision.

Study assessments

The observation period for the study was one year from the date of enrollment. Assessments were performed on the day of enrollment, and at 1, 3, 6, 9, and 12 months after enrollment. Assessments involved (1) a case survey, in which the attending physicians completed a case questionnaire based on medical charts, and (2) a patient survey, in which patients completed a patient questionnaire; both surveys were conducted independently.

Table 1
Patient characteristics.

Characteristics	Without exacerbations N = 2020	With exacerbations N = 1207	P values
Age (mean $\pm$ SD; years)	50.4 $\pm$ 15.1	52.3 $\pm$ 15.1	< 0.001 ¹⁾
Sex Male (%) / Female (%)	764 (37.8) / 1256 (62.2)	353 (29.2) / 854 (70.8)	< 0.001 ²⁾
BMI (mean $\pm$ SD)	22.9 $\pm$ 3.8	23.5 $\pm$ 4.0	< 0.001 ¹⁾
Age at diagnosis of asthma (years) $\pm$ SD	41.4 $\pm$ 17.7	41.8 $\pm$ 18.7	0.539 ¹⁾
Respiratory function (%)			
FEV ₁	79.6 $\pm$ 11.2	77.2 $\pm$ 11.7	< 0.001 ¹⁾
Forced Expiratory Flow 50% of FVC	77.3 $\pm$ 32.7	72.6 $\pm$ 34.6	< 0.001 ¹⁾
Forced Expiratory Flow 75% of FVC	69.6 $\pm$ 38.1	61.1 $\pm$ 35.9	< 0.001 ¹⁾
Smoking (%)			
Never	1284 (63.6)	881 (73.0)	< 0.001 ²⁾
Past	372 (18.4)	82 (6.8)	
Current	361 (17.9)	244 (20.2)	
Use of oral or injectable corticosteroids within the last one year: Yes (%) / No (%)	411 (20.3) / 1598 (79.1)	231 (19.1) / 962 (79.7)	0.4543 ²⁾
Treatment steps (inhaled corticosteroid)			
Low dose ($\leq$ 200 μ)	280 (13.9)	99 (8.2)	< 0.001 ²⁾
Low/med dose (200 < $\leq$ 400 μ)	436 (21.6)	210 (17.4)	
Med/high dose (400 < $\leq$ 800 μ)	544 (26.9)	379 (31.4)	
High dose (800 μ <)	92 (4.6)	129 (10.7)	
Sinusitis Yes (%) / No (%)	333 (16.5) / 1678 (83.1)	299 (24.8) / 905 (75.0)	< 0.001 ²⁾
Rhinitis symptom Yes (%) / No (%)			
Watery rhinorrhea	1814 (89.8) / 206 (10.2)	1054 (87.3) / 153 (12.7)	0.030 ²⁾
Sneezing	1421 (70.3) / 599 (29.7)	893 (74.0) / 314 (26.0)	0.026 ²⁾
Nasal congestion	1127 (55.8) / 893 (44.2)	785 (65.0) / 422 (35.0)	< 0.001 ²⁾
ARIA classification (%)			
Mild and intermittent	607 (30.0)	197 (16.3)	< 0.001 ²⁾
Mild and persistent	894 (44.3)	450 (37.3)	
Moderate/severe and intermittent	52 (2.6)	80 (6.6)	
Moderate/severe and persistent	247 (12.2)	254 (21.0)	
Antigen Yes (%) / No (%)			
House dust/mite	665 (32.9) / 1335 (67.1)	577 (47.8) / 630 (52.2)	< 0.001 ²⁾
Animal dander	187 (9.3) / 1833 (90.7)	197 (16.3) / 1010 (83.7)	< 0.001 ²⁾
Pollen	1072 (53.1) / 948 (46.9)	800 (66.3) / 407 (33.7)	< 0.001 ²⁾
Causative plant Yes (%) / No (%)			
Cedar	940 (46.5) / 1080 (53.5)	686 (56.8) / 521 (43.2)	< 0.001 ²⁾
Cypress	379 (18.8) / 1641 (81.2)	247 (20.5) / 960 (79.5)	0.237 ²⁾
Rice	54 (2.7) / 1966 (97.3)	47 (3.9) / 1160 (96.1)	0.054 ²⁾
Ragweed	145 (7.2) / 1875 (92.8)	140 (11.6) / 1067 (88.4)	< 0.001 ²⁾
Birch	9 (0.4) / 2011 (99.6)	15 (1.2) / 1192 (98.8)	0.011 ²⁾
Most common time of onset Yes (%) / No (%)			
Spring	867 (42.9) / 1153 (57.1)	562 (46.6) / 645 (53.4)	0.044 ²⁾
Summer	53 (2.6) / 1967 (97.4)	52 (4.3) / 1155 (95.7)	0.009 ²⁾
Autumn	173 (8.6) / 1847 (91.4)	159 (13.2) / 1048 (86.8)	< 0.001 ²⁾
Winter	34 (1.7) / 1986 (98.3)	35 (2.9) / 1172 (97.1)	0.021 ²⁾

P values were determined by 1) unpaired t-test, 2) Chi-square test and expressed as bold when a value is <0.05.

In the case survey, baseline patient characteristics were collected. These included age, sex, body height, body weight, body mass index (BMI), concurrent conditions, date of diagnosis of asthma, smoking history, symptoms of rhinitis, pathogenic antigens, the most common time of symptomatic condition (common time of rhinitis), severity, and use of oral or injectable corticosteroids within the last one year. We collected information on asthma which included current treatment steps and severity, presence/absence of asthmatic attacks within the previous month (including frequency and intensity of attacks when attacks were present), spirometric measurements consisting of forced expiratory volume in one second (FEV₁), forced expiratory flow 50% of forced vital capacity (FVC) (FEF50%) and forced expiratory flow 75% of FVC (FEF75%), and use of oral or injectable corticosteroids within the last one year.

In the patient survey, QOL was assessed at each assessment time point using a QOL questionnaire for adult asthma (Asthma Health Questionnaire-33-Japan: AHQ-33-Japan),³ which was also used to collect information on symptoms of asthma with rhinitis.

Statistical analysis

The sample population for this study consisted of patients who completed a one-year observation and had all case and patient surveys available from all the time points. The “asthma” and “allergic rhinitis” were defined on the basis of “Asthma Prevention and Management Guideline” and “Practical Guideline for the Management of Allergic Rhinitis in Japan”, respectively. Exacerbations of asthma were episodes characterized by a progressive increase in symptoms of shortness of breath, cough, wheezing or chest tightness and progressive decrease in lung function, i.e. they represented a change from the patient's usual status that was sufficient to require a change in treatment.⁴ We made comparisons between asthmatics with and without exacerbations, by defining as “the group with exacerbations” and “the group without exacerbations”, respectively, over a period of one year after enrollment and therefore, excluded patients experiencing asthmatic attacks within 4 weeks before enrollment. Moreover, the study analyzed two groups matched using propensity scores involving age, sex, and baseline treatment step for asthma.

Summarized statistics were expressed as mean $\pm$ standard deviation (SD) or number and percentage of participants (%).

In the comparisons between the two groups according to the presence or absence of asthma exacerbations, unpaired t-test was used for continuous data and Chi-square test was used for frequency data. For the evaluation of variables that might potentially affect asthma exacerbations, odds ratios (OR) and associated 95% confidence intervals (95% CI) were determined by employing a multivariate logistic regression model with patient characteristic variables that were significant in the two-group comparisons by either unpaired t-test or Chi-square test in the univariate analysis. In order to compare the two groups in terms of the changes in the AHQ-33 score from baseline to post-enrollment assessment time points, the analysis of variance (ANOVA) was used with results expressed as mean $\pm$ SD. We used Chi-square test for two-group comparisons of the frequency of unscheduled hospital or clinic visit and absence from work or school. All statistical analyses were performed using SAS software version 9.3 (SAS Inc., Cary, USA) and were two-sided at a 5% significance level ($p < 0.05$).

Ethical conduct

This study was reviewed and approved by the institutional review board of the local committee at Asano Clinic and the ethics committees of the participating sites, and was conducted in

accordance with the ethical principles of the Declaration of Helsinki as well as the Ethical Guidelines for Epidemiological Research (full revision: August 16, 2007, partial revision: December 1, 2008, Ministry of Education, Culture, Sports, Science and Technology and Ministry of Health, Labor and Welfare).

In addition, this study was registered in the University Hospital Medical Information Network-Clinical Trials Registry (UMIN-CTR; Study ID: UMIN000004652).

Results

Study population and patients' characteristics

After excluding 1691 patients who had asthmatic attacks within 4 weeks prior to enrollment, 3227 patients consisting of 2020 in “the group without exacerbations” and 1207 in “the group with exacerbations” remained.

Table 1 summarizes the characteristics of the 3227 patients who had before propensity score matching. A significant difference was observed between two groups in most of the items. Therefore, matching data was extracted using the age, sex, and asthma treatment after enrollment (treatment step) as explanatory variable and using the propensity scores, and finally a total of 761 patients were included in each group (Fig. 1).

A total of 1522 patients included for comparison were comprised of 459 male patients (30.2%) and 1063 female patients (69.8%), with an average age of 52.6 ± 15.1 years and a BMI value of 23.2 ± 3.8 . Furthermore, the age at asthma diagnosis was 42.5 ± 18.4 years. In addition, the baseline respiratory function tests revealed % prediction of FEV₁ as 77.4 ± 11.8 , % prediction of FEF50% as 73.4 ± 33.4 and FEF75% as 61.3 ± 35.0 . The smoking history showed that 6.4% of the patients were current smokers, 20.2% were past smokers, and 73.2% were never-smokers. Moreover, 17.7% of the patients had a history of prescription of corticosteroids (oral/injectable) within the previous one year, while 81.4% did not. Symptoms of allergic rhinitis included watery rhinorrhea in 86.8% of the patients, sneezing in 71.9%, and nasal

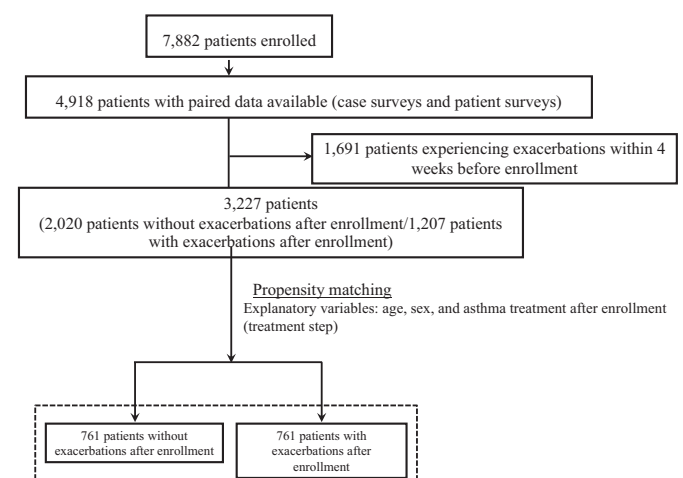


Fig. 1. The flow diagram of patients. This study enrolled 7882 patients with asthma and rhinitis. After the completion of the one-year observation period, a total of 4918 patients had all case surveys and patient surveys available at all time points. After exclusion of 1691 patients who had asthmatic attacks within 4 weeks prior to enrollment, 3227 patients remained. Regarding the characteristics of the 3227 patients before propensity score matching, a significant difference was observed between the two groups, i.e. with and without exacerbations, in most of the items (Table 1). Therefore, matching data was extracted using the age, sex, and asthma treatment after enrollment (treatment step) as explanatory variable and using the propensity scores, and finally a total of 761 patients were included in each group.

Table 2
Comparisons according to the presence/absence of asthma exacerbations after propensity matching.

	Without exacerbations N = 761	With exacerbations N = 761	Total N = 1522	P values
Age (mean $\pm$ SD; years)	52.9 $\pm$ 15.1	52.3 $\pm$ 15.1	52.6 $\pm$ 15.1	0.513 ¹⁾
Sex Male (%) / Female (%)	236 (31.0) / 525 (69.0)	223 (29.3) / 538 (70.7)	459 (30.2) / 1063 (69.8)	0.468 ²⁾
BMI (mean $\pm$ SD)	22.9 $\pm$ 3.7	23.5 $\pm$ 3.9	23.2 $\pm$ 3.8	0.003 ¹⁾
Age at diagnosis of asthma (years) $\pm$ SD	43.1 $\pm$ 18.2	42.0 $\pm$ 18.7	42.5 $\pm$ 18.4	0.241 ¹⁾
Respiratory function (%)				
FEV ₁	77.8 $\pm$ 12.1	76.9 $\pm$ 11.4	77.4 $\pm$ 11.8	0.177 ¹⁾
Forced Expiratory Flow 50% of FVC	74.4 $\pm$ 32.7	72.3 $\pm$ 34.1	73.4 $\pm$ 33.4	0.150 ¹⁾
Forced Expiratory Flow 75% of FVC	63.4 $\pm$ 36.0	59.3 $\pm$ 34.0	61.3 $\pm$ 35.0	0.039 ¹⁾
Smoking (%)				
Never	561 (73.7)	553 (72.7)	1114 (73.2)	0.463 ²⁾
Past	155 (20.4)	153 (20.1)	308 (20.2)	
Current	43 (5.7)	55 (7.2)	98 (6.4)	
Use of oral or injectable corticosteroids within the last one year: Yes (%) / No (%)	127 (16.7) / 629 (82.7)	142 (18.7) / 610 (80.2)	269 (17.7) / 1239 (81.4)	0.291 ²⁾
Treatment steps (inhaled corticosteroid)				
Low dose ($\leq$ 200 μ)	106 (13.9)	99 (13.0)	205 (13.5)	0.698 ²⁾
Low/med dose (200 < $\leq$ 400 μ)	190 (25.0)	210 (27.6)	400 (26.3)	
Med/high dose (400 < $\leq$ 800 μ)	387 (50.9)	375 (49.3)	762 (50.1)	
High dose (800 μ <)	78 (10.2)	77 (10.1)	155 (10.2)	
Sinusitis: Yes (%) / No (%)	175 (23.0) / 538 (76.6)	192 (25.2) / 567 (74.5)	367 (24.1) / 1150 (75.6)	0.315 ²⁾
Rhinitis symptom Yes (%) / No (%)				
Watery rhinorrhea	661 (86.9) / 100 (13.1)	660 (86.7) / 101 (13.3)	1321 (86.8) / 201 (13.2)	0.936 ²⁾
Sneezing	535 (70.3) / 226 (29.7)	559 (73.5) / 202 (26.5)	1094 (71.9) / 428 (28.1)	0.171 ²⁾
Nasal congestion	452 (59.4) / 309 (40.6)	476 (62.5) / 285 (37.5)	928 (61.0) / 594 (39.0)	0.207 ²⁾
ARIA classification (%)				
Mild and intermittent	330 (43.4)	296 (38.9)	626 (41.1)	0.007 ²⁾
Mild and persistent	285 (37.5)	269 (35.3)	554 (36.4)	
Moderate/severe and intermittent	25 (3.3)	48 (6.3)	73 (4.8)	
Moderate/severe and persistent	121 (15.9)	148 (19.4)	269 (17.7)	
Antigen Yes (%) / No (%)				
House dust/mite	341 (44.8) / 420 (55.2)	355 (46.6) / 406 (53.4)	696 (45.7) / 826 (54.3)	0.471 ²⁾
Animal dander	108 (14.2) / 653 (85.8)	117 (15.4) / 644 (84.6)	225 (14.8) / 1297 (85.2)	0.516 ²⁾
Pollen	470 (61.8) / 291 (38.2)	514 (67.5) / 247 (32.5)	984 (64.7) / 538 (35.3)	0.018 ²⁾
Causative plant Yes (%) / No (%)				
Cedar	408 (53.6) / 353 (46.4)	430 (56.5) / 331 (43.5)	838 (55.1) / 684 (44.9)	0.257 ²⁾
Cypress	158 (20.8) / 603 (79.2)	151 (19.8) / 610 (80.2)	309 (20.3) / 1213 (79.7)	0.656 ²⁾
Rice	24 (3.2) / 737 (96.8)	28 (3.7) / 733 (96.3)	52 (3.4) / 1470 (96.6)	0.573 ²⁾
Ragweed	73 (9.6) / 688 (90.4)	85 (11.2) / 676 (88.8)	158 (10.4) / 1364 (89.6)	0.313 ²⁾
Birch	3 (0.4) / 758 (99.6)	10 (1.3) / 751 (98.7)	13 (0.9) / 1509 (99.1)	0.051 ²⁾
Most common time of onset Yes (%) / No (%)				
Spring	355 (46.6) / 406 (53.4)	360 (47.3) / 401 (52.7)	715 (47.0) / 807 (53.0)	0.797 ²⁾
Summer	27 (3.5) / 734 (96.5)	35 (4.6) / 726 (95.4)	62 (4.1) / 1460 (95.9)	0.300 ²⁾
Autumn	79 (10.4) / 682 (89.6)	104 (13.7) / 657 (86.3)	183 (12.0) / 1339 (88.0)	0.049 ²⁾
Winter	17 (2.2) / 744 (97.8)	20 (2.6) / 741 (97.4)	37 (2.4) / 1485 (97.6)	0.618 ²⁾

P values were determined by 1) unpaired t-test, 2) Chi-square test and expressed as bold when a value is < 0.05.

congestion in 61.0%, with 18.2% of the patients showing bilateral rhinitis symptoms, which could affect difficulty in breathing than unilateral ones. The classification on the ARIA (Allergic Rhinitis and its Impact on Asthma)⁵ showed that the distribution of the severity of rhinitis as mild and intermittent in 41.1%, mild and persistent in 36.4%, moderate/severe and intermittent in 4.8%, and moderate/severe and persistent in 17.7% of the patients. The most common pathogenic antigens were house dust/mite (45.7%) and pollen (64.7%) and the most common causative plants were cedar (55.1%), cypress (20.3%), orchard grass (11.2%), and ragweed (10.4%). Allergic rhinitis appeared most commonly in spring (47.0%) and autumn (12.0%).

An assessment of variables revealed a significant difference between “the group with exacerbations” and “the group without exacerbations”. Briefly, “the group with exacerbations” had higher BMI values, lower FEF75% values, bilateral rhinitis symptoms, severe disease as determined by the classification of the severity and persistence of rhinitis based on the ARIA classification (2008), pollen-induced rhinitis, and common time of rhinitis as autumn (Table 2).

Evaluation of the factors associated with asthma exacerbations

For the evaluation of factors associated with asthma exacerbations, odds ratios (OR) and associated 95% confidence intervals (95% CI) were determined using a multivariate logistic regression model

Table 3
Factors associated with asthma exacerbation by multivariate logistic regression analysis.

Variables	Multivariate Analysis	
	OR (95%CI)	P values
BMI	1.05 (1.02–1.08)	0.002
Forced Expiratory Flow 75% of FVC	0.997 (0.994–0.999)	0.039
ARIA classification (trend)	1.12 (1.01–1.24)	0.032
Antigen (pollen)	1.22 (0.97–1.54)	0.087
Most common time of onset of rhinitis (autumn)	1.32 (0.94–1.85)	0.107

Based on the ARIA (Allergic Rhinitis and its Impact on Asthma) classification.

OR, Odds ratio; 95% CI, 95% Confidence Interval.

Bold P values are statistically significant.

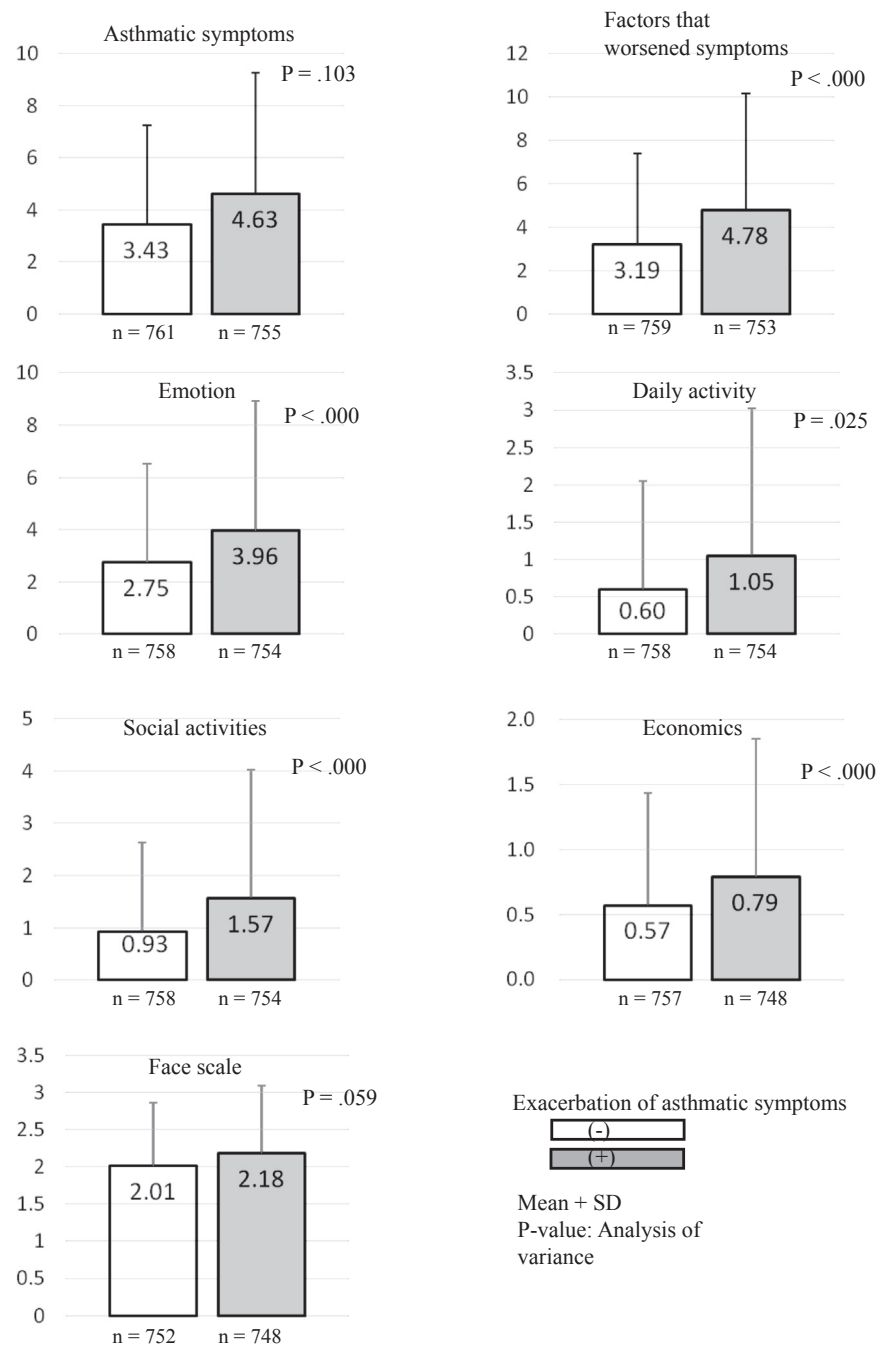


Fig. 2. AHQ-33-Japan subscale scores at baseline by presence/absence of exacerbation of asthmatic symptoms. The QOL scores as measured by the patients themselves at baseline using the AHQ-33-Japan were assessed by scale and by presence or absence of asthma exacerbations.

with patient characteristic variables that were found to be significant in the two-group comparisons. The results suggested that a higher BMI value, lower FEF75% value, and severe disease based on the classification of ARIA were significant and independent predictors of exacerbations (Table 3).

Evaluation of the effects of asthma exacerbations on QOL

Assessment of QOL at baseline in patients with asthma exacerbations

The QOL scores as measured by the patients themselves at baseline using the AHQ-33-Japan were assessed by scale and by presence or

absence of asthma exacerbations (Fig. 2). Since it has been essential to employ propensity scores to complete observational study with accumulated real-life clinical data, we have the data converted to propensity scores and analyzed to reach some conclusion. Regarding asthmatic symptoms and face scale (a patient's assessment of overall QOL during the previous 7 days), "the group with exacerbations" (4.63 and 2.18, respectively) showed higher mean scores than "the group without exacerbations" (3.43 and 2.01, respectively), but their differences were not statistically significant. In contrast, scores on the other scales such as emotion, social activities, worsening factors, daily activity and economics were significantly higher in "the group with exacerbations" than in "the group without exacerbations."

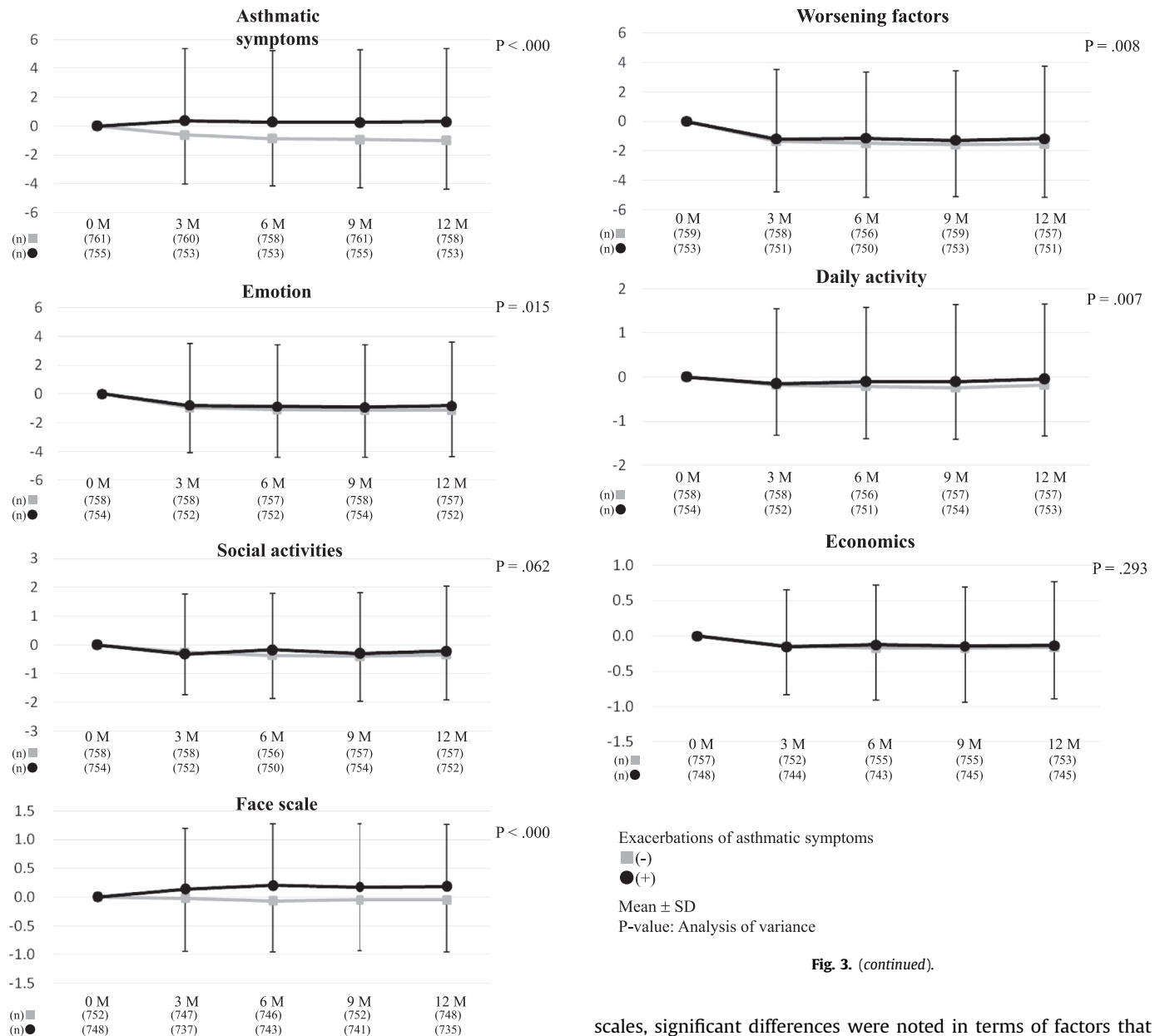


Fig. 3. (continued).

scales, significant differences were noted in terms of factors that worsened symptoms, emotion, and daily activity.

Unscheduled hospital or clinic visits and absence from work or school

An evaluation of unscheduled hospital or clinic visits due to asthma according to the presence/absence of asthma exacerbations showed that the proportion of patients with unscheduled visits was significantly higher in "the group with exacerbations" at any post-enrollment time point (Fig. 4). The proportion of patients with absence from work or school due to asthma was significantly higher at baseline and after enrollment (except at 9 months after enrollment; Fig. 4).

Discussion

A recent nation-wide survey was conducted to comprehend the actual state of comorbid allergic rhinitis in Japanese patients with asthma.⁶ The results revealed that a high percentage (67.3%) of patients with asthma had also allergic rhinitis and that comorbid rhinitis in patients with asthma was associated with poor control of

Changes in QOL after enrollment in patients with asthma exacerbations

Changes from baseline in QOL scores as measured using the AHQ-33-Japan were assessed by scale and by presence or absence of asthma exacerbations. Asthmatic symptoms and face scale showed decreased mean scores as early as 3 months after enrollment in "the group without exacerbations" and a trend of worsening scores in "the group with exacerbations," resulting in significant differences between the two groups in terms of the changes over a period of one year (Fig. 3). Although no substantial differences were found in the changes of mean scores on the other

asthma and impairment of QOL. Other reports^{1,2} have also found that worsening of asthmatic symptoms was noted in patients with both asthma and allergic rhinitis. Thus, we conducted a one-year observational study in patients with both asthma and rhinitis to characterize patients experiencing asthma exacerbations in terms of QOL.

Although disease-specific QOL questionnaires (such as AHQ-33-Japan) and non-disease-specific QOL questionnaires (such as Euroqol-5D [EQ-5D] and short-form 36 [SF-36] Health Survey) are available for QOL assessment in patients with asthma, disease-specific questionnaires are considered more sensitive to changes in disease than non-disease-specific questionnaires.⁷ In addition, it has been reported that AHQ-33-Japan was more effective in QOL assessment in Japanese patients with asthma compared with SF-36.⁸ Thus, in this study, we used AHQ-33-Japan for QOL assessment in patients with asthma and rhinitis. However, inasmuch as baseline patient characteristic variables (such as severity of asthma) were thought to have effects on asthma exacerbations in patients with asthma and rhinitis, this study compared two groups distinguished by presence or absence of asthmatic attacks during the observation period. Importantly, since it is essential to employ propensity scores to complete observational study with accumulated real-life clinical data, we have the data converted to propensity scores and analyzed to reach some conclusion.

First, the multivariate analysis of significant patient characteristic variables was conducted according to the presence or absence of asthmatic attacks to evaluate factors associated with asthma exacerbations and suggested that a higher BMI value, lower FEF75% value, and severe disease as based on ARIA and persistence of rhinitis were factors associated with asthma exacerbations. As previously reported,^{9–11} a higher BMI, even not satisfying the criteria for obesity, has been found to be a risk factor for asthma both in male and female patients, and this could be true in rhinitis judging from our data, i.e. “the group with exacerbations” showed significantly higher BMI and the worsening of rhinitis. A report showed a higher frequency of emergency room visits due to asthma

or the cost of drugs prescribed for asthma in patients with asthma and rhinitis, with a large number of prescriptions of short-acting β -agonist (SABA) and higher prescribed doses of inhaled corticosteroids at baseline.¹² These previous findings combined with our present results may suggest that symptoms of asthma are likely to be exacerbated in patients with severe symptoms of asthma (patients with lower FEF75% values) or patients with severe and persistent rhinitis. In the treatment of patients with asthma and rhinitis, especially those with higher BMI or severe asthma and/or rhinitis, it is important to bear in mind that such patients are likely to experience exacerbations during treatment.

On the other hand, QOL in patients with asthma and rhinitis, as measured by the AHQ-33-Japan, was examined for each characteristic in patients with asthma exacerbations. Partly due to matching using propensity scores in this study, the scores from scales other than baseline asthmatic symptoms and face scale were significantly higher in “the group with exacerbations,” suggesting that QOL was significantly impaired at baseline in patients with asthma exacerbations. Changes in QOL scores after enrollment indicated a trend of worsening scores of asthmatic symptoms and face scale with asthma exacerbations in “the group with exacerbations” and a tendency towards improvement of QOL in “the group without exacerbations,” with a major difference in changes over time between the two groups. However, the other scales showed high scores at baseline, but exhibited similar changes over time in both groups after enrollment, indicating no evidence of further QOL impairment due to asthma exacerbations or adverse effects on specific QOL scales.

The frequency of unscheduled hospital or clinic visits or absence from work or school due to asthma was significantly higher in “the group with exacerbations,” suggesting both a greater increase in healthcare resource utilization and greater loss of productivity by asthma exacerbations. This study also evaluated the effect of seasonal variation on asthma exacerbations in asthmatic patients with rhinitis. However, an analysis matching the time points of patient assessment with the season yielded no effects of any seasonal

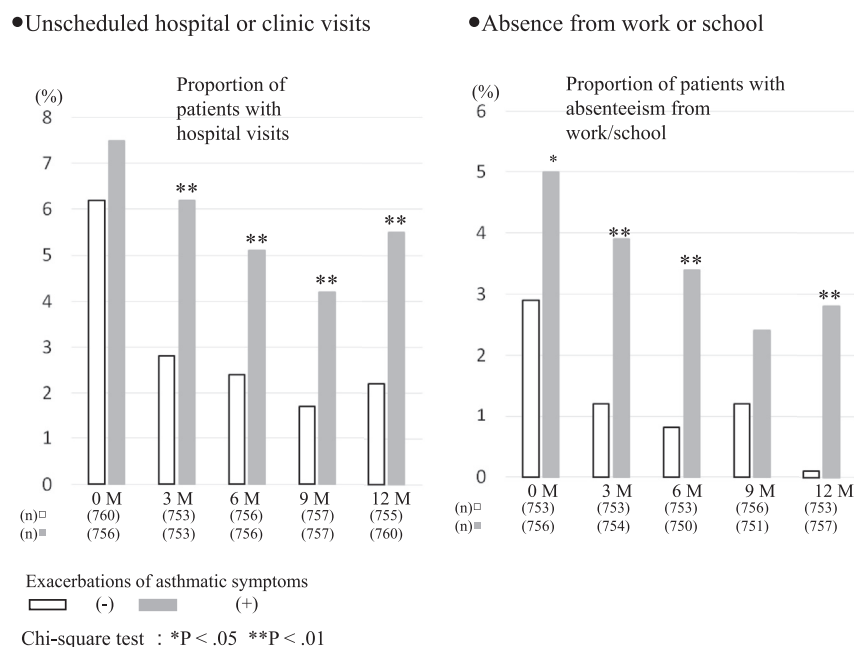


Fig. 4. Unscheduled hospital or clinic visits and absence from work or school by presence or absence of asthma exacerbations. An evaluation of unscheduled hospital or clinic visits due to asthma according to the presence/absence of asthma exacerbations showed that the proportion of patients with unscheduled visits was significantly higher in “the group with exacerbations” at any post-enrollment time point. The proportion of patients with absence from work or school due to asthma was significantly higher at baseline and after enrollment except at 9 months after enrollment.

variation on asthma exacerbations. This is probably due to the fact that enrollment occurred over a period of several years, resulting in year-related differences in the amounts of airborne pollen of cedar and cypress, which are common causative antigens for allergic rhinitis in Japanese people. Indeed, the amounts of airborne pollen of cedar and cypress were larger in 2011 and 2013, while the amounts were the level of average in 2012. Moreover, regional differences (smaller amounts of airborne pollen in Hokkaido and Okinawa) may have had an additional influence.

This one-year observational study in Japanese patients with both asthma and rhinitis suggested that a higher BMI and severe asthma or rhinitis were factors associated with asthma exacerbations. Although patients with asthma exacerbations had significantly impaired QOL at baseline, including economic aspects, in addition to physical, mental, and social activities, no further reduction in these QOL scales associated with asthma exacerbations was observed. Asthma exacerbations were associated with an increased frequency of unscheduled hospital or clinic visits or absence from work or school, suggesting an increase in healthcare resource utilization and loss of productivity.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.alit.2019.04.008>.

Conflict of interest

YT received honoraria from Nippon Boehringer Ingelheim as a lecture fee. GT received honoraria from Astellas, Astra Zeneca, Ono Pharmaceutical, Kyorin, Nippon

Boehringer Ingelheim, Novartis Pharma, and MSD as a lecture fee. GT is CEO of Airway Institute in Sendai. The rest of the authors have no conflict of interest.

Authors' contributions

All of the authors participated in designing the study, and KO and GT confirmed the final protocol and wrote the manuscript. HT, YT, HK, JC, HS and MA contributed to data collection. GT performed the statistical analysis with the biostatistician (listed in the acknowledgement) and interpretation of the results with KO. All authors read and approved the final manuscript.

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