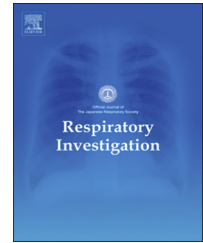




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Co-existence and seasonal variation in rhinitis and asthma symptoms in patients with asthma



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ABSTRACT

Background: Asthma and rhinitis are common diseases that often occur concomitantly. However, in patients with asthma, the concurrent assessment of seasonal variation in rhinitis and asthma symptoms has not been comprehensively addressed. We prospectively evaluated seasonal changes in rhinitis and asthma symptoms over one year.

Methods: Fifty-six patients with asthma were enrolled. Asthma and rhinitis symptoms were assessed by using the State of the Impact of Allergic Rhinitis on Asthma Control (SACRA) questionnaire, developed and validated in Japan by the committee of Global Initiative for Asthma and the committee of Allergic Rhinitis for asthma and its impact on Asthma.

Results: Fifty-three patients completed the study. Forty-five patients (85%) had nasal symptoms during at least one or more seasons and 15 patients (28%) had perennial rhinitis. The association between asthma symptoms and rhinitis symptoms, assessed by a visual analogue scale (VAS), was significant during each season; seasonal variations of symptoms were synchronous. Uncontrolled asthma was more prevalent in patients with moderate-to-severe rhinitis compared to those with mild rhinitis. The VAS score of asthma symptoms in patients with asthma and perennial rhinitis was significantly higher than that in patients with non-perennial rhinitis or without rhinitis, across every season, except for spring. Correlations were more significant in patients less than 65 years of age than in older patients.

Conclusion: Rhinitis is common in patients with asthma. Symptoms of rhinitis and asthma often co-exist, and the association between these symptoms may be stronger in younger patients with asthma than older.

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Abbreviations: GINA, Global Initiative for Asthma; ARIA, Allergic Rhinitis for asthma and its Impact on Asthma; SACRA, State of the Impact of Allergic Rhinitis on Asthma Control; VAS, visual analogue scale; PR, perennial rhinitis; NPR, non-perennial rhinitis; ICS, inhaled corticosteroids; HDM, house dust mites

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1. Introduction

Allergic rhinitis and asthma are inflammatory diseases of the airways that share a common genetic characteristic. Approximately 20–60% of patients with allergic rhinitis have clinical asthma, whereas over >80% of patients with asthma have concomitant symptoms of rhinitis [1–3]. Pathophysiological studies have demonstrated that allergen challenge in the nasal or bronchial airways leads to marked inflammatory responses in the lower or upper airways [4,5]. Allergic rhinitis may negatively affect the clinical course of asthma. For example, in patients with asthma and allergic rhinitis, asthma-related emergency room admissions and hospitalization may be more frequent, and treatment costs may be higher, than in patients with asthma alone [6,7].

Two Japanese committees, the Global Initiative for Asthma and the Allergic Rhinitis for Asthma and its Impact on Asthma, developed the Self Assessment of Allergic Rhinitis and Asthma (SACRA) questionnaire, to evaluate asthma control and the presence and severity of allergic rhinitis and asthma symptoms in patients with asthma. Patients' perception of the disease was assessed using a visual analog scale (VAS). A cross-sectional nationwide study involving 29,518 patients with asthma in Japan used the SACRA questionnaire and found that 67.3% of patients with asthma also had rhinitis [8]. The study also demonstrated that most patients with asthma had moderate/severe rhinitis, and that patients with rhinitis had poorer asthma control than those without rhinitis [8].

Most epidemiological studies evaluating the link between rhinitis and asthma are cross-sectional [8–13], and few studies have concurrently examined seasonal changes in both asthma and rhinitis symptoms. We aimed to use the SACRA questionnaire to investigate the relationship between asthma and rhinitis symptoms in response to seasonal changes.

2. Patients and methods

This was a prospective, observational study. Fifty-six consecutive adult patients with asthma (age 32–86 years) were recruited from the Respiratory Disease Center at Kitano Hospital, Japan between March 2012 and May 2012. The diagnosis of asthma was made based on the clinical history, presence of episodic dyspnea and wheezing, and response to inhaled bronchodilators. Serum levels of total and specific immunoglobulin (Ig)E antibodies against common aeroallergens were measured using radioimmunosorbent tests and the CAP method (Pharmacia Diagnostics, Uppsala, Sweden). Tests for specific IgE antibodies were considered positive if the response level exceeded 0.35 IU/ml [14]. Specific IgE antibody responses were measured for 6 allergens: house dust mites (HDM), Japanese cedar pollen, mixed Gramineae pollens (orchard grass, sweet vernal grass, Bermuda grass, timothy, reeds), mixed weed pollens (ragweed, mugwort, goldenrod, dandelion, oxeye daisy), mixed molds (*Penicillium*, *Cladosporium*, *Aspergillus*, *Candida*, *Alternaria*), and animal dander (cat, dog). Patients with asthma were treated

according to the Asthma Prevention and Management Guidelines (Japan) [15]. Subjects were enrolled after oral informed consent was obtained. The study was approved by the Institutional Review Board of Kitano Hospital, according to the ethical guidelines of the 1975 Declaration of Helsinki (ethics approval date, reference number: April 27, 2011, E10-04-004).

2.1. Self-assessment of allergic rhinitis and asthma (SACRA) questionnaire

A detailed description of the SACRA questionnaire is provided elsewhere [8,9,16]. Briefly, the questionnaire included 4 questions on asthma control and a VAS assessment of the severity of symptoms, with scores ranging from “not at all bothersome” (0 cm) to “extremely bothersome” (10 cm). Patients were arbitrarily classified as having “poorly-controlled asthma” when answering “yes” to at least 1 in 4 questions on the following: the presence of daytime symptoms (more than 3 times), any limitation in activities of daily living, the presence of nocturnal symptoms, and the need for rescue medication (more than 3 times) in the preceding week.

The rhinitis questionnaire consisted of 4 questions on rhinitis symptoms, 2 on duration of symptoms, 4 on severity of the disease, and the same VAS assessment was used in the asthma questionnaire. The SACRA questionnaire was completed by patients in the waiting room, prior to their appointment with a respiratory physician. Based on the SACRA questionnaire, patients with asthma were classified as having one of the following: perennial rhinitis (PR), if they experienced rhinitis symptoms in all 4 seasons; non-perennial rhinitis (NPR), if they experienced rhinitis symptoms in 1, 2, or 3 seasons; and no rhinitis (None) if they did not experience any rhinitis symptoms throughout the year.

2.2. Statistical analysis

Values are expressed as mean $\pm$ SD or median (range). Data were analyzed using Stat View 5.0 (SAS Institute, Cary, NC, USA). The Mann–Whitney U-test was used to analyze differences between groups. Comparisons among multiple groups were made using analysis of variance and Fisher's protected least significant difference test or the chi-square test. Correlations between data were analyzed by Spearman's rank correlation test. A *p* value less than 0.05 was considered significant.

3. Results

3.1. Prevalence of rhinitis in patients with asthma

Of 56 patients with asthma, 53 responded with usable information (95% response rate). Of these, 35 (66%) experienced rhinitis symptoms in spring, 24 (45%) in summer, 32 (60%) in the fall, and 36 (68%) in winter. A total of 45 (85%) experienced rhinitis symptoms in 1 or more seasons (Fig. 1).

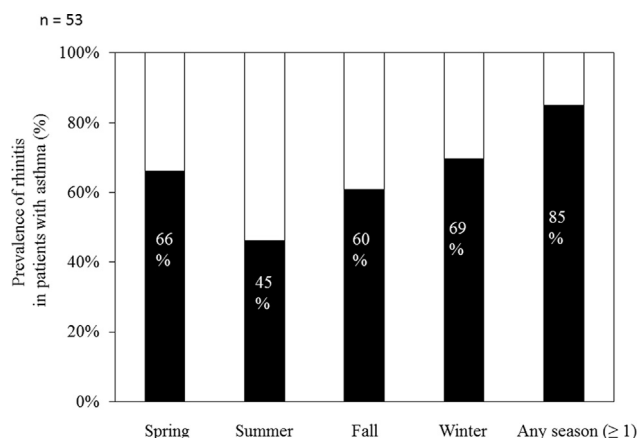


Fig. 1 – Percentage of patients with asthma answering “yes” to each question of the SACRA questionnaire about rhinitis (N=53). Black bar, rhinitis symptoms (+); White bar, rhinitis symptoms (–); SACRA, Self Assessment of Allergic Rhinitis and Asthma.

Fifteen patients (28%) with asthma were classified as PR, 30 (57%) as NPR, and 8 (15%) as None (Table 1).

3.2. Comparison of patients’ characteristics by presence or absence of rhinitis

Age, sex, duration of asthma, severity of asthma, and total IgE levels did not differ among the 3 groups. All patients were provided with inhaled corticosteroids (ICS) and 26 (49.1%) also received a leukotriene modifier. The dose of ICS and the distribution of leukotriene modifier use did not differ among the 3 groups. Similarly, the prevalence of sensitization to 6 measured allergens did not differ among the 3 groups.

3.3. Relationship between rhinitis severity and asthma control

Of 45 patients with asthma, classified as PR or NPR, 3 in 10 (33%) with mild rhinitis, 3 in 13 (23%) with moderate-to-severe/intermittent rhinitis, and 6 in 12 (50%) with moderate-to-severe/persistent rhinitis, had poorly controlled asthma. In summer, 1 in 4 (25%) patients with mild rhinitis, 2 in 6 (33%) patients with moderate-to-severe/intermittent rhinitis, and 6 in 14 (43%) patients with moderate-to-severe/persistent rhinitis, had poorly controlled asthma. In the fall, 2 in 10 (20%) patients with mild rhinitis, 5 in 11 (45%) with moderate-to-severe/intermittent rhinitis, and 6 in 11 (55%) patients with moderate-to-severe/persistent rhinitis, had poorly controlled asthma. In winter, 1 in 6 (17%) patients with mild rhinitis, 7 in 16 (44%) with moderate-to-severe/intermittent rhinitis, and 7 in 14 (50%) patients with moderate-to-severe/persistent rhinitis, had poorly controlled asthma. Patients with moderate to severe rhinitis were more likely to have poorly controlled asthma compared to patients with mild rhinitis, across all seasons (Fig. 2).

Table 1 – Characteristics of patients with asthma with or without rhinitis.

Rhinitis	None	NPR	PR	p
n	8	30	15	
Age	62.9 (16.6)	60.2 (15.3)	65.9 (15.3)	0.41
Sex (Male : Female)	4 : 4	14 : 16	8 : 7	0.91
Duration of disease (years)	13.2 (12.8)	12.7 (13.2)	14.8 (17.5)	0.58
Severity of asthma				
Mild : Moderate : Severe	3 : 3 : 2	11 : 10 : 9	3 : 6 : 6	0.82
Inhaled corticosteroid dose (μg/day) ^a	860 (500)	820 (400)	860 (420)	0.55
Leukotriene modifier use (yes : no)	2 : 6	14 : 16	10 : 5	0.15
Serum total IgE (IU) (n=50)	139	161	173	0.97
Sensitization to specific allergen (n=51)	n=7	n=29	n=15	
House-dust mite	2 (29%)	13 (45%)	7 (47%)	0.69
Japanese cedar pollen	1 (14%)	14 (48%)	7 (47%)	0.25
Mixed weed pollens	0 (0%)	4 (14%)	1 (7%)	0.53
Mixed gramineas pollen	1 (14%)	11 (38%)	4 (27%)	0.43
Mixed molds	3 (43%)	4 (14%)	1 (7%)	0.09
Dog or cat dander	0 (0%)	3 (10%)	3 (15%)	0.22
Sensitization to any allergen (≥ 1)	5 (71%)	18 (62%)	10 (67%)	0.88

PR, perennial rhinitis; NPR, non-perennial rhinitis; None, patients without rhinitis; IgE, immunoglobulin E.

^a Equivalent dose of CFC-BDP (chlorofluorocarbon-beclomethasone dipropionate).

3.4. Relationship of VAS score of asthma and rhinitis symptoms

There was a positive correlation between the VAS score of asthma symptoms and the VAS score of rhinitis symptoms across all seasons (spring: $r=0.49$, $p=0.0005$; summer: $r=0.38$, $p=0.007$; fall: $r=0.59$, $p<0.0001$; winter: $r=0.62$, $p<0.0001$) and seasonal variation in these symptoms was synchronous (Fig. 3).

In spring, the VAS score of rhinitis symptoms was significantly higher in patients with sensitization to Japanese cedar pollen (major aeroallergens in spring) than in those without sensitization (5.0 ± 3.7 vs. 2.1 ± 2.1 , $p=0.0047$). However, the VAS score of asthma symptoms did not differ between patients with or without sensitization to Japanese cedar pollen (data not shown). In other seasons, no significant association between the prevalence of sensitized allergens and respectively, asthma and rhinitis symptoms, was identified (data not shown).

3.5. Comparison of seasonal changes of asthma VAS scores between patients with PR and NPR

The VAS score of asthma symptoms, stratified according to rhinitis, was significantly higher in asthmatic patients with PR than in patients with NPR or in patients without rhinitis

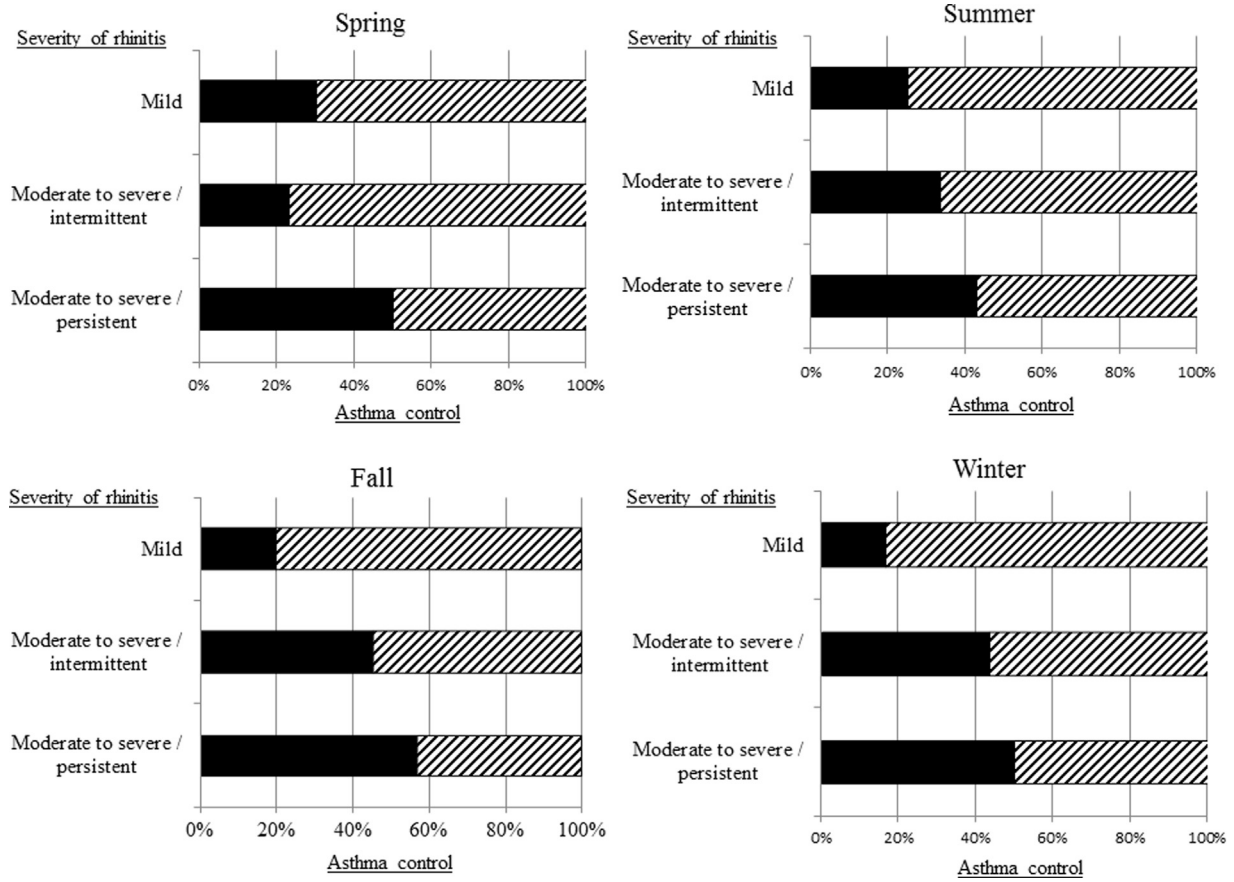


Fig. 2 – Relationship between severity of rhinitis and asthma control in each season in patients with asthma. Black bar, percentage with poorly controlled asthma; hatched bar, percentage with controlled asthma.

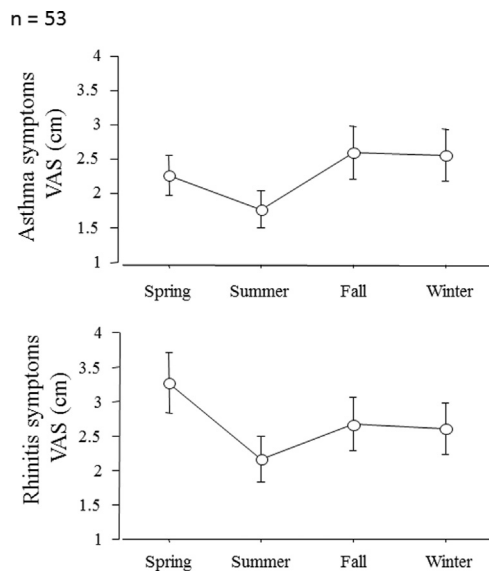


Fig. 3 – Seasonal variation of asthma (top) and rhinitis (bottom) symptoms, assessed using a visual analogue scale (VAS).

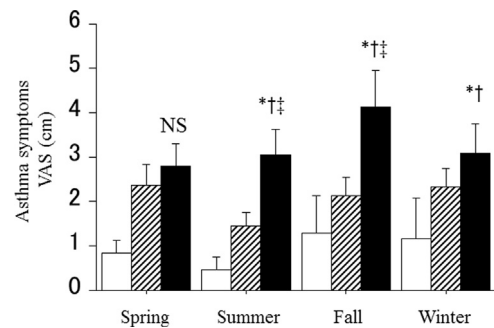


Fig. 4 – Seasonal variation of asthma symptoms assessed using a visual analogue scale (VAS) according to rhinitis type. White bar, patients with asthma but without rhinitis; hatched bar, patients with asthma and non-perennial rhinitis (NPR); black bar, patients with asthma and perennial rhinitis (PR). * $p < 0.05$ Kruskal-Wallis among 3 groups; $^{\dagger}p < 0.05$ PR vs. no rhinitis; $^{\ddagger}p < 0.05$ PR vs. NPR.

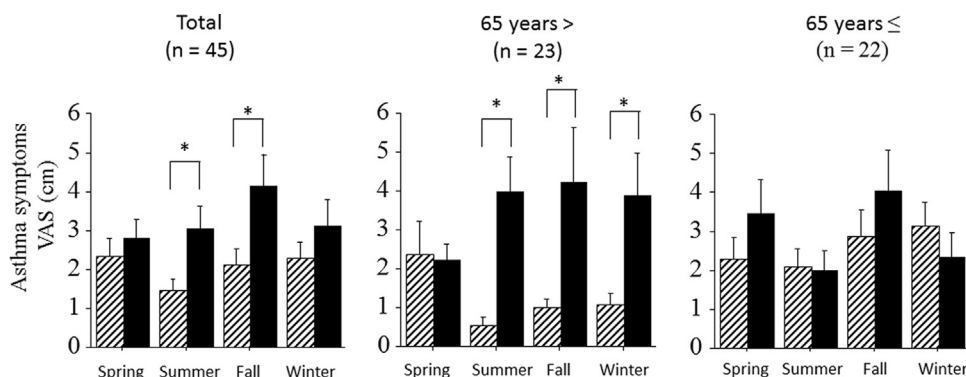


Fig. 5 – Seasonal variation of asthma symptoms according to age. Hatched bar, patients with asthma and non-perennial rhinitis (NPR); closed bar, patients with asthma and perennial rhinitis (PR). * $p < 0.05$ PR vs. NPR.

(None) across all seasons, except for spring (Fig. 4). Moreover, among 45 asthmatic patients with PR or NPR, the differences in VAS score were more significant in patients aged <65 years than in patients aged ≥ 65 years (Fig. 5). The median number of positive allergens per patient was significantly higher in patients aged <65 years than in patients aged ≥ 65 years (1.0 vs. 0.5, $p=0.0039$). Prevalence of sensitization to HDM ($p<0.0001$), animal dander ($p=0.0066$), and at least 1 in 6 measured allergens ($p=0.019$) was significantly higher in patients aged <65 years than in those aged ≥ 65 years.

4. Discussion

High rates of asthma and allergic rhinitis comorbidity have been reported [2,3,17]. Greisner et al. found that 85.7% of patients with asthma in the United States had a history of allergic rhinitis [17]. Linnerberg et al. reported that 89–100% of 734 patients with allergic asthma in Denmark also had allergic rhinitis [3]. In Japan, using the SACRA questionnaire in a cross-sectional nationwide study of 29,518 patients, 67.3% of patients with asthma were found to have rhinitis [8]. In the present study, we demonstrated that allergic rhinitis and asthma comorbidity rates, assessed by the SACRA questionnaire, varied from season to season (45–68% of patients), and 85% of patients with asthma had rhinitis symptoms in 1 or more seasons. We confirmed the high prevalence of comorbidity of rhinitis in patients with asthma and identified the need to manage rhinitis symptoms in patients with asthma throughout the year.

The upper and lower airways are interrelated. Many studies have investigated the link between rhinitis and the presence of inflammation and functional disorders in the lower airways [4,5]. Braunstahl et al. studied the expression of adhesion molecules in nasal and bronchial mucosa after nasal allergen provocation in patients without asthma, with allergic rhinitis. They found a significant influx of eosinophils in the nasal epithelium and lamina propria, as well as in the bronchial epithelium. This increase was directly related to the expression of adhesion molecules [5]. Nasal inflammatory response after segmental bronchial provocation with allergens was also assessed in patients without asthma, with allergic rhinitis. They found that this procedure induced nasal and bronchial symptoms and increased peripheral

eosinophilia and eosinophilic and basophilic infiltration of the nasal and bronchial mucosa [4], suggesting the possibility of nasobronchial cross-talk. Several mechanisms have been proposed to explain the interrelationship between the nose and the bronchi in allergic respiratory diseases. To date, most studies point toward a systemic pathway linking the upper and lower airways, and involving both circulating blood and bone marrow.

Rhinitis activity may influence asthma control. Oka et al. studied 520 patients with asthma who were taking ICS and examined their symptoms and inflammatory markers. They found a significant difference in the population of patients with incomplete asthma control, depending on the presence of and the severity of rhinitis. They also showed a significant elevation of fractional exhaled nitric oxide levels in accordance with the activity of rhinitis [10]. A large-scale, observational, cross-sectional survey in France showed that the frequency and severity of allergic rhinitis increased with the severity of asthma, resulting in impairment of quality of life [11]. Increasing evidence suggests that the worsening of rhinitis symptoms in patients with asthma can be associated with worsening asthma symptoms. Our study corroborated earlier studies and found that asthma control was worse in patients with asthma and rhinitis compared to patients with asthma but without rhinitis. It also concluded that the severity of rhinitis increased, and uncontrolled asthma became more prevalent, independently of the seasons.

It is well known that seasonal variations occur in both asthma and rhinitis symptoms [18–20]; however, to date, the concurrent assessment of seasonal changes in rhinitis and asthma symptoms has not been fully addressed. A large-scale cross-sectional questionnaire survey regarding the comorbidity of asthma and allergic rhinitis was conducted in Japan [12]. In this survey, patients were asked in which months they had rhinitis symptoms and in which months they had asthma symptoms. This study revealed that asthma and rhinitis symptoms co-existed, particularly in spring and in the fall. We postulated that asthma and rhinitis share a common pathogenesis in the upper and lower airway. Furthermore, we found that the VAS score of asthma symptoms positively correlated with the VAS score of rhinitis symptoms across all seasons, and that seasonal variation of these symptoms were synchronous. It is possible that exposure to ambient allergens may represent a common

pathogenesis in asthma and rhinitis and this may explain the co-existence of symptoms of asthma and rhinitis. In Japan, HDM and pollen allergens are the main aeroallergens and their allergen levels show seasonal variation [21,22]. In our study, however, the VAS of asthma symptoms in each season was not associated with any of the 6 measured allergens. This may mean that other factors, such as humidity, cold air, and pollution, are associated with asthma symptoms.

Our study showed that asthma symptoms were more severe in patients with PR than in patients with NPR. It is reported that patients with PR show more airway hyper-responsiveness compared to those with seasonal rhinitis [23]. Moreover, we demonstrated that the association between asthma and rhinitis was more significant in younger patients with asthma (<65 years). This may be explained by differences in atopic status according to age, or by the existence of different asthma and/or rhinitis phenotypes and their interaction in elderly patients with asthma [24]. Further research is required to confirm this. The long-term effects of rhinitis treatment on asthma remain unknown. However, in view of the high comorbidity of rhinitis and asthma and the effect of rhinitis on asthma control, patients with asthma and rhinitis should be treated for both conditions.

The present study has several limitations. First, our study population was relatively small. The sensitivity and specificity of the SACRA questionnaire for the diagnosis of allergic rhinitis have been reported as 92% and 66%, respectively [9]. These are not significantly inferior to the ARIA questionnaire, although in the present study, allergic and nonallergic rhinitis could not be differentiated using the SACRA questionnaire. Second, approximately 50% of subjects had been administered a leukotriene modifier, which influences both asthma and rhinitis symptoms. Ideally, leukotriene modifier-naïve patients with asthma and rhinitis should be enrolled; however, it is difficult to find a large number of these patients in a clinical setting. Finally, airway outcomes were not monitored by using pulmonary function and objective inflammatory markers, such as exhaled or nasal nitric oxide and sputum cell differentiation. However, several recent studies have reported that a VAS scale and classification of asthma and rhinitis severity based on a self-reported questionnaire can be used as a quantitative evaluation and serve as a tool to assess the efficacy of treatment [17,25,26].

5. Conclusions

Using the SACRA questionnaire as a screening tool for diagnosing the presence of rhinitis in patients with asthma, we confirmed the high rates of asthma and rhinitis comorbidity and found that the prevalence of rhinitis in patients with asthma varies across seasons. The seasonal variation in rhinitis and asthma symptoms showed synchronicity and the association between these symptoms was stronger in younger patients with asthma and PR.

Author contributions

M. T., M. F. contributed to the study concept and design; M. T., D. I., K. T., R. I., and M. I. contributed to the data acquisition and analysis; M. T., M. S., and M. F. contributed to drafting the manuscript and data. M. T. and M. F. approved the final version of this manuscript.

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Conflict of interest

The authors have no conflicts of interest.

REFERENCES

- [1] Bousquet J, Vignola AM, Demoly P. Links between rhinitis and asthma. *Allergy* 2003;58:691–706.
- [2] Leynaert B, Neukrich C, Kony S, et al. Association between asthma and rhinitis according to atopic sensitization in a population-based study. *J Allergy Clin Immunol* 2004;113:86–93.
- [3] Linneberg A, Henrik Nielsen N, Frolund L, et al. The link between AR and allergic asthma: a prospective population-based study. *Cph Allergy Study Allergy* 2002;57:1048–52.
- [4] Braunstahl GJ, KleinJan A, Overbeek SE, et al. Segmental bronchoprovocation in allergic rhinitis patients. *Am J Respir Crit Care Med* 2000;161:2051–7.
- [5] Braunstahl GJ, Overbeek SE, KleinJan A, et al. Nasal allergen provocation induces adhesion molecule expression and tissue eosinophilia in upper and lower airways. *J Allergy Clin Immunol* 2001;107:469–76.
- [6] Bousquet J, Gaugris S, Koccar VS, et al. Increased risk of asthma attacks and emergency visits a subgroup analysis of the improving asthma control trial. *Clin Exp Allergy* 2005;35:723–7.
- [7] Price D, Zhang Q, Koccar VS, et al. Effect of a concomitant diagnosis of allergic rhinitis on asthma-related health care use by adults. *Clin Exp Allergy* 2005;35:282–7.
- [8] Ohta K, Bousquet PJ, Aizawa H, et al. Prevalence and impact of rhinitis in asthma. SACRA, a cross-sectional nation-wide study in Japan. *Allergy* 2011;66:1287–95.
- [9] Hojo M, Ohta K, Iikura M, et al. Clinical usefulness of a guideline-based screening tool for the diagnosis of allergic rhinitis in asthmatics: the self assessment of allergic rhinitis and asthma questionnaire. *Respirology* 2013;18:1016–21.
- [10] Oka A, Matsunaga K, Kamei T, et al. Ongoing allergic rhinitis impairs asthma control by enhancing the lower airway inflammation. *J Allergy Clin Immunol Pract* 2014;2:172–8.
- [11] Magnan A, Meunier JP, Saugnac C, et al. Frequency and impact of allergic rhinitis in asthma patients in everyday general medical practice: a French observational cross-sectional study. *Allergy* 2008;63:292–8.
- [12] Yamauchi K, Tamura G, Akasaka T, et al. Analysis of the comorbidity of bronchial asthma and allergic rhinitis by questionnaire in 10,009 patients. *Allergol Int* 2009;58:55–61.

- [13] Bugiani M, Carosso A, Migliore E, et al. Allergic rhinitis and asthma comorbidity in a survey of young adults in Italy. *Allergy* 2005;60:165–70.
- [14] Takemura M, Niimi A, Matsumoto H, et al. Atopic features of cough variant asthma and classic asthma with wheezing. *Clin Exp Allergy* 2007;37:1833–9.
- [15] Japanese Society of Allergology. Asthma prevention and management guidelines of Japan 2012, Japan (JGL2012). Tokyo, Kyowa Kikaku; 2012 (in Japanese).
- [16] Hojo M, Ohta K, Iikura M, et al. The impact of co-existing seasonal allergic rhinitis caused by Japanese Cedar Pollinosis (SAR-JCP) upon asthma control status. *Allergol Int* 2015;64:150–5.
- [17] Greisner III WA, Settipane RJ, Settipane GA. Co-existence of asthma and allergic rhinitis: a 23-year follow up study of college students. *Allergy Asthma Proc* 1998;19:185–8.
- [18] Platts-Mills TA, Hayden ML, Chapman MD, et al. Seasonal variation in dust mite and grass-pollen allergens in dust from the houses of patients with asthma. *J Allergy Clin Immunol* 1987;79:781–91.
- [19] Tilles AS, Bardana Jr. EJ. Seasonal variation in bronchial hyperreactivity (BHR) in allergic patients. *Clin Rev Allergy Immunol* 1997;15:169–85.
- [20] Bousquet J, Boushey HA, Busse WW, et al. Characteristics of patients with seasonal allergic rhinitis and concomitant asthma. *Clin Exp Allergy* 2004;34:897–903.
- [21] Miyazawa H, Sakaguchi M, Inouye S, et al. Seasonal changes in mite allergen (Der I and Der II) concentrations in Japanese homes. *Ann Allergy Asthma Immunol* 1996;76:170–4.
- [22] Ito Y, Kimura T, Miyamura T. Gramineae pollen dispersal and pollinosis in the city of Hisai in Mie Prefecture. A 14-year study of gramineae pollen dispersal and cases of sensitization to gramineae experienced at an allergy clinic over a 15-year period. *Arerugi* 2002;51:9–14.
- [23] Riccioni G, Della Vecchia R, Castronuovo M, et al. Bronchial hyperresponsiveness in adults with seasonal and perennial rhinitis: is there a link for asthma and rhinitis? *Int J Immunopathol Pharmacol* 2002;15:69–74.
- [24] Busse PJ, Kilaru K. Complexities of diagnosis and treatment of allergic respiratory disease in the elderly. *Drugs Aging* 2009;26:1–22.
- [25] Bousquet PJ, Combescure C, Neukirch F, et al. Visual analog scales can assess the severity of rhinitis graded according to ARIA guidelines. *Allergy* 2007;62:367–72.
- [26] Bousquet PJ, Combescure C, Klossek JM, et al. Change in visual analog scale score in a pragmatic randomized cluster trial of allergic rhinitis. *J Allergy Clin Immunol* 2009;123:1349–54.