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Prevalence of ocular symptoms in patients with allergic rhinitis: Korean multicenter study

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ABSTRACT

Background: *Allergic rhinitis (AR) is often accompanied by multiple ocular symptoms. This study aimed to evaluate the prevalence of ocular symptoms and the impact of ocular symptoms on the quality of life in patients with AR.*

Methods: *One thousand one hundred seventy-four patients with AR were enrolled from 24 centers in Korea. They were classified into four groups according to the Allergic Rhinitis and Its Impact on Asthma (ARIA) guideline and also classified into perennial AR (PAR) and seasonal AR groups. All patients were asked to complete the questionnaire regarding the presence of ocular symptoms, such as eye itching, watery eyes, and red eyes. The correlation between ocular symptoms and the rest of the quality-of-life areas in the Mini-Rhinoconjunctivitis Quality of Life Questionnaire (Mini-RQLQ) was also asked.*

Results: *Seven hundred nineteen (61.2%) of 1174 patients had ocular symptoms. In detail, the numbers of patients with eye itching, watery eyes, red eyes, and other ocular symptoms were 605 (51.5%), 313 (26.7%), 207 (17.6%), and 66 (5.6%), respectively. Female patients (72.5%) complained of ocular symptoms more commonly than male patients (55.1%). The patients with moderate–severe persistent AR showed the highest prevalence of ocular symptoms. The correlation coefficients between ocular symptoms and the rest of the quality-of-life areas in the Mini-RQLQ were statistically significant ($p < 0.05$).*

Conclusion: *Sixty-one percent of Korean AR patients experienced ocular symptoms. The patients who were women and had PAR and more severe AR showed higher prevalence of ocular symptoms. The ocular symptoms might have a significant impact on the quality of life in patients with AR.*

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Allergic rhinitis (AR) is one of the prevalent allergic diseases that considerably affect quality of life of patients in various aspects such as sleep, learning ability, and work. This prevails in a wide range of populations worldwide across all ages, races, and nations. It has been reported that the prevalence of AR in Korea ranges from 6.2 to 10.2%.[1,2] The International Study of Asthma and Allergies in Childhood reported that the prevalence rate of AR in Korean adolescents aged 13–14 years was 10%.[3]

Major symptoms of AR include sneezing, rhinorrhea, nasal obstruction, and nasal itching. Ocular symptoms, such as eye itching, lacrimation, and bloodshot eyes, are also commonly accompanied with AR. The Disease Specific Programme survey conducted in Europe on AR burdens reported that 71% of the patients with AR experienced both nasal and ocular symptoms, and 21% of the patients deemed ocular itching to be the most distressful symptom.[4] Ocular symptoms are noticeable especially in seasonal AR (SAR), whereas they tend to be less serious in perennial AR (PAR).[5] Nevertheless, the symptoms tend to persist with continuous exposures to an allergen.[6]

Despite the fact that ocular symptoms in patients with AR are prevalent and bothersome, Korean research still has to be conducted in regard to this. In addition, taking into account the medical delivery system in Korea where it is relatively easy for a patient to seek specialists in each area of medicine, it is anticipated that there are many patients with AR who do not complain about ocular symptoms to their medical professionals at the Department of Otolaryngology or Allergology. In this context, this study is aimed at surveying the prevalence of ocular symptoms in patients with AR who visit an otolaryngologist/allergist, as well as the impact of ocular symptoms on the quality of life in these patients.

METHODS

This was a cross-sectional, observational, multicenter study conducted in 24 hospitals/clinics in Korea.

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Patients with AR were recruited consecutively between April and November 2010. They were between the ages of 18 and 70 years and the diagnosis of AR was made by allergic symptoms, such as rhinorrhea, sneezing, itching, or nasal obstruction, and positivity on either allergic skin-prick test (SPT) or multiple antigen simultaneous test conducted at the time of enrollment. A battery of eight airborne allergens was used for SPT (Allegro-Pharma, Reinbek, Germany): house-dust mites including *Dermatophagoides farina, Dermatophagoides pteronyssinus, Tyrophagus putrescentiae,* and *Tetranychus utricae;* outdoor mold mixture including *Alternaria, Cladosporium, Fusarium, Aspergillus niger,* and *Candida albicans;* indoor mold mixture including *Aspergillus fumigatus, Mucor, Neurospora,* and *Penicillium;* animal danders including cat, dog, rat, chicken, and rabbit; cockroach including German cockroach and American cockroach; tree pollen mixture 1 including alder, hazel, popular, elm, willow tree, ash, and elder; tree pollen mixture 2 including birch, beech, oak, plane tree, and Japanese ceder; grass pollen mixture including velvet, orchard, rye, Timothy, Kentucky, meadow, nettle, and Bermuda; weeds including ragweed, mugwort, Hop j, chrysanthemum, dandelion, golden rod, and plantain; and histamine (10 mg/mL of histamine phosphate) as positive and 0.9% saline as negative control. SPTs were evaluated 15 minutes after application and it was interpreted as 3+ when the mean wheal diameter was same as that of histamine control and 2+ when the mean wheal diameter was 50% of that of histamine control. Positive response was defined as more than two or more positive (2+, 3+, or 4+) to the allergen tested.

Patients were classified according to the Allergic Rhinitis and Its Impact on Asthma (ARIA) guideline. Patients with nonallergic rhinitis, other ocular diseases causing watery and/or red eyes, or other serious medical conditions requiring hospitalization were excluded.

Information about medical history and concomitant disease including allergic diseases, concomitant medication, duration of AR, and presence of ocular symptoms were collected during the enrollment through interviews and physical examinations. Subjects were also asked to complete a self-reporting questionnaire, the Mini Rhinoconjunctivitis Quality of Life Questionnaire (Mini-RQLQ[7]) and the verified version of the RQLQ. The questionnaire was comprised of five areas including activity, actual difficulty, nasal symptoms, ocular symptoms, and other symptoms, which could be interpreted into a single overall satisfaction score thereafter. The scores ranged from 0 to 6, 6 indicating the most discomfort. This study started and ended at a single time point; therefore, all items were evaluated based on a single visit of the subjects.

As the primary end point, prevalence of ocular symptoms in patients with AR was presented in a percentage with its 95% confidence interval. For the secondary end point, prevalence of ocular symptoms according to the classification of AR based on the ARIA guidelines and conventional classification into PAR and SAR was assessed with ANOVA and chi-square tests and presented as a frequency and percentage for each classification. In addition, correlations between ocular symptoms and the rest of the quality-of-life areas in the Mini-RQLQ were also assessed with Pearson's correlation analysis and indicated with correlation coefficients.

This study was conducted in accordance with the Declaration of Helsinki and the laws and regulations adopted by the World Medical Association and approved by the Institutional Review Board of all institutions. All patients signed the informed consent.

RESULTS

A total of 1174 patients who met the eligibility criteria were enrolled. The mean age was 35.6 years (±13.6 years), and 64.7% (n = 759) were men. The patients were diagnosed with AR by either SPT (n = 659) or multiple antigen simultaneous test (n = 730). The mean age at diagnosis was 34.1 years (±14.2 years), and the mean duration of AR was 2.0 years (±4.8 years). The subgroups of AR according to the ARIA guidelines were mild intermittent (MI; n = 335; 28.6%), moderate–severe intermittent (SI; n = 309; 26.3%), mild persistent (MP; n = 206; 17.6%), and moderate–severe persistent (SP; n = 323; 27.5%) AR groups. The subgroups according to the conventional classification were SAR (n = 462; 38.6%) and PAR (n = 721; 61.4%; Table 1).

Table 1 **Demographics by groups of interest**

Item		
Age (yr)	Mean ± SD	35.6 ± 13.6
Gender	Male, n (%)	759 (64.7)
	Female, n (%)	415 (35.3)
Age (yr) at the time of AR diagnosis	Mean ± SD	34.1 ± 14.2
History of AR (yr)	Mean ± SD	1.96 ± 4.76
Classification of AR according to the ARIA guidelines	MI, n (%)	335 (28.6)
	SI, n (%)	309 (26.3)
	MP, n (%)	206 (17.6)
	SP, n (%)	323 (27.5)
Classification of SAR/PAR	Seasonal, n (%)	462 (38.6)
	Perennial, n (%)	721 (61.4)
Comorbid allergic disease	Allergic dermatitis, n (%)	31 (2.6)
	Asthma, n (%)	45 (3.8)

AR = allergic rhinitis; MI = mild intermittent; SI = moderate–severe intermittent; MP = mild persistent; SP = moderate–severe persistent; ARIA = Allergic Rhinitis and Its Impact on asthma; PAR = perennial allergic rhinitis; SAR = seasonal allergic rhinitis.

One hundred fifty-four (13.1%) patients had comorbidities. Among them, asthma was prevalent in 3.8% (n = 45) and atopic dermatitis in 2.5% (n = 31) as an allergic disease.

Of the 1174 patients with AR, 719 patients (61.2%) reported at least one ocular symptom (95% confidence interval, 58.5–64.0%). Symptoms of eye itching, lacrimation, and red eyes occurred in 605 (51.5%), 313 (26.7%), and 207 (17.6%) patients, respectively (Table 2). The 72.5% of female patients complained of ocular symptoms versus 55.1% of male patients. This difference was statistically significant ($p < 0.01$).

The percentages of patients complaining of ocular symptoms in each group based on the ARIA guidelines were 50.1, 61.5, 67.0, and 69.0% in MI, SI, MP, and SP groups, respectively. The percentages of patients by the individual ocular symptoms in MI, SI, MP, and SP groups are summarized in Table 2. The severity and duration of allergic symptoms were significantly correlated with the prevalence of ocular symptoms ($p < 0.05$).

Meanwhile, the prevalence of ocular symptoms was 57.5 and 63.2% in patients with SAR and PAR, respectively (p = 0.055). The percentages of patients with eye itching, lacrimation, and red eyes were 47.8% versus 53.3%, 21.7% versus 29.5%, and 13.7% versus 19.8% between the SAR and PAR groups, respectively. Differences in the percentages of lacrimation and red eyes between SAR and PAR reached statistical significance ($p < 0.01$; Table 3). The percentages of patients by the individual ocular symptoms in the SAR/PAR classification according to the severity are summarized in Table 3. The prevalence of ocular symptoms was correlated with the severity and duration of allergic symptoms in patients with SAR and PAR.

A similar trend was observed in the summarized results of the Mini-RQLQ. Among the four groups according to the ARIA guidelines, the ocular symptom score of the SP group was the highest, whereas that of the MI group was the lowest. The mean scores in the other areas of the Mini-RQLQ were also significantly different among the groups (Tables 4 and 5). In all areas, the Mini-RQLQ scores were significantly higher in patients with PAR than those with SAR (Tables 4 and 5). Moreover, the correlation coefficients between ocular symptoms and the rest of the items in the Mini-RQLQ showed statistical significance (Fig. 1).

Table 2 **Overall status of ocular symptoms following classification of AR according to the ARIA guidelines**

Ocular Symptom	*n* (%) 95% CI	MI (*n* = 335)	SI (*n* = 309)	MP (*n* = 206)	SP (*n* = 323)	*p* Value
Eye itching	605 (51.5) (48.7–54.4)	143 (42.7)	157 (50.8)	117 (56.8)	188 (58.2)	<0.01*
Watery eyes	313 (26.7) (24.1–29.2)	61 (18.2)	73 (23.6)	61 (29.6)	118 (36.5)	<0.01*
Red eyes	207 (17.6) (15.5–19.8)	42 (12.5)	42 (13.6)	39 (18.9)	84 (26.0)	<0.01*
Others	66 (5.6) (4.3–6.9)	13 (3.9)	16 (5.2)	18 (8.7)	19 (5.9)	0.12
Total	719 (61.2) (58.5–64.0)	168 (50.1)	190 (61.5)	138 (67.0)	223 (69.0)	<0.01*

**Chi-square test.*

AR = allergic rhinitis; ARIA = Allergic Rhinitis and Its Impact on asthma; MI = mild intermittent; SI = moderate–severe intermittent; MP = mild persistent; SP = moderate–severe persistent.

Table 3 **Status of ocular symptoms following classification of SAR/PAR, *n* (%)**

Ocular Symptoms *n* (%)	Seasonal AR (*n* = 452)				Perennial AR (*n* = 711)				*p* Value
	MI *n* = 179	SI *n* = 176	MP *n* = 45	SP *n* = 52	MI *n* = 154	SI *n* = 132	MP *n* = 154	SP *n* = 270	
Ocular itching	65 (36.3)	87 (49.4)	29 (64.4)	35 (67.3)	76 (49.4)	69 (52.3)	82 (53.3)	152 (56.3)	0.07
Watery eyes	31 (17.3)	41 (23.3)	10 (22.2)	16 (30.8)	30 (19.5)	31 (23.5)	47 (30.5)	102 (37.8)	<0.01*
Red eyes	20 (11.2)	22 (12.5)	3 (6.7)	17 (32.7)	22 (14.3)	19 (14.4)	33 (21.4)	67 (24.8)	<0.01*
Others	8 (4.5)	11 (6.3)	6 (13.3)	3 (5.8)	4 (2.6)	5 (3.8)	11 (7.1)	15 (5.6)	0.35
Total number	82 (45.8)	107 (60.8)	33 (73.3)	38 (73.1)	84 (54.6)	82 (62.1)	99 (64.3)	184 (68.2)	0.06

**Chi-square test.*

AR = allergic rhinitis; MI = mild intermittent; SI = moderate–severe intermittent; MP = mild persistent; SP = moderate–severe persistent; PAR = perennial allergic rhinitis; SAR = seasonal allergic rhinitis.

Table 4 **Summary of the Mini-RQLQ following the ARIA guidelines–based classification of AR**

Items	MI	SI	MP	SP	*p* Value
Activity					
n	332	305	205	323	<0.01*
Mean ± SD	1.86 ± 1.20	2.58 ± 1.34	2.39 ± 1.27	2.85 ± 1.46	
Actual difficulty					
n	328	300	204	321	<0.01*
Mean ± SD	2.12 ± 1.43	2.81 ± 1.46	2.71 ± 1.47	3.29 ± 1.66	
Nasal symptom					
n	329	301	203	319	<0.01*
Mean ± SD	2.32 ± 1.26	2.86 ± 1.35	2.67 ± 1.36	3.19 ± 1.49	
Ocular symptom					
n	328	306	201	321	<0.01*
Mean ± SD	1.28 ± 1.18	1.52 ± 1.33	1.45 ± 1.23	1.76 ± 1.53	

**ANOVA test.*

ARIA = Allergic Rhinitis and Its Impact on asthma; Mini-RQLQ = Mini-Rhinoconjunctivitis Quality of Life Questionnaire; AR = allergic rhinitis; MI = mild intermittent; SI = moderate–severe intermittent; MP= mild persistent; SP = moderate–severe persistent.

DISCUSSION

In this study of 1174 patients with AR, 719 patients (61.2%) experienced ocular symptoms, such as eye itching, watery eyes, and red eyes in the order of decreasing frequency. Female patients who had PAR and more severe AR according to the ARIA guidelines showed higher prevalence of ocular symptoms. The ocular symptoms have a significant impact on quality of life in patients with AR.

This study also showed that the severity and duration of AR symptoms were significantly correlated with the prevalence of ocular symptoms. There was a slightly higher prevalence of ocular symptoms in PAR than SAR without statistical significance. These results indicate that the severity and duration of AR symptoms are more crucial in provoking ocular symptoms than a seasonal or perennial allergen itself. Moreover, the severity of ocular symptoms correlated significantly with the activity, actual difficulty, and nasal symptoms.

The occurrence of ocular allergy has increased in developed countries and now affects >20% of the U.S. population.[8,9] It is also reported that ocular allergy accounts for 25% of all ocular surface diseases.[10] Ocular symptoms can be easily ignored and often underdiagnosed among patients with AR because the nasal symptoms of congestion and rhinorrhea are more common complaints than ocular symptoms. Thus, we tried to provide an accurate prevalence study of ocular allergy in Korean AR patients.

It is well known that allergen-exposed conjunctiva induce an allergic response. The tarsal and bulbar conjunctiva contain a significant number of mast cells, along with a localized potential for IgE synthesis.[11] The allergic response in conjunctiva was proved by conjunctival biopsy specimens having the increased numbers of mast cells, neutrophils, eosinophils, macrophages, and basophils.[12] As with other allergic reactions, allergic conjunctivitis is characterized by both early and late-phase reactions. Inflammatory changes after 6-hour allergen challenge were shown by the cytological analysis of conjunctival

Table 5 **Summary of the Mini-RQLQ following the conventional classification of AR**

Items	SAR	PAR	*p* Value
Activity			
n	449	706	<0.01*
Mean ± SD	2.27 ± 1.32	2.51 ± 1.41	
Actual difficulty			
n	442	701	0.01*
Mean ± SD	2.59 ± 1.53	2.82 ± 1.59	
Nasal symptom			
n	444	698	0.04*
Mean ± SD	2.67 ± 1.39	2.84 ± 1.41	
Ocular symptom			
n	445	701	<0.01*
Mean ± SD	1.35 ± 1.24	1.60 ± 1.40	

**Chi-square test.*
Mini-RQLQ = Mini-Rhinoconjunctivitis Quality of Life Questionnaire; AR = allergic rhinitis; PAR = perennial allergic rhinitis; SAR = seasonal allergic rhinitis.

scrapings or tears.[13,14] However, one study reported that without direct exposure of conjunctiva to allergens, 20% of AR sufferers experienced ocular symptoms during nasal provocation with grass pollen.[15] Other known mechanisms causing ocular symptoms include nasal-ocular reflex and nasonasal reflex. When a subject was challenged with a nasal allergen in one nostril, there were increases in symptoms and secretion weights in both nostrils and eyes by this mechanism.[12] In association with this mechanism, a few studies showed that use of intranasal steroids relieved nasal and ocular symptom of AR.[16–18]

Based on the clinical presentation, ocular allergy can be classified into a number of categories: seasonal/perennial allergic conjunctivitis, vernal/atopic keratoconjunctivitis, and contact allergy. Seasonal allergic conjunctivitis is known to be the most common form of ocular allergy and is associated with SAR. Compared with seasonal allergy, the perennial form is the more chronic type of ocular allergy caused by sensitization to allergens that are present all year round, such as house-dust mites, animal dander, and molds. Although it is known to be presented as a mild-to-moderate disease, vernal/atopic keratoconjunctivitis is a more severe, often chronic, and IgE-mediated allergic disease, which has a sight-threatening risk.

The triad of redness, swelling, and itching is an accurate description of allergic conjunctivitis.[19] One survey conducted in the United States reported that the respondents ranked redness and itching eyes as the most troublesome symptoms. Unfortunately, ocular symptoms such as redness, tearing, and irritation are quite nonspecific in some cases, so it is important to make an accurate diagnosis before prescription. It is clinically manifested by symptoms that occur a few minutes after exposure to nonspecific stimuli such as wind, light, smoke, or cold or warm air/water. This condition is known as nonspecific conjunctival hyperreactivity and it may reflect disease of the ocular surface from different causes.[20] Also, allergic subjects exhibit more conjunctival hyperreactivity than nonallergic subjects, even when asymptomatic.[21] Moreover, Ciprandi *et al.* indicated that patients allergic to dust mites exhibited conjunctival hyperreactivity as a result of minimal persistent inflammation caused by frequent exposure of the conjunctival mucosa to the allergen present all year round.[22] From this point of view, one can not always distinguish ocular allergy from other types of ocular inflammation by considering history, offending allergen, seasonality, and symptomatology. Actually, in our study, some of those suffering from ocular symptoms may also have nonallergic conjunctivitis because we did not perform objective tests to specifically diagnose allergic conjunctivitis.

The overall prevalence rate of 61.2% of ocular symptoms in this study was lower than the 65–85.3% reported in previous studies of

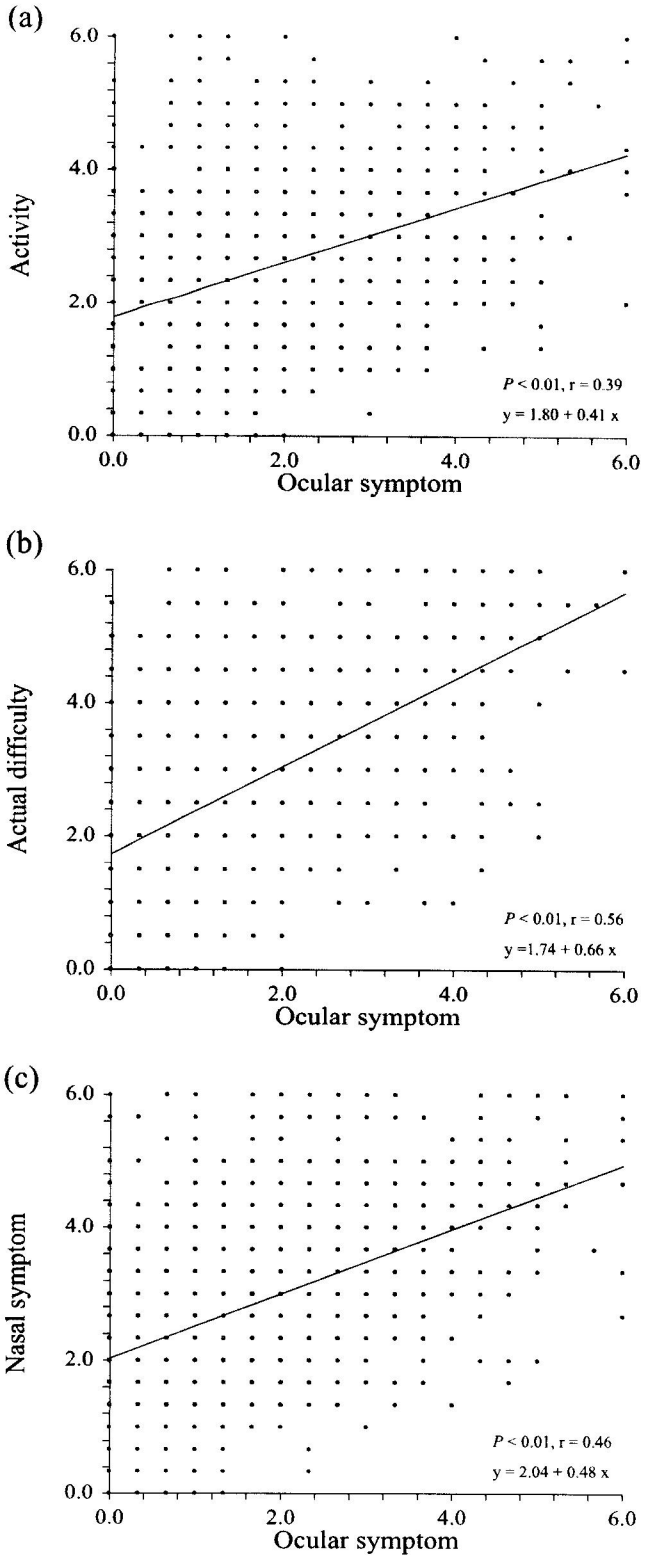

Figure 1. *(a–c) Correlation coefficients between ocular symptoms and the rest of the quality-of-life areas in the Mini Rhinoconjunctivitis Quality of Life Questionnaire (Mini-RQLQ). Positive correlation with statistical significance between ocular symptoms and the rest of the quality-of-life area could be seen.*

several other countries.[23] This difference might be related to the young age population enrolled in this study (mean age of 35.6 years). It was reported that there was an increase in the frequency of combined nasal and ocular symptoms in those <50 years of age, while those ≥50 years of age had a higher frequency of isolated ocular symptoms.[24] This might be partly caused by other ocular conditions that could develop later in life such as tear film dysfunction, which appears to increase with age, whereas atopy decreases with age. Besides the age factor, because the diagnosis was often made subjectively based on the self-reported ocular symptoms rather than laboratory test results, the prevalence in one study might be different from others.

Meanwhile, it was reported that ocular symptoms were more frequent in patients with SAR than those with PAR.[25] In a French cohort study on patients with severe allergy, conjunctivitis was found in 81% of patients with pollen allergy, compared with 58% of those with mite allergy.[26] However, in our study, the ocular symptoms were more frequent in patients with PAR than those with SAR. This might be caused by the characteristic of AR in Korea that house-dust mite, a perennial allergen, is the most significant offending allergen throughout the year, rather than seasonal allergens such as pollen.

Importantly, AR is rarely found in isolation and should be considered in the context of systemic allergic disease. The presence of AR has been associated with numerous comorbid disorders, including asthma, atopic dermatitis, and so on, with 38% of AR patients reporting that they have been previously diagnosed with asthma.[27–29] However, the comorbid rate of asthma was only 3.8% in this study. This disparity might result from the interracial character difference. This variation in prevalence of asthma suggests that environmental factors may be critical to the development of this disorder and major risk factors for them may be different or may involve different latency periods and time trends. Another interesting point in our study is that female patients (72.5%) complained of ocular symptoms more commonly than male patients (55.1%). The cause of this result is still uncertain; however, one of the speculations is that women have higher chances of developing eye irritation due to cosmetics than men. Additional studies using objective measurements would be needed to stratify among various eye conditions.

In conclusion, more severe AR patients show higher prevalence of ocular symptoms, and ocular symptoms may have a significant impact on the quality of life in patients with AR.

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