Developing Nomograms for Identifying Allergic Rhinitis Among Chronic Rhinitis: A Real-world Study

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Research

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Abstract

Background

It is difficult to discriminate allergic rhinitis (AR) and nonallergic rhinitis (NAR) in clinical practice due to the similar clinical manifestations. The study was to assess both the demographical and clinical features of AR and NAR in the real-world data of outpatients in China.

Methods

It was a cross-sectional real-world study. AR and NAR were defined based on both subjective symptoms and objective specific serum IgE test. General demographic characteristics as well as clinical information was documented. Patients were further classified according the seasons of initial visiting hospital (during pollen seasons or not). A scoring system presented as nomograms for presence of AR was performed.

Results

In pollen season group, age distribution, the duration of rhinitis, comorbidity of asthma, food allergies and score of coughing were found significantly associated with AR. Besides, in non pollen season group, we found that ethnicity, age distributions, duration of rhinitis, comorbidity of asthma, food allergies, family history of allergy, together with scores of gritty eyes were associated factors of AR. Based on multivariate logistic model, we built two nomograms which included previously identified significant risk factors that could be easily acquired during clinical practice with predictive variables to assess their roles in predicting the risk of AR among outpatients with rhinitis.

Conclusions

The characteristics of patients with different phenotypes of chronic rhinitis are distinctive in different seasons and the developed monogram in this study might be beneficial for clinical practice.

Background

Chronic rhinitis, a common inflammatory disease of nasal mucosa, is usually manifested as two or more nasal symptoms such as nasal congestion, rhinorrhea, sneezing and itching for more than 12 weeks per year\(^1\). With great financial burden and tremendous impairment of quality of life, it is estimated that chronic rhinitis affected around 30% of the global population\(^2,3\). Clinically, considering the etiology, chronic rhinitis is divided into 2 phenotypes, allergic rhinitis (AR) and nonallergic rhinitis (NAR).

Worldwide, AR affects 10%-40% of the population\(^3\), while the prevalence of NAR is reported to be around 7% in the United States\(^4\). An epidemiological survey reported that based on results of skin prick test, the prevalence of AR and NAR at a rural area of northern China was 16.78% and 24.60%, respectively \(^5\). Although both
diseases are resembled in symptoms, the clinical characteristics of AR and NAR remain distinctive. For example, patients with AR are usually accompanied with more severe conjunctivitis symptoms and higher percentage of lower airway involvement, compared with patients with NAR. What's more, AR is further classified into 2 phenotypes according to different onset period, seasonal AR (SAR) and perennial AR (PAR). As far as we know, the symptoms of AR are the result caused by specific inhalant allergens, which is mediated by specific immunoglobulin E (sIgE), and Pollen is the most important cause of SAR.

As mentioned before, the discrimination between AR and NAR should be based on the results of allergic sensitization; yet only a limited number of researches have included objective methods such as skin prick test and serum sIgE test, which is responsible for the inaccurate data of prevalence.

In daily clinical practice, only patients with nasal symptoms would seek medical treatment at hospital. For those with chronic rhinitis (coexistence of AR (both SAR and PAR) and NAR), showing similar clinical manifestations, it is difficult to discriminate without objective examinations, which are relatively expensive. As a result, especially in China, a still developing country, such objective examination could not widely cover all the outpatients with nasal symptoms. Additionally, outpatients that seek for medical care during pollen seasons include a large amount of SAR patients, while they are less commonly seen at the outpatient department out of pollen seasons. However, for the patients with NAR, whose symptoms are more likely to be perennial and associated with environmental factors, their visit time to hospitals is not limited to pollen seasons. Therefore, the pattern of outpatients in different seasons should be inconsistent, showing distinctive characteristics.

To sum up, real-world studies focused on the epidemiological and clinical characteristics of chronic rhinitis strictly based on objective tests are scarce. The aim of the present study was therefore to assess both the demographical and clinical features of AR and NAR in the real-world data of outpatients in China, using both subjective and objective tests, and develop nomograms for predicting the risk of AR among chronic rhinitis patient, providing a point of reference for clinical practice.

**Methods**

**Data Source and Study Design**

Participants included in this analysis were outpatients suffering from chronic rhinitis, with or without asthma, at the Department of Otorhinolaryngology and Allergy of Beijing TongRen Hospital. Only patients at the first visit would be counted. Patients that sought for medical care from January 2018 to December 2019 were included. In this retrospective cross-sectional study, subjects were defined as patients with rhinitis if they had more than two of the four following typical symptoms of rhinitis; including sneezing, rhinorrhea, nasal congestion and itching in the past 12 months, excluding the effect of upper respiratory infections. All the participants were assessed for serum sIgE sensitization test. The population characteristics and medical history were documented in the medical record. All participants completed a specifically designed questionnaire, as detailed below, under the supervision of a group of experienced interviewers. All the children’s questionnaires were completed by their guardians.
The study protocol was approved by the Ethics Committee of Beijing TongRen Hospital and Beijing Institute of Otolaryngology, P.R. China in accordance with the Declaration of Helsinki; and written informed consent was obtained from all adult participants or guardians of pediatric patients before enrolment into the study.

**Definition of AR and NAR**

Allergic sensitization was defined by positive sIgE to common aeroallergens measured by UniCAP system (Phadia, Uppsala, Sweden), using a panel of aeroallergen mixtures including house dust mites, weed/grass pollen, molds, trees, as well as animal daner (specific IgE ≥ 0.7KUA/L). Based on the results of allergic sensitization, subjects were further classified into AR and NAR group; while the subjects showing positive serum allergic sensitization defined as AR group, and the subjects with negative serum allergic sensitization defined as NAR group.

**Definition of pollen season**

Based on the data of total pollen concentration provided by Beijing Meteorological Bureau, the start of pollen season was defined as when the pollen count was ≥ 5 pollen grains/m$^3$ per day for more than 3 consecutive days; the end of pollen season was defined as when the pollen count fell to ≤10 pollen grains/m$^3$ per day for more than 3 consecutive days. The pollen seasons of 2018 were from 13th March to 28th May and 20th August to 1st October; the pollen seasons of 2019 were from 2nd March to 3rd June and from 13th August to 2nd October.

**Clinical Evaluation**

The questionnaire included questions to provide information on a subject's general demographic characteristics (age, gender, ethnicity), as well as clinical information on nasal symptoms, ocular symptoms, duration and severity, smoking history and medical history. Symptoms were scored with 10-point visual analogue scale (VAS), including sneezing, rhinorrhea, nasal congestion and itching, conjulitis symptoms(watery eyes and gritty eyes), cough, and chest tightening.

**Statistical Analysis**

Data were analyzed using SPSS V.22 software package (IBM Corp., Armonk, NY, USA) and nomograms were performed by the R package version 3.6.1 (http://cran.us.r-project.org/). Descriptive statistics were used for demographic and general information of the study population. Chi-square analysis was performed to analyze the clinical evaluation. Univariate analysis was used, followed by the multivariate logistic regression, to evaluate associated factors of AR and NAR. A value of $p < 0.05$ was considered to be significant. A scoring system presented as nomograms for presence of AR based on the results of multivariable logistic regression analysis was then performed. Based on converting coefficient in multivariable logistic regression model, the nomogram presented a 0-100 scale for risk prediction. The predictive accuracy of nomograms was evaluated by concordance index (C index). Calibrations were performed with 1000 bootstrap samples.

**Results**

**Demographic and Survey Information of the Study Population**
The demographic characteristics of the study population are shown in Table 1. A total of 5174 outpatients with symptoms of rhinitis in the last 12 months were included in this study, including 1772 AR patients and 3402 NAR patients, having available data on demographic information and clinical evaluations. Overall, in the AR group, 813 (45.9%) were male and 959 (54.1%) were female and participants were on average 32.5 years old; while in the NAR group, 1596 (46.9%) were male and 1806 (53.1%) were female and participants were on average 34.5 years old. Significant difference was found in the ethnicity distribution between 2 groups (AR group, 93% Han and 6.4% minority; NAR group, 95.9% Han and 4.1% minority; P = 0.003). More patients acknowledged the history of food allergies in the AR group compared with the NAR group (8.5% versus 4.7%, P = 0.001).
|                        | Total N = 5174 | Pollen season group N = 2993 | Non pollen season group N = 2181 |
|------------------------|----------------|-----------------------------|----------------------------------|
|                        | n (%)          | n (%)                       | n (%)                            |
| **Gender**             |                |                             |                                  |
| Male                   | 813(45.9)      | 1596(46.9)                  | 494(47.9)                        |
| Female                 | 959(54.1)      | 1806(53.1)                  | 538(52.1)                        |
| **Ethnicity**          |                |                             |                                  |
| Han                    | 1659(93.6) **  | 3262(95.9) **               | 966(93.6)                        |
| Minority               | 113(6.4) **    | 140(4.1) **                 | 66(6.4)                          |
| **Age**                | 32.5 ± 8.2 *** | 34.5 ± 8.3 ***              | 32.7 ± 8.2 ***                   |
| Asthma                 | 203(11.5) ***  | 164(4.8) ***                | 115(11.1) ***                    |
| Atopic dermatitis      | 199(11.2)      | 349(10.3)                   | 123(11.9)                        |
| Food Allergies         | 150(8.5) ***   | 159(4.7) ***                | 94(9.1) ***                      |
| Family history of allergies | 489(27.6)  | 859(25.2)                   | 261(25.3)                        |
| Smoking habit          | 203(11.5)      | 449(13.2)                   | 131(12.7)                        |
| Duration of disease (month) | 63.0 ± 57.9 *** | 50.3 ± 54.5 ***            | 60.9 ± 57.9 **                   |
| Persistence            | 1024(57.8)     | 1917(56.3)                  | 568(55.0)                        |
| Disturb                | 1457(82.2) *** | 2619(77.0) ***             | 857(83.0) ***                    |

AR, allergic rhinitis; NAR, nonallergic rhinitis. *, P < 0.05; **, P < 0.01; ***, P < 0.001; AR group versus NAR group. #, P < 0.05; ##, P < 0.01; ###, P < 0.001; comparisons of AR or NAR group in different seasons.
|                          | Total N = 5174 | Pollen season group N = 2993 | Non pollen season group N = 2181 |
|--------------------------|----------------|-----------------------------|----------------------------------|
|                          | n (%)          | n (%)                       | n (%)                            |
| Nasal Symptoms           |                |                              |                                  |
| Itching                  | 5.3 ± 2.9      | 5.6 ± 2.8                   | 4.9 ± 3.0###                    |
| Sneezing                 | 6.3 ± 2.6      | 6.5 ± 2.4                   | 6.0 ± 2.8##                     |
| Rhinorhea                | 5.2 ± 3.0      | 5.5 ± 2.9                   | 4.9 ± 3.2                      |
| Congestion               | 5.5 ± 2.8***   | 5.1 ± 2.9***                | 5.3 ± 2.8                      |
| Conjunctivitis           | 598(33.7)***   | 969(28.5)***                | 228(30.8)#                     |
| Watery eyes              | 3.4 ± 3.1**    | 3.8 ± 3.1***                | 3.0 ± 3.0###                   |
| Gritty eyes              | 4.8 ± 3.2***   | 5.5 ± 3.1***                | 3.8 ± 3.2***                   |
| Symptoms of lower        |                |                              |                                  |
| respiratory tract        |                |                              |                                  |
| Cough                    | 2.5 ± 2.8***   | 2.7 ± 2.8***                | 2.0 ± 2.6                      |
| Chest tightness          | 1.9 ± 2.6      | 2.0 ± 2.6***                | 1.8 ± 2.6#                     |

AR, allergic rhinitis; NAR, nonallergic rhinitis. *, P < 0.05; **, P < 0.01; ***, P < 0.001; AR group versus NAR group. #, P < 0.05; ##, P < 0.01; ###, P < 0.001; comparisons of AR or NAR group in different seasons.

In total, 2993 patients initially visited during pollen seasons; the pollen seasons of 2018 were from 13th March to 28th May and 20th August to 1st October; the pollen season of 2019 which were from 2nd March to 3rd June and from 13th August to 2nd October. In the univariate analysis, in the pollen season group, more patients with asthma and food allergy in the AR patients compared with NAR patients (P < 0.001). Also, AR patients in the pollen season group tended to be younger and suffer longer in rhinitis than those with NAR (32.7 ± 8.2 years versus 34.4 ± 8.3 years, P < 0.001; 60.9 ± 57.9 months versus 49.1 ± 53.9 months, P < 0.001; respectively).

Out of pollen seasons, a total of 2181 patients with rhinitis visited. In the univariate analysis, similar to the results of the pollen season group, more patients with asthma and food allergy in AR patients compared with NAR patients (11.9% versus 6.2%, P < 0.001; 7.6% versus 5.1%, P = 0.023; respectively); AR patients tended to be younger and suffer longer in rhinitis than those in NAR group (32.1 ± 8.3 years versus 34.6 ± 8.7 years, P <
What’s more, the percentage of minorities in AR group was higher than in NAR group (6.3% versus 3.7%, P = 0.03). To be noted, patients in AR group with family history of allergies and smoking habit were significantly different with those in NAR group (30.8% versus 24.6, P = 0.002; 9.7% versus 13.7%, P = 0.007; respectively).

**Clinical evaluation**

In general, compared with patients with NAR, patients with AR suffered longer and experienced more severe symptoms, which could seriously affect the quality of life. Specifically, with higher scores of nasal congestion and 2 conjunctivitis symptoms in AR group, more patients with AR considered them seriously disturbed by the disease.

Similarly, in the univariate analysis, during pollen seasons, patients with AR tended to have more severe symptoms of nasal congestion, conjunctivitis symptoms (gritty eyes and watery eyes), cough and chest tightness. compared with patients with NAR (5.5 ± 2.8 versus 5.2 ± 2.8, P = 0.002; 5.5 ± 3.1 versus 4.1 ± 3.3, P < 0.001; 3.8 ± 3.1 versus 3.5 ± 3.2, P = 0.003; 2.7 ± 2.8 versus 2.0 ± 2.6, P < 0.001; 2.0 ± 2.6 versus 1.6 ± 2.4, P < 0.001).

However, in the non pollen season group, symptoms of lower airway such as cough and chest tightening, as well as scores of watery eyes were comparable between 2 groups (2.3 ± 2.8 versus 2.1 ± 2.8, P = 0.128; 1.8 ± 2.6 versus 1.7 ± 2.5, P = 0.359; 3.0 ± 3.0 versus 2.9 ± 3.1, P = 0.359). Only scores of nasal congestion and gritty eyes were found significantly different in 2 groups (AR group versus NAR group, 5.3 ± 2.8 versus 5.0 ± 3.0, P = 0.002; 3.8 ± 3.2 versus 3.2 ± 3.2, P = 0.001).

**Clinical characteristics of AR and NAR in different seasons**

The characteristics of patients with different phenotypes of chronic rhinitis are distinctive in different seasons. Patients with NAR in pollen seasons had more persistent, more severe ocular and nasal symptoms but shorter duration of disease than those out of pollen seasons. Similarly, patients with AR in pollen seasons had more severe ocular and nasal symptoms, more aggressive symptoms of lower respiratory tract, but less persistent and shorter duration of disease than those out of pollen seasons.

**Multivariate evaluation**

Furthermore, based on the above significant results of univariate analysis, we evaluated the associated factors of AR and NAR using the multivariate logistic regression, which was shown as Table 2. In the pollen season group, age distribution, the duration of rhinitis, comorbidity of asthma, food allergies and score of coughing were found significantly associated with AR (Fig. 1). Besides, out of pollen seasons, we found that ethnicity, age distributions, duration of rhinitis, comorbidity of asthma, food allergies, family history of allergy, together with scores of gritty eyes were associated factors of AR (adjusted OR: 1.171, 0.964, 1.004, 2.963, 1.849, 0.818 and 1.143, respectively; Fig. 1).
Table 2
Risk variables of allergic rhinitis during pollen seasons in the multiple logistic regression.

| Variables                          | Odds ratio | 95% CI for odds ratios |
|------------------------------------|------------|------------------------|
| Pollen season group                |            |                        |
| Age ***                            | 0.965      | 0.960–0.979            |
| Duration of disease ***            | 1.004      | 1.002–1.005            |
| Asthma ***                         | 2.636      | 1.918–3.603            |
| Food allergies ***                 | 1.803      | 1.430–2.676            |
| Cough ***                          | 1.043      | 1.036–1.097            |
| Non pollen season group            |            |                        |
| Age ***                            | 0.964      | 0.958–0.984            |
| Ethnicity *                        | 1.171      | 1.121–1.252            |
| Duration of disease ***            | 1.004      | 1.002–1.006            |
| Asthma ***                         | 2.963      | 1.635–3.720            |
| Food allergies ***                 | 1.849      | 1.380–2.767            |
| Family history of allergies *      | 0.818      | 0.725–0.920            |
| Gritty eyes ***                    | 1.143      | 1.059–1.230            |

CI, confidence index. *, P < 0.05; **, P < 0.01; ***, P < 0.001

Development of a Nomogram for identification of AR

Based on multivariate logistic model, we built two nomograms (Fig. 2&3) which included previously identified significant risk factors that could be easily acquired during clinical practice with predictive variables (pollen season group: age distribution, the duration of rhinitis, comorbidity of asthma, food allergies and score of coughing; non pollen season group: ethnicity, age distributions, duration of rhinitis, comorbidity of asthma, food allergies, family history of allergy and scores of gritty eyes), to assess their roles in predicting the risk of AR among outpatients with rhinitis. Calibration plot graphically showed the moderate predictive accuracy of the nomograms (Fig. 4).

Discussion

As mentioned before, studies focused on the epidemiological and clinical characteristic of chronic rhinitis strictly based on objective tests are limited. This is the first large-sample real-world study assessing clinical
characteristics in patients with chronic rhinitis based on both subjective and objective tests and develop a nomogram for predicting the risk of allergy among chronic rhinitis patient, providing a point of reference for clinical practice.

With a large population and a vast territory, China contributes a large number of patients with chronic rhinitis, for studying its epidemiology and clinical features. In recent years, with the emerging studies of the phenotyping of rhinitis, the concept has been acknowledged that rhinitis is an umbrella term defining a set of upper airway disease with similar nasal symptoms but with distinctive etiologies and various features. Constrained by the lack of objective tests in the relative studies, the prevalence of chronic rhinitis, especially prevalence of NAR, is still unclear. Without doubt, the global prevalence of AR is markedly increasing over the recent years. It is estimated that AR and NAR affect 20%-30% and 17%-52% of the population. Unlike AR, NAR is a heterogeneous disease characterized by nasal symptoms but with negative specific allergen tests. Clinically, the diagnosis of NAR is dependent on elaborate medical history and exclusion of positive objective allergen tests. Nasal hyperreactivity, defined by a nasal abnormal reaction towards stimuli, used to be considered as the prominent feature of NAR only. However, a study later confirmed the prevalence of nasal hyperreactivity in patients with AR. A large amount of patients with merely an epidemiologic diagnosis of ‘AR’ do not have positive objective results, not only in developing countries, but also in developed countries. Precisely because the clinical manifestations are so confusing that it is difficult to distinguish AR and NAR in clinical practice, it is essential to evaluate the pattern of outpatients with chronic rhinitis based on a large-sampled real-world study.

In our study, among outpatients with chronic rhinitis that visited hospital seeking medical care in 2 years, the percentage of AR was around 34% (total, 34.25%; pollen season group, 34.48%; non pollen season group, 33.93%) and the percentage of NAR was around 66% (total, 65.75%; pollen season group, 65.52%; non pollen season group, 66.07%). It's clear that in the real-world clinical practice, patients with NAR even outnumbered those with AR. Consistently, in fact, approximately half of the adult patients with chronic rhinitis are deemed to have NAR. Our results indicated a fact that currently NAR was prevalent but at least grossly underemphasized and more attention should be paid into this specific phenotype of chronic rhinitis. In this sense, the nomograms developed in this study might be useful in clinical practice.

Besides, in this study, we found that patients with AR was significantly younger than those with NAR, regardless the visiting seasons. Our result is consistent with the previous study, where Wuthrich et al. reported that the prevalence of AR in the elderly (age≥60) was lower than in the younger age group (age ≤ 60). In a retrospective study, Wang et al. demonstrated that increasing age was associated with a decreased positivity in sIg27, which might be the cause of our result. Yet, other researches showed that both AR and NAR are more common among the elderly than the younger population.

In this study, we also found the significant difference in comorbidity of asthma, food allergies and symptoms of lower respiratory tract and conjunctivitis between AR and NAR group. Several previous studies have reported that family history of allergies, comorbidity of asthma and other allergic diseases were associated with increased risk for AR and NAR. AR, an IgE-mediated disease, is associated with comorbid asthma and other allergic diseases, which are also IgE-mediated diseases. Although regardless of different seasons,
the comorbidity of asthma was higher in AR patients than NAR patients, differences on symptoms of lower respiratory tract were only found significant during pollen seasons between both groups. This result indicates that during pollen seasons, AR patients with comorbidity of asthma suffer from more severe symptoms of lower respiratory tract than those out of pollen seasons. Similarly, the comorbidity of conjunctivitis was higher in AR patients than NAR patients regardless of seasons. However, differences on both symptoms of conjunctivitis (watery eyes and gritty eyes) were found significant during pollen seasons between both groups, while only one symptom was significantly different out of pollen seasons. As a matter of fact, Perkin et al. reported that allergic conjunctivitis was more common in patients with seasonal symptoms30.

The findings of our current study, however, have some limits. Firstly, as mentioned above, as a real-world study, the subjects we included were limited by hospital operation process, national holidays, and so on. Secondly, since China has a large population and a vast territory, our results could only demonstrate the characteristics of patients with chronic rhinitis in the northern China. Thirdly, large-scale, multi-center studies are needed to further confirm and improve the results of the present study.

Conclusions

In summary, this study has provided preliminary information of the discrimination of AR and NAR in outpatients of chronic rhinitis according to both subjective and objective results of real-world data. In general, AR patients that visited during pollen seasons would experience more severe symptoms of conjunctivitis and lower respiratory tract. The characteristics of patients with different phenotypes of chronic rhinitis are distinctive in different seasons and the developed monogram in this study might be beneficial for clinical practice.

Abbreviations

AR, allergic rhinitis; NAR nonallergic rhinitis; PAR, perennial allergic rhinitis; SAR, seasonal allergic rhinitis; sIgE: specific immunoglobulin E.

Declarations

Consent for publication: Not applicable

Availability of data and material: We would like to provide the raw data to support the information presented in this publication.

Competing interests: All authors declare no competing interests.

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Author contributions: HY and ZY collected the data. All authors performed statistical analyses, read and approved the final manuscript.

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**Figures**
Figure 1

Multivariate analysis on the demographical and clinical characteristics of AR and NAR. A, age distribution in pollen season group. B, age distribution in non-pollen season group. C, duration of rhinitis in the pollen season group. D, duration of rhinitis in non-pollen season group. E, scores of coughing during pollen seasons. F, scores of eye itching out of pollen seasons. G, comorbidity of asthma and food allergy in pollen season group. H, comorbidity of asthma and food allergies, and family history of allergies in non-pollen season group.
Figure 2
Nomogram for predicting the risk of allergic rhinitis among outpatients in the pollen season group. AR, allergic rhinitis.

Figure 3
Nomogram for predicting the risk of allergic rhinitis among outpatients in the non pollen season group. AR, allergic rhinitis.
Figure 4

Calibration curve of the nomograms for evaluating the predictive risks of allergic rhinitis among outpatients (A, during non-pollen season; B, during pollen seasons).