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Developing nomograms for identifying allergic rhinitis among chronic rhinitis: A real-world study

Yanran Huang[a,1], Chengshuo Wang[a,1], Yuan Zhang[a,b,c]** and Luo Zhang[a,b,c]*

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 were 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 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. Additionally, in the non-pollen season group, we found that ethnicity, age distributions, duration of rhinitis, comorbidity of asthma, food allergies, and 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 acquired easily 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 nomogram in this study might be beneficial for clinical practice.

Keywords: Allergic rhinitis, Real-world study, Nomogram, Nonallergic rhinitis

[a]Department of Otolaryngology Head and Neck Surgery, Beijing TongRen Hospital, Capital Medical University, Beijing, China
*Corresponding author. Beijing Institute of Otolaryngology, No. 17, HouGouHuTong, DongCheng District, Beijing, 100005, PR China. E-mail: dr.luozhang@139.com
**Corresponding author. Beijing Institute of Otolaryngology, No. 17, HouGouHuTong, DongCheng District, Beijing, 100005, PR China. Email: summer_zhang1211@126.com
[1] These authors contributed equally to this work.

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INTRODUCTION

Chronic rhinitis, a common inflammatory disease of nasal mucosa, usually characterized with 2 or more nasal symptoms such as nasal congestion, rhinorrhea, sneezing and itching for more than 12 weeks per year.[1] With profound 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 its etiology, chronic rhinitis is divided into 2 phenotypes, allergic rhinitis (AR) and nonallergic rhinitis (NAR).

AR affects 10%–40% of the global population,[3] while the prevalence of NAR is reported to be approximately 7% in American population.[4] An epidemiological study 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 instance, patients with AR are usually accompanied with more severe conjunctivitis symptoms and higher percentage of lower airway involvement, compared with patients with NAR.[6] Moreover, AR is further classified into 2 phenotypes according to different onset period, seasonal AR (SAR) and perennial AR (PAR). 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 essential cause of SAR.

As mentioned above, the discrimination between AR and NAR should be based on the results of allergen sensitization; yet only a limited number of studies have included objective methods such as skin prick test and serum sIgE test, which is responsible for the inaccurate data of prevalence.[7]

In daily clinical practice, only patients suffering from 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. Normally, outpatients who seek 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.[8] However, for the patients with NAR, whose symptoms are more likely to be perennial and associated with environmental factors,[9] 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 patients, 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 medical care from January 2018 to December 2019 were included. In this retrospective cross-sectional study, subjects were defined as patients with chronic rhinitis if they had more than 2 of the 4 following typical symptoms of rhinitis; including sneezing, rhinorrhea, nasal congestion, and itching for more than 12 weeks, excluding the effect of upper respiratory infections. Detailed medical history was acquired and physical examination by means of anterior rhinoscopy and nasal endoscopy was performed by experienced doctors. Patients with clinical-diagnosed chronic rhinosinusitis (2 or more typical symptoms including nasal blockage, purulent nasal discharge, facial pain, and reduction of smell; visible sign of nasal polyps or mucopurulent discharge) and severe anatomical abnormities were excluded from the current study. 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. Previous medical history such as the diagnosis of asthma and atopic dermatitis was in accordance of the medical history provided by the patients themselves and the previously existing diagnosis in the electronic medical record system of the hospital.

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 (*Dermatophagoides farina* and *Dermatophagoides pteronyssinus*), seasonal allergens (ragweed, mugwort, humulus, willow, poplar, and elm), molds, animal (cat and dog) dander, and cockroach (sIgE $\geq$ 0.7KUA/L). Based on the results of allergen sensitization, subjects were further classified into either AR or NAR group; while the subjects showing positive serum allergen sensitization defined as the AR group, and the subjects with negative serum allergen sensitization defined as the 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 $\geq$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 13 March to 28 May and 20 August to 1 October; the pollen seasons of 2019 were from 2 March to 3 June and from 13 August to 2 October. During pollen seasons, the mean pollen concentration was 133.5 $\pm$ 199.2 grains/m;[3] out of pollen seasons, the mean of total concentration was 8.22 $\pm$ 13.5 grains/m.[3]

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 chronic rhinitis 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

	Total N = 5174 n (%)		Pollen season group N = 2993 n (%)		Non pollen season group N = 2181 n (%)	
	AR N = 1772	NAR N = 3402	AR N = 1032	NAR N = 1961	AR N = 740	NAR N = 1441
Gender						
Male	813(45.9)	1596(46.9)	494(47.9)	971(49.5)	313(43.1)	625(43.4)
Female	959(54.1)	1806(53.1)	538(52.1)	990(50.5)	414(56.9)	816(56.6)
Ethnicity						
Han	1659(93.6)[b]	3262(95.9)[b]	966(93.6)	1875(95.6)	693(93.6)	1387(96.3)[a]
Minority	113(6.4)[b]	140(4.1)[b]	66(6.4)	86(4.4)	47(6.3)	54(3.7)[a]
Age	32.5 ± 8.2[c]	34.5 ± 8.3[c]	32.7 ± 8.2[c]	34.4 ± 8.3	32.1 ± 8.3	34.6 ± 8.7[c]
Asthma	203(11.5)[c]	164(4.8)[c]	115(11.1)[c]	74(3.8)	88(11.9)	90(6.2)[c]
Atopic dermatitis	199(11.2)	349(10.3)	123(11.9)	193(9.8)	76(10.3)	156(10.8)
Food Allergies	150(8.5)[c]	159(4.7)[c]	94(9.1)[c]	85(4.3)	56(7.6)	74(5.1)[a]
Family history of allergies	489(27.6)	859(25.2)	261(25.3)	5.4(25.7)	228(30.8)	355(24.6)[b]
Smoking habit	203(11.5)	449(13.2)	131(12.7)	251(12.8)	72(9.7)	198(13.7)[b]
Duration of disease (month)	63.0 ± 57.9[c]	50.3 ± 54.5[c]	60.9 ± 57.9[c]	49.1 ± 53.9[d]	66.0 ± 57.8[e]	51.9 ± 55.3[c]
Persistence	1024(57.8)	1917(56.3)	568(55.0)	1069(54.5)[e]	456(61.6)[d]	848(58.8)
Disturbance	1457(82.2)[c]	2619(77.0)[c]	857(83.0)[c]	1521(77.6)	600(81.1)	1098(76.2)[b]
Nasal Symptoms						
Itching	5.3 ± 2.9	5.3 ± 3.0	5.6 ± 2.8	5.4 ± 2.9[f]	4.9 ± 3.0[f]	5.1 ± 3.0
Sneezing	6.3 ± 2.6	6.3 ± 2.8	6.5 ± 2.4	6.4 ± 2.6[d]	6.0 ± 2.8[e]	6.1 ± 2.9
Rhinorrhea	5.2 ± 3.0	5.3 ± 3.1	5.5 ± 2.9	5.4 ± 3.0[d]	4.9 ± 3.2	5.2 ± 3.2
Congestion	5.5 ± 2.8[c]	5.1 ± 2.9[c]	5.5 ± 2.8[b]	5.2 ± 2.8[d]	5.3 ± 2.8	5.0 ± 3.0[b]
Conjunctivitis	598(33.7)[c]	969(28.5)[c]	370(35.9)[b]	606(30.9)[f]	228(30.8)[d]	363(25.2)[b]

Watery eyes	3.4 ± 3.1[b]	3.2 ± 3.1[b]	3.8 ± 3.1[c]	3.5 ± 3.2[f]	3.0 ± 3.0[f]	2.9 ± 3.1
Gritty eyes	4.8 ± 3.2[c]	3.7 ± 3.3[c]	5.5 ± 3.1[c]	4.1 ± 3.3[f]	3.8 ± 3.2[f]	3.2 ± 3.2[c]
Symptoms of lower respiratory tract						
Cough	2.5 ± 2.8[c]	2.1 ± 2.7[c]	2.7 ± 2.8[c]	2.0 ± 2.6	2.3 ± 2.8[d]	2.1 ± 2.8
Chest tightness	1.9 ± 2.6	1.6 ± 2.4	2.0 ± 2.6[c]	1.6 ± 2.4	1.8 ± 2.6[d]	1.7 ± 2.5
Sensitization rate to inhaled allergens						
House dust mites	964 (54.4)	-	517(50.1)	-	447(60.4)[d]	-
Seasonal pollens	1139(64.3)	-	707(68.5)	-	432(58.4)[f]	-
Animal dander	530 (29.9)	-	285(27.6)	-	245(33.1)[d]	-
Cockroach	132(7.4)	-	80(7.8)	-	52(7.0)	-
Molds	31 (1.7)	-	14(1.4)	-	17(2.3)	-

Table 1. Demographic and Clinical characteristics of the Study Population. *AR, allergic rhinitis; NAR, nonallergic rhinitis. a. $P < 0.05$. b. $P < 0.01$. c. $P < 0.001$; AR group versus NAR group. d. $P < 0.05$. e. $P < 0.01$. f. $P < 0.001$; comparisons of AR or NAR group in different seasons.*

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%, $P = 0.001$). Among the panel of aeroallergen mixture, the 3 most common inhaled allergens in the AR group are seasonal pollens (64.3%), house dust mites (54.4%), and animal dander (29.9%). Significantly higher sensitization rate to seasonal pollen was found in the AR group during pollen season (68.5% versus 58.4%, $P < 0.001$). However, significantly higher sensitization rate to several perennial inhaled allergens including house dust mites and animal dander was found in the AR group out of the pollen seasons (60.4% versus 50.1%, $P = 0.013$; 33.1% versus 27.6%, $P = 0.012$; respectively).

In total, 2993 patients initially visited during pollen seasons; the pollen seasons of 2018 were from 13 March to 28 May and 20 August to 1 October; the pollen season of 2019 which were from 2 March to 3 June and from 13 August to 2 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 $\pm$ 8.2 years versus 34.4 $\pm$ 8.3 years, $P < 0.001$; 60.9 $\pm$ 57.9 months versus 49.1 $\pm$ 53.9 months, $P < 0.001$; respectively).

Out of pollen seasons, a total of 2181 patients with chronic 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 the NAR group (32.1 $\pm$ 8.3 years versus 34.6 $\pm$ 8.7 years, $P < 0.001$; 66.0 $\pm$ 57.8 months versus 51.9 $\pm$ 55.3 months, $P < 0.001$; respectively). Moreover, the percentage of minorities in the AR group was higher than in the NAR group (6.3% versus 3.7%, $P = 0.03$). To be noted, patients in the AR group with family history of allergies and smoking habit were significantly higher compared with those in the 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 quality of life. Specifically, with more severe symptoms (nasal congestion and 2 conjunctivitis symptoms), more patients with AR reported to be seriously disturbed in daily life.

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 $\pm$ 2.8 versus 5.2 $\pm$ 2.8, $P = 0.002$; 5.5 $\pm$ 3.1 versus 4.1 $\pm$ 3.3, $P < 0.001$; 3.8 $\pm$ 3.1 versus 3.5 $\pm$ 3.2, $P = 0.003$; 2.7 $\pm$ 2.8 versus 2.0 $\pm$ 2.6, $P < 0.001$; 2.0 $\pm$ 2.6 versus 1.6 $\pm$ 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 the 2 groups (2.3 $\pm$ 2.8 versus 2.1 $\pm$ 2.8, $P = 0.128$; 1.8 $\pm$ 2.6 versus 1.7 $\pm$ 2.5, $P = 0.359$; 3.0 $\pm$ 3.0 versus 2.9 $\pm$ 3.1, $P = 0.359$). Only scores of nasal congestion and gritty eyes were found significantly different in the 2 groups (AR group versus NAR group, 5.3 $\pm$ 2.8 versus 5.0 $\pm$ 3.0, $P = 0.002$; 3.8 $\pm$ 3.2 versus 3.2 $\pm$ 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 by 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, and 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).

Development of a nomogram for identification of AR

Based on multivariate logistic model, we built 2 nomograms (Figs. 2 and 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 epidemical 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.

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

Table 2. Risk variables of allergic rhinitis during pollen seasons in the multiple logistic regression. *CI, confidence index. a. $P < 0.05$. b. $P < 0.001$*

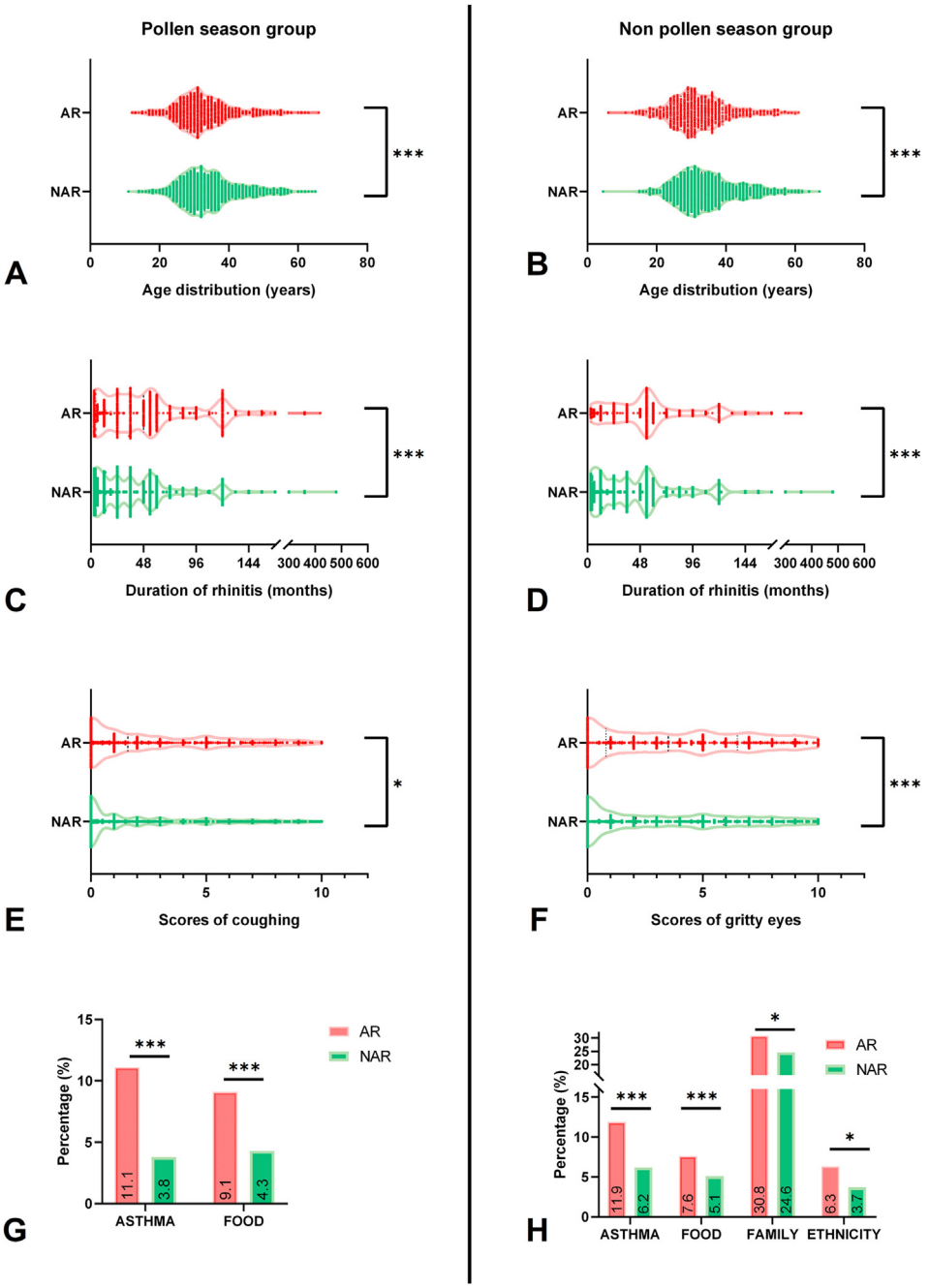

Fig. 1 Multivariate analysis on the demographical and clinical characteristics of AR and NAR. A, age distribution in pollen season group. B, age distribution in non-pollen season group. C, duration of rhinitis in the pollen season group. D, duration of rhinitis in non-pollen season group. E, scores of coughing during pollen seasons. F, scores of gritty eyes in non-pollen season group. 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

Chronic rhinitis is defined as a symptomatic mucosal disease characterized by more than 2 typical nasal symptoms, including nasal blockage, anterior or posterior rhinorrhea, sneezing and itching for no less than 1 h per day and for over 12 weeks per year. In recent years, both clinical presentations (phenotypes) and underlying pathophysiological mechanisms (endotypes) of chronic rhinitis have aroused scientists' interest since the high heterogeneities of the disease make it difficult to achieve precise diagnosis and treatment. Normally, based on the etiological factors, 3 most

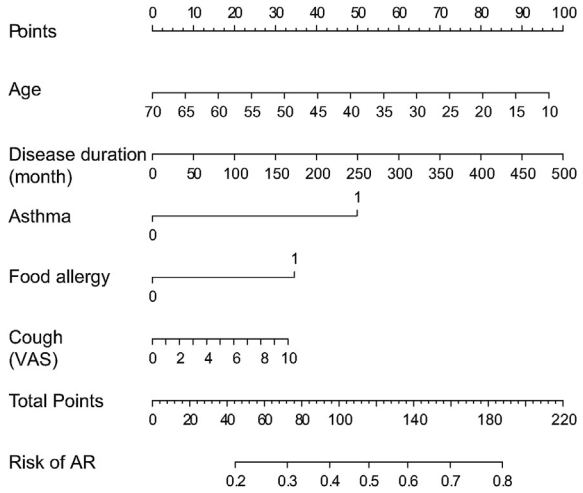

Fig. 2 Nomogram for predicting the risk of allergic rhinitis among outpatients in the pollen season group. AR, allergic rhinitis

widely accepted rhinitis subgroups are AR, NAR, and infectious rhinitis. Infectious rhinitis often presents as acute and self-limiting viral driven disease such as common cold, or prolonged inflammation extending in the nasal cavities such as chronic rhinosinusitis. On the other hand, endotypes of rhinitis are based on distinct mechanistic pathways, such as IgE-mediated inflammation, non-IgE inflammation, neurogenic inflammation and structural abnormalities. In the current study, patients with severe anatomical abnormalities and infectious rhinitis were excluded since the differentiation between infectious rhinitis and non-infectious rhinitis (AR and NAR) is relatively accurate based on detailed history and careful physical examination. Additionally, another phenotype of chronic rhinitis called local allergic rhinitis (LAR) is relatively difficult to clinically discriminate and usually underdiagnosed since its clinical manifestation is similar with AR. LAR is characterized by negative skin prick test and/or undetectable serum sIgE but positive nasal allergen provocation test.[10]

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.[11] 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 recent years.[12,13] It is estimated that AR and NAR affect 20%–30% and 17%–52%

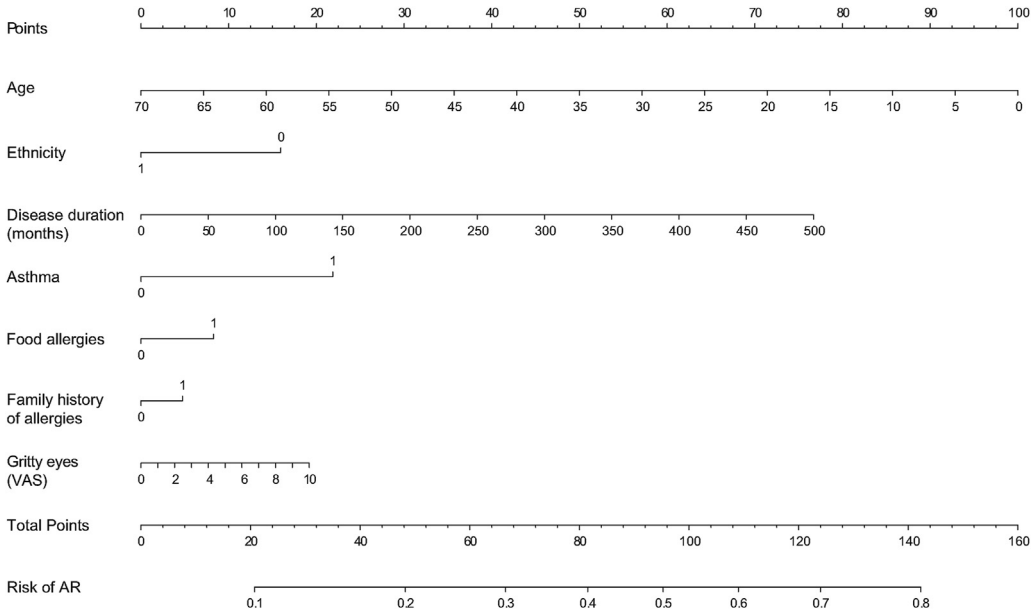

Fig. 3 Nomogram for predicting the risk of allergic rhinitis among outpatients in the non pollen season group. AR, allergic rhinitis

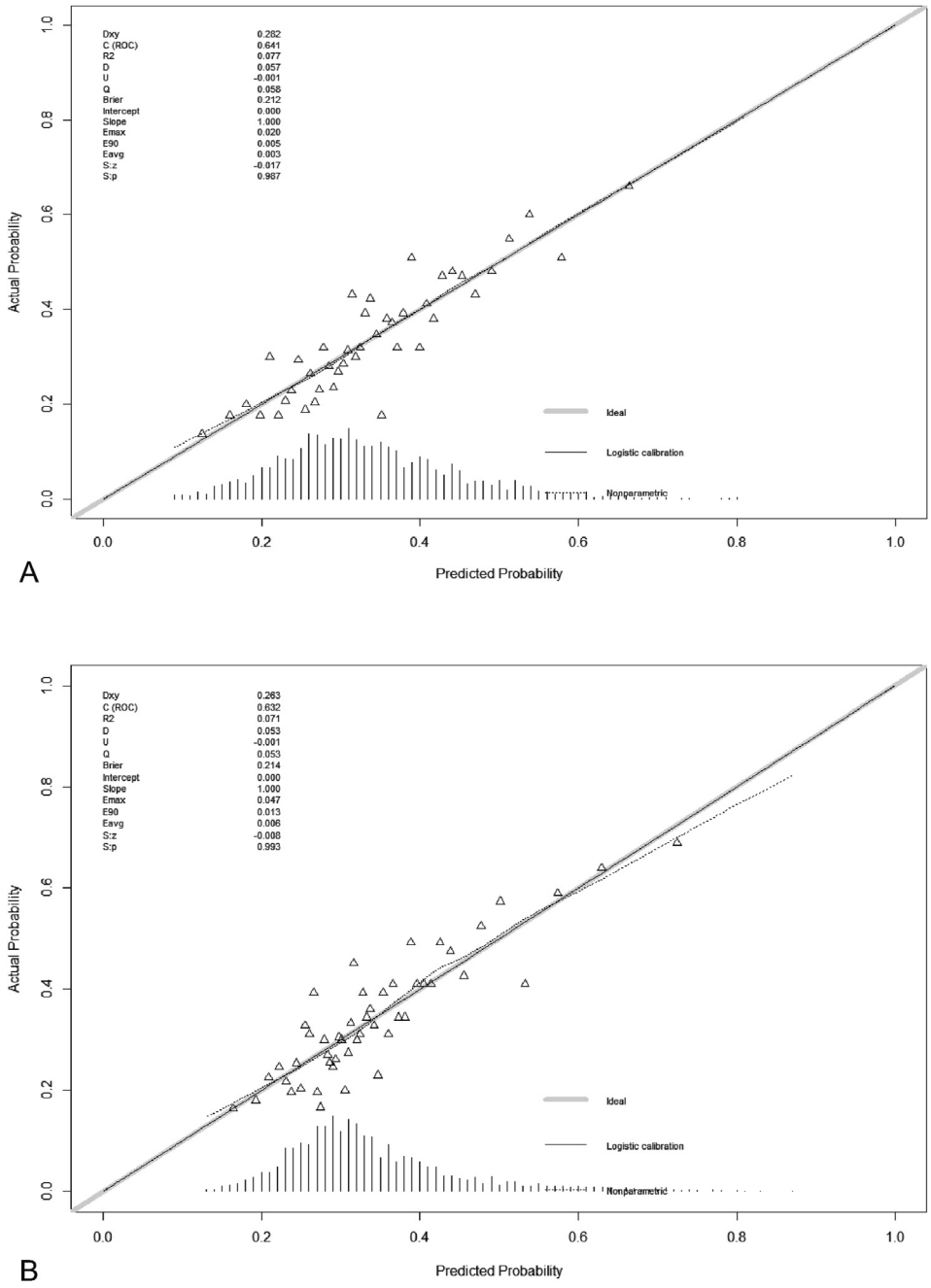

Fig. 4 Calibration curve of the nomograms for evaluating the predictive risks of allergic rhinitis among outpatients (A, during non-pollen season; B, during pollen seasons)

of the population.[11,14–16] Unlike AR, NAR is a heterogeneous disease characterized by nasal symptoms but with negative specific allergen tests.[17] 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.[18] However, a study later confirmed the prevalence of nasal hyperreactivity in patients with AR.[18] 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.[19–24] 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-sample real-world study. As a real world study, the enrolled subjects are representative as the real patient population in daily clinical practice, providing useful information of authentic clinical characteristics. Currently, studies focus on the clinical characteristics are relatively scarce. In the present study, we found that patients with NAR suffered from severer symptoms in pollen seasons, indicating as a possibly unspecific stimuli, pollens account for the aggravation of both nasal and ocular symptoms in patients with NAR (but not lower airway symptoms). Unlike patients with AR, whose symptoms of lower airway (including cough and chest tightness) exacerbated in the pollen season, patients with NAR reported comparable lower airway symptoms regardless of seasons. A population-based, cross sectional study in Denmark reported that NAR (diagnosed by serum sIgE) was associated with asthma (odds ratio = 2.51). More studies regarding the underlying mechanism especially among different ethnicities are needed in the future to clarify the association.[25]

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 is 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.[6,26,27] 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 of the visiting seasons. To be noted, although the statistical index did meet significance, the age increment between the AR and NAR groups was around 2 years, which was indeed not so obvious particular in clinical practice. Previous studies reported that AR was more common in young people than the elder population which might be due to the specific IgE level diminished in aging individuals.[28] A similar trend could be observed in our data that aging population in the NAR group was more common than those in the AR group (Fig. 1A&B). A small increment shall be due to the large sample in which the major age population ranged from 20 to 40 years. Wuthrich et al reported that the prevalence of AR in the elderly (age > 60) was lower than in the younger age group (age≤60).[29] In a retrospective study, Wang et al demonstrated that increasing age was associated with a decreased positivity in sIg,[30] 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.[31,32]

In this study, we also found the significant difference in comorbidity of asthma, food allergies, and symptoms of lower respiratory tract and conjunctivitis between the AR and NAR groups. 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.[5,11] 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 symptoms.[33]

Based on the current results, clinical characteristics of both NAR and AR in different seasons present distinctive features, which might be helpful in better differential diagnosis in clinical practice. The developed nomograms map the predicted probabilities of AR into points scaled from 0 to 100 within a user-friendly interface. With these easily obtained data, clinicians and patients could calculate the risk of AR prior to further examinations. For instance, for patients with low risk of AR, high risk of NAR should be noticed and, therefore, targeted further examination such as nasal provocation tests should be considered. Especially for the patients that are reluctant to perform specific IgE tests, empirical treatment could be applied. Combination therapy with an intranasal antihistamine and a topical corticosteroid is the most effective treatment for most patients with NAR.[34] The combination of topical corticosteroids and oral antihistamine is the best solution for SAR and intranasal corticosteroids alone is recommended to treat PAR.[3]

A recent study found that allergen homologous group was responsible for the prolonged symptomatic period.[35] The concept of pollen food allergy syndrome was put forward in 1995 for better describing the symptoms of food allergies in aeroallergen-allergic patients,[36] which could be the reasons why SAR patients suffer from nasal discomforts even out of the pollen seasons. In this study, we classified the patients into AR/NAR groups based on the serum specific IgE and defined the pollen season with the pollen counts. In the current study, we did not classify patients with SAR and PAR based on the specific allergen. Without doubt, further investigation on specific allergens especially for those with homologous cross-reactivities should be carried out in the future.

The findings of our current study, however, have some limits. First, as mentioned above, as a real-world study, the subjects we included were limited by hospital operation process, national holidays, and so on. Second, 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 region of China. Third, large-scale, multi-center studies are needed to further confirm and improve the results of the present study. Last, limited by further precise examination such as nasal provocation test, phenotypes such as LAR could not be discriminated in this 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.

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Consent for publication

All authors agreed to publication of the work.

Author contributions

HY and ZY collected the data. All authors performed statistical analyzed, read and approved the final manuscript.

Availability of data and material

We would like to provide the raw data to support the information presented in this publication.

Ethical approval

The study protocol was approved by the Ethics Committee of Beijing Tongren Hospital 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.

Declaration of competing interest
All authors declare no competing interests.

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Author details
[a]Department of Otolaryngology Head and Neck Surgery, Beijing TongRen Hospital, Capital Medical University, Beijing, China. [b]Beijing Key Laboratory of Nasal Diseases, Beijing Institute of Otolaryngology, Beijing, China. [c]Department of Allergy, Beijing TongRen Hospital, Capital Medical University, Beijing, China.

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