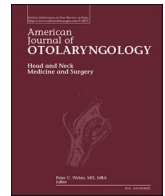




Contents lists available at ScienceDirect

American Journal of Otolaryngology–Head and Neck Medicine and Surgery

journal homepage: www.elsevier.com/locate/amjoto

Risk factors for asthma in patients with allergic rhinitis in eastern China

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ARTICLE INFO

Keywords:

Allergic rhinitis
Asthma
Risk factor
Skin-prick tests

ABSTRACT

Background: Asthma is one of the most common chronic diseases among children and adults and can lead to a high health and socioeconomic burden. Allergic rhinitis (AR) often precedes the development of asthma. This study aims to clarify the risk factors for concurrent asthma in patients with AR in eastern China.

Methods: A cross-sectional study of 3739 patients with AR was performed in eastern China. Patients meeting the criteria for AR were evaluated using a skin-prick test (SPT) of 16 common aeroallergens. A logistic regression analysis was used to assess the risk factors of asthma in patients with AR.

Results: The prevalence of asthma in patients with AR was 14.23%. The patients sensitive to dust mites (*D. farinae* and *D. pteronyssinus*) had the highest prevalence (76.84% and 73.68%). A significant difference was found in sensitization to four types of allergens (*D. farinae*, *D. pteronyssinus*, dog dander, *Alternaria alternata*) in patients with AR with and without asthma. The strongest risk factor for asthma in patients with AR was an allergy to *Aspergillus fumigatus* (adjusted OR, 2.42; 95% CI, 1.50–3.90), followed by allergy to *D. pteronyssinus* (adjusted OR, 2.06; 1.30–3.27), and allergy to dog dander (adjusted OR, 1.92; 1.24–2.97). Various risk factors that are independently associated with asthma in patients with AR were found in different age groups.

Conclusions: We observed a difference in risk factors in patients with AR with and without asthma. Clarifying the risk factors for asthma in patients with AR is important and may be beneficial to the optimal interventions of asthma.

1. Introduction

Allergic rhinitis (AR) has a close epidemiological relationship with asthma. About 40% of children with AR have concurrent asthma, and 60–80% with asthma have AR. Many epidemiological studies have shown a link between rhinitis and asthma, and rhinitis often precedes the development of asthma [1]. In addition to more impact on patients' health and quality of life, AR was associated with poorer control of asthma symptoms [2–4]. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines recommend that patients with asthma be evaluated for the presence of AR and a combined treatment strategy for asthma and AR be administered. A recent cross-sectional study of 203 asthmatic children reported that allergic rhinitis was common in asthmatic patients and had negative effects on the prevention and treatment of asthma [2]. Exacerbation of asthma symptoms and the need to present

to an emergency room for asthma were also associated with AR. A cross-sectional study of moderate/severe asthma treated with inhaled corticosteroids (ICS) in children and adolescents suggests that concurrent AR may be a risk factor for the use of emergency care services in asthmatic patients [5].

Treatment of AR in patients with asthma can reduce up to 80% of asthma-related health risks. Because of the co-existence and similar pathophysiological features of AR and asthma, both are considered to cause continuous inflammation of the upper and lower airways [6]. There are many explanations for the occurrence of asthma in patients with AR, however, it is still unclear why only some cases of AR develop asthma. Risk factors for asthma in AR are likely distinct from those for AR or asthma alone. It is important to clarify the risk factors for asthma in patients with AR to help identify the optimal interventions of asthma.

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<https://doi.org/10.1016/j.amjoto.2022.103426>

Received 22 November 2021;

Available online 10 April 2022

0196-0709/© 2022 Published by Elsevier Inc.

2. Materials and methods

2.1. Study design

A total of 3739 patients with AR were enrolled at Qilu Hospital of Shandong University and the Second Hospital of Shandong University from January 2017 to June 2020. AR was defined by the patient's case history, significant nasal symptoms (sneezing, rhinorrhea, itchy nose, and nasal congestion) and signs, and a positive atopic status. Patients meeting the criteria for AR [7] were evaluated using a skin-prick test (SPT) of common inhalant allergens. Asthma was defined as self-reported physician-diagnosed asthma and either reported asthma symptoms in the past year or current use of medications for asthma [8].

Informed written consent was obtained from all patients. Medical records were used to access information on age, sex, and relevant family history. The investigator analyzed the positive results of allergens and counted the total number of allergens sensitized. Approval for this study was obtained from the institutional review board (IRB) of Qilu Hospital of Shandong University and the Second Hospital of Shandong University, China.

2.2. Skin-prick tests

Skin-prick tests were performed for the following 16 common aeroallergens: *Dermatophagoides pteronyssinus* (*D. pteronyssinus*), *Dermatophagoides farinae* (*D. farinae*), giant ragweed, dog dander, *Alternaria alternata*, *Aspergillus fumigatus*, *Penicillium*, *Humulus scandens*, cat dander, *Alnus incana*, *Platanus orientalis*, *Triticum sativum*, *Robinia pseudoacacia*, *Artemisia vulgaris*, cockroach and *Taraxacum*. Standardized allergen extracts and control solutions were obtained from the ALK-Abello Co. (Horsholm, Denmark).

Positive histamine and negative saline controls were used in all cases. A positive response was defined as a wheal at least 3 mm greater in diameter than that of the negative control. Wheal reaction was measured 15 min after SPT was placed. Participants with one or more positive reactions were considered atopic.

2.3. Statistical analysis

All data were expressed in median (25%–75%) and analyzed using SPSS software (version 18.0, SPSS, Chicago, IL). The chi-square test was used to assess the difference between patients with AR with and without asthma. A logistic regression analysis was used to assess risk factors of patients with or without concomitant asthma, and the result was presented as the odds ratio (OR) and a 95% confidence interval (CI). Values of $p < 0.05$ were considered statistically significant.

3. Results

3.1. Patient characteristics

Patient characteristics are shown in Table 1. A total of 3739 patients with AR, 2002 (53.54%) males and 1734 (46.46%) females were recruited for this study. The median age of the group was 28 (15–40) years (range: 5–64 years). 532 (14.23%) of the patients were found to have concomitant asthma.

The age of the patients with AR without asthma (28, 16–39) seemed to be younger than those with asthma (31, 14–44, $p = 0.01$). A significant difference number of AR patients with and without asthma was observed in different age groups (5–18 years; 19–45 years, older than 46 years), but not in genders. There was a significant difference in the number of positive aeroallergens in patients with AR with and without asthma. 308 (9.60%) patients with AR without asthma only tested positive for one allergen while 25 (4.70%) patients with AR with asthma did. More than 6 positive aeroallergens were identified in 18.86% patients without asthma and 25.19% patients with asthma. There was no

Table 1
Patients characteristic.

	Total patients n (%)	With asthma n (%)	Without asthma n (%)	P Value
n (%)	3739	532 (14.23)	3207 (85.77)	
Age (yr)	28 (15–40)	31 (14–44)	28 (16–39)	0.01
Age group				0.0001
5–18	1080 (28.88)	164 (30.83)	916 (28.56)	
19–45	2083 (55.71)	252 (47.37)	1831 (57.09)	
≥46	576 (15.41)	116 (21.80)	460 (14.34)	
No. of positive aeroallergens				0.0001
1	333 (8.91)	25 (4.70)	308 (9.60)	
2–5	2667 (71.33)	373 (70.11)	2294 (71.53)	
≥6	739 (19.76)	134 (25.19)	605 (18.86)	
Gender				0.072
Male	2002 (53.54)	282 (53.00)	1720 (53.63)	
Female	1737 (46.46)	250 (47.00)	1487 (46.37)	
Family history of AR				0.108
Yes	1346 (36.0)	175 (32.89)	1171 (36.51)	
No	2393 (64.00)	357 (67.11)	2036 (63.49)	

difference in the percentage of positive family history between patients with AR with and without asthma.

3.2. Prevalence of common aeroallergen sensitization in patients with AR

Among the allergens tested, we found that clinically relevant sensitization to dust mites (*D. farinae* and *D. pteronyssinus*) was the most prevalent (76.84% and 73.68%). The prevalence of sensitization to the other six allergens was 35.60% (cockroach), 24.04% (giant ragweed), 22.95% (*Taraxacum*), 20.17% (*Artemisia vulgaris*), 19.28% (*Robinia pseudoacacia*), 17.65% (*Platanus orientalis*), 15.65% (*Alnus incana*), 13.69% (*Alternaria alternata*), 12.41% (Cat dander) and 11.50% (*Triticum sativum*).

A significant difference was found in sensitization to six types of allergens in patients with AR with and without asthma. The percentages of patients with AR with asthma sensitized to *D. farinae* (84.02%), *D. pteronyssinus* (81.95%), dog dander (13.16%), *Alternaria alternata* (18.61%), *Aspergillus fumigatus* (11.65%), and *Penicillium* (15.60%) were higher than patients with AR without asthma (75.65%, 72.31%, 8.42%, 12.88%, 5.43%, 10.48%). (Table 2).

3.3. Multivariate analysis of risk factors for asthma comorbidity

By performing a multivariate logistic regression analysis on the entire study population (Table 3), we found that the strongest risk factor for concomitant asthma in patients with AR was allergy to *Aspergillus fumigatus* (adjusted OR, 2.42; 95% CI, 1.50–3.90), followed by allergy to *D. pteronyssinus* (adjusted OR, 2.06; 95% CI, 1.30–3.27), allergy to dog dander (adjusted OR, 1.92; 95% CI, 1.24–2.97), allergy to *D. farinae* (adjusted OR, 1.70; 95% CI, 1.06–2.74), allergy to *Alternaria alternata* (adjusted OR, 1.68; 95% CI, 1.08–2.60), allergy to *Penicillium* (adjusted OR, 1.57; 95% CI, 1.03–2.39), and age (adjusted OR, 1.01; 95% CI, 1.01–1.02).

3.4. Independent association with asthma comorbidity stratified by age

The entire population was stratified into subgroups including a 5–18

Table 2
Prevalence of common aeroallergen sensitization in patients with AR.

	Total patients n (%)	With asthma n (%)	Without asthma n (%)	P value
<i>D. farinae</i>	2873 (76.84)	447 (84.02)	2426 (75.65)	0.0001
<i>D. pteronyssinus</i>	2755 (73.68)	436 (81.95)	2319 (72.31)	0.0001
Giant ragweed	899 (24.04)	146 (27.44)	753 (23.48)	0.049
Dog dander	340 (9.09)	70 (13.16)	270 (8.42)	0.001
<i>Alternaria alternata</i>	512 (13.69)	99 (18.61)	413 (12.88)	0.001
<i>Aspergillus fumigatus</i>	236 (6.31)	62 (11.65)	174 (5.43)	0.0001
<i>Penicillium</i>	419 (11.21)	83 (15.60)	336 (10.48)	0.001
<i>Humulus scandens</i>	331 (8.85)	60 (11.28)	271 (8.45)	0.039
Cat dander	464 (12.41)	79 (14.85)	385 (12.01)	0.076
<i>Alnus incana</i>	585 (15.65)	85 (15.98)	500 (15.59)	0.821
<i>Platanus orientalis</i>	660 (17.65)	90 (16.92)	570 (17.77)	0.631
<i>Triticum sativum</i>	430 (11.50)	70 (13.16)	360 (11.23)	0.222
<i>Robinia pseudoacacia</i>	721 (19.28)	113 (21.24)	608 (18.96)	0.239
<i>Artemisia vulgaris</i>	754 (20.17)	104 (19.55)	650 (20.27)	0.727
Cockroach	1331 (35.60)	206 (38.72)	1125 (35.08)	0.107
<i>Taraxacum</i>	858 (22.95)	128 (24.06)	730 (22.76)	0.512

The chi-square test was used to assess the difference between patients with AR with and without asthma. Values of $p < 0.05$ were considered statistically significant.

Table 3
Multivariate analysis of risk factors for asthma comorbidity.

	OR	95% CI	P value
Gender	0.97	0.08–1.17	0.73
<i>D. farinae</i>	1.70	1.06–2.74	0.03
<i>D. pteronyssinus</i>	2.06	1.30–3.27	0.0001
Cockroach	1.28	0.88–1.85	0.20
Giant ragweed	1.54	0.98–2.42	0.06
<i>Taraxacum</i>	1.46	0.85–2.51	0.17
No. of aeroallergens	0.76	0.56–1.05	0.10
Family history	0.86	0.70–1.05	0.13
Age	1.01	1.01–1.02	0.0001
Dog dander	1.92	1.24–2.97	0.0001
<i>Alnus incana</i>	1.10	0.69–1.74	0.70
<i>Platanus orientalis</i>	1.20	0.78–1.85	0.40
<i>Triticum sativum</i>	1.46	0.92–2.34	0.11
<i>Alternaria alternata</i>	1.68	1.08–2.60	0.02
<i>Aspergillus fumigatus</i>	2.42	1.50–3.90	0.0001
<i>Penicillium</i>	1.57	1.03–2.39	0.04
<i>Robinia pseudoacacia</i>	1.43	0.93–2.21	0.11
Cat dander	1.46	0.95–2.24	0.08
<i>Humulus scandens</i>	1.72	1.06–2.80	0.03

A logistic regression analysis was used to assess risk factors of patients with AR and the result was presented as the odds ratio (OR) and a 95% confidence interval (CI). Values of $p < 0.05$ were considered statistically significant.

Table 4
Independent association with asthma comorbidity stratified by age.

Population	Variable	OR	95% CI	P Value
5–18 yr	<i>D. farinae</i>	5.17	1.78–14.96	0.0001
	<i>D. pteronyssinus</i>	2.94	1.11–7.79	0.03
	No. of aeroallergens	0.54	0.29–0.99	0.0001
	Dog dander	2.62	1.16–5.91	0.02
	<i>Triticum sativum</i>	2.58	1.01–6.55	0.047
	<i>Aspergillus fumigatus</i>	4.39	1.88–10.28	0.0001
	Cat dander	2.24	1.05–4.79	0.04
19–45 yr	Age	1.04	1.02–1.06	0.0001
	<i>D. pteronyssinus</i>	2.57	1.31–5.05	0.01
	Family history	0.68	0.50–0.92	0.01
≥46 yr	Family history	0.61	0.38–1.00	0.049

A logistic regression analysis was used to assess risk factors of patients with AR in different age group and the result was presented as the odds ratio (OR) and a 95% confidence interval (CI). $p < 0.05$ were considered statistically significant.

year-old group, a 19–45 year-old group, and an older than 46 years group to investigate the risk factors independently associated with concomitant asthma (Table 4).

In the 5–18 year-old group, allergy to *Aspergillus fumigatus* (adjusted OR, 4.39; 95% CI, 1.88–10.28), allergy to *D. pteronyssinus* (adjusted OR, 2.94; 95% CI, 1.11–7.79), allergy to dog dander (adjusted OR, 2.62; 95% CI, 1.16–5.91), allergy to *D. farinae* (adjusted OR, 5.17; 95% CI, 1.78–14.96), allergy to cat dander (adjusted OR, 2.24; 95% CI, 1.05–4.79), allergy to *Triticum sativum* (adjusted OR, 2.58; 95% CI, 1.01–6.55), and the number of positive allergens (adjusted OR, 0.54; 95% CI, 0.29–0.99) were independently strong risk factors for concomitant asthma.

We found that allergy to *D. pteronyssinus* (adjusted OR, 2.57; 95% CI, 1.31–5.05), age (adjusted OR, 1.04; 95% CI, 1.02–1.06), and family history of AR (adjusted OR, 0.68; 95% CI, 0.50–0.92) were independently strong risk factors for concomitant asthma in the 19–45 year-old group. In patients older than 46 years, only family history of AR (adjusted OR, 0.61; 95% CI, 0.38–1.00) was an independently strong risk factor for concomitant asthma.

4. Discussion

Asthma is one of the most common chronic diseases among children and adults leading to a high health and socioeconomic burden. The prevalence of asthma is increasing, affecting approximately 235 million people worldwide [9]. The prevalence of asthma was found to be 1.24% in eight provinces/cities of seven areas in mainland China in 2018 [10]. Another study involving 57,779 adults age 20 years or older found that the overall prevalence of asthma was 4.2%, representing 45.7 million Chinese adults [11]. AR often coexists with asthma, and rhinitis is an important risk factor for asthma. The intensity and duration of AR are closely related to the occurrence of asthma [12]. A recent survey of patients with asthma and/or rhinitis in China reported higher rates of positive skin-prick tests (SPT) and specific IgE for most allergens in patients with rhinitis combined with asthma as compared to those with asthma or AR alone [13].

Data from the western population have shown that 19–38% of patients with AR may have bronchial asthma comorbidity [5]. One meta-analysis reported that prevalence estimates of AR with asthma ranged from 6.69% to 14.35% in China [14]. We found that the prevalence of asthma in patients with AR in eastern China is 14.23%. In contrast, Hong et al reported that the bronchial asthma prevalence is much lower (5.33%) in patients with AR in southern China [3].

There are at least two factors that may explain the discrepancy. First, given the similar genetic background among the various Chinese populations, environmental factors are likely to be important in explaining the observed differences. Guangzhou and Zhuhai are located in the subtropical and humid region while Shandong is located in the warm temperate zone and sub-humid area. The different distribution of indoor and outdoor allergens were observed due to different climate. Additionally, the diagnostic criteria used to define asthma were not standardized between these two studies.

Additionally, the previous findings reported that asthma patients with AR were younger than those without AR. Age has always been a significant factor influencing the prevalence and impact of concomitant AR in individuals with asthma [5]. In this study, the age of patients with AR combined with asthma was higher than that of patients in the AR only group and age is an independent risk factor associated with the development of asthma (OR: 1.01 95%CI: 1.01–1.02). The study showed that a 1-year increase in age was associated with a 1.012-fold increase in risk of asthma.

A survey of patients with moderate to severe asthma showed that patients' age older than 46 years was closely related to increased severity of the disease. In particular, patients older than 65 years showed nearly doubled risk of exacerbation as compared with the patients aged 20–44 years. [6]. Additionally, it has also been suggested that the

gender-related differences in asthma severity are age-dependent. More male patients are found in children while more female patients in adolescents. Meta-analysis of seven observational studies showed that the risk of asthma increased by 37% in women who had their first period prior to age 12 [15]. The high incidence and low remission rates associated with asthma in women in late adolescence could be attributed to the role of female hormones.

House dust mite is a common and persistent respiratory allergen, therefore it is important to understand its role in asthma [16]. One study evaluating the relationship between house dust mites and asthma symptoms showed that respiratory symptoms were associated with higher levels of dust mite weight. Asthma and wheezing were twice as common in patients exposed to the highest weights of dust mites compared with those exposed to the lowest weights. When considering the weight of dust mites in a specific home location, the bed in the bedroom is closely associated with asthma and wheezing, while the furniture in the living room is closely associated with wheezing. Prolonged contact with the bed and the close proximity of the pillow and mattress to the airway may result in high intensity contact in the short term [17].

In our study, the positive rates of *D. farinae* and *D. pteronyssinus* in patients with AR with asthma were significantly higher than patients with AR without asthma. Moreover, using the multivariate logistic regression analysis, it was shown that *D. farinae* and *D. pteronyssinus* were independent risk factors related to the occurrence of asthma, which increased the risk of asthma by 1.70 times and 2.06 times, respectively. This finding is consistent with another study involving 2485 household bedrooms with dust mite endotoxins (927 of them were asthmatic patients) where the levels of dust mite endotoxins increased the risk of asthma, while early rural exposure reduced this risk [18]. Although the exact biological mechanism of living in rural areas reducing the risk of asthma is not fully understood, it has been proposed that these early exposures may help to promote the transition to Th1-mediated immune responses that prevent many inflammatory diseases [19].

People come into contact with mold every day which could lead to a variety of diseases. Mold contact is undoubtedly associated with severe respiratory diseases, including infections (sinusitis and lungs) and allergies (allergic pulmonary aspergillosis and asthma). Most patients with severe asthma are allergic to mold. We found that *Alternaria alternata*, *Aspergillus fumigatus*, and *Penicillium* increased the risk of asthma in patients with AR and a higher positive rate of *Alternaria alternata*, *Aspergillus fumigatus*, and *Penicillium* in patients with AR combined with the asthma group.

Strong evidence was found that outdoor mold exposure could exacerbate symptoms of asthma. For example, exposure of American *Streptomyces*, which is a common mold in Mid-western United States, has a temporal relationship to the severity of asthma. Large numbers of wind-borne spores at peak times can immediately worsen symptoms and even increase asthma mortality in allergic patients [20,21]. Members of the public and doctors believe that indoor mold was mainly found in bathrooms or areas where water seeps into walls and ceilings. However, there are other important sources of indoor mold. A recent study used mass spectrometry to detect and culture large amounts of mold and volatile fungal toxins on pillows. Direct inhalation of mold from bedding can be a significant source of exposure resulting in allergies or infections [22].

The American National Academy of Sciences has concluded that there is sufficient evidence to suggest an association between fungal exposure and worsening symptoms in patients with sensitized asthma. Wheezing is reported to be about twice as likely in moldy homes [23]. Additionally, the prevalence of mold sensitivity is increasing among adults with increasingly severe asthma. People exposed to indoor mycospora for longer than 2 years are more likely to develop asthma than those who are not [24].

Because most people are exposed to animals in their living environment, studying animal exposure in various areas and environmental

conditions to clarify their risk of causing allergic diseases is important to guide our clinical work. In our study we found increased positive rates of dog epithelium in patients with AR with asthma. Moreover, the incidence of asthma in patients with AR was increased with sensitivity to dog epithelium (1.92 times).

In western countries, about 50–80% of households have pets. Animal allergens can be detected in public areas and individual homes. Therefore, everyone is susceptible to allergen exposure even without direct contact with animals. Although animal dander and secretions are considered major allergens, conflicting evidence was found in regard to the relationship between exposure to animals and the occurrence of asthma. Some suggest an increased risk of asthma while others suggest the opposite. In Finland, the incidence of allergic asthma was reduced among children exposed to dogs, although there is some evidence that exposure to cats in the first year of life can increase the risk of allergic asthma in children. Dog exposure was not found to be a protective factor for asthma in Russian children, instead, cat exposure increased the risk of AS in the first year of life [25]. A meta-analysis included thirty-two studies found that exposure to dogs increases the risk of asthma slightly [26].

Our study has some limitations. The first limitation concerns the cross-sectional nature of this hospital-based research project, which has focused on risk factors for asthma in patients with AR. The participants enrolled from the medical unit likely had a higher AR severity and asthma prevalence than individuals in the general population. The second limitation is that the subjects were enrolled from Otolaryngology department. As all investigators are Otorhinolaryngologists in those hospitals, there might be some deficits in diagnostic procedures of asthma. For these reasons, future studies are required to assess possible risk and protective factors for concomitant asthma in AR patients in eastern China.

5. Conclusions

In conclusion, AR is closely related to the occurrence of asthma. In this study, multiple logistic regression analyses showed that age, *D. farinae*, *D. pteronyssinus*, dog dander, *Alternaria alternata*, *Aspergillus fumigatus* and *Penicillium* allergies in patients with AR are independent risk factors for asthma. Various risk factors that are independently associated with concomitant asthma in patients with AR were found in different age groups. It is important to note that identifying risk factors for the occurrence of asthma in patients with AR was beneficial to the diagnosis and treatment of asthma.

CRedit authorship contribution statement

Li Zhao: Writing - original draft, Writing - review & editing, Formal analysis, Investigation.

Yan Yang: Writing - original draft, Writing - review & editing, Formal analysis, Investigation.

Yi Ran Zang: Methodology, Writing - original draft, Writing - review & editing.

Qin Qin Zhang: Methodology, Writing - original draft, Writing - review & editing.

Xu Liang: Methodology, Writing - original draft, Writing - review & editing.

Guang Mei Yuan: Writing - review & editing.

Peng Jin: Funding acquisition, Methodology, Writing - original draft, Writing - review & editing, Formal analysis, Resources.

Xiao Xue Zi: Funding acquisition, Methodology, Writing - original draft, Writing - review & editing, Formal analysis, Resources.

Ke Na Yu: Methodology, Writing - original draft, Writing - review & editing.

Hai Ling Zhang: Conceptualization, Funding acquisition, Writing - original draft, Writing - review & editing.

Li Shi: Conceptualization, Supervision, Funding acquisition,

Methodology, Writing - original draft, Writing - review & editing, Investigation.

Author contributions

The conception and design of this article is by Li Shi and Hai Ling Zhang. The collection of data is by Hai Ling Zhang, Li Zhao, Ke Na Yu, Yan Yang, Peng Jin, Xiao Xue Zi, Xu Liang, Qin Qin Zhang, Yi Ran Zang, Guang Mei Yuan. The analysis and interpretation of this article is by Hai Ling Zhang, Li Zhao, Yan Yang.

Funding details

This study was supported by the National Natural Science Foundation of China [grant numbers 81800885, 82101195 and 81873692]; Key Research and Development Project of Shandong [grant number 2018CXGC1214].

Declaration of competing interest

None.

Acknowledgments

The authors wish to thank MD. Shan Gao for kindly reviewing this manuscript.

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