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Clinical profiles of patients with wheat-induced anaphylaxis at various ages of onset

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ABSTRACT

Background: Wheat-induced anaphylaxis (WIA) is a serious and potentially life-threatening wheat allergy, more common in adults than in children. Little is known about the differences in clinical profiles in WIA among patients of various ages in China.

Methods: We analyzed data retrospectively from an allergy department in a tertiary hospital that included 248 patients (208 adults and 40 children and adolescents) with a history of WIA.

Results: We found that alcohol was more frequent in patients aged ≥50 years [older adults] (19.0%, 4/21) than in those aged 12–17 years [adolescents] (0%, 0/33; $p = 0.019$). The frequency of NSAID use in older adults (42.9%, 9/21) was significantly higher than that in adolescents (0%, 0/33; $p < 0.001$), and patients aged 18–49 years [young adults] (2.8%, 5/178; $p < 0.001$). During WIA, cardiovascular symptoms in children were less frequent than those in other age groups (children, 28.6%; adolescents, 87.9%; young adults, 93.0%; older adults, 95.2%; $p < 0.001$). The consciousness loss rate in adults (both age groups; $p < 0.001$) and the hypotension rate in older adults ($p = 0.006$) were higher than those in other age groups. Compared with adults (young and older adults), children had a higher rate of allergic comorbidities ($p = 0.004$, 0.001, respectively) and a higher rate of other food allergies ($p < 0.001$, <0.001, respectively). Compared with the mild-to-moderate anaphylaxis group, the severe anaphylaxis group had a higher onset age ($p = 0.001$), higher cofactor prevalence ($p = 0.004$), lower allergic comorbidity rate ($p = 0.014$), and higher positive rate of specific IgE to omega-5 gliadin (ω-5 gliadin) ($p = 0.023$).

Conclusion: Clinical profiles of patients with WIA are different among various onset age/severity groups. An improved understanding of WIA symptoms in various age/severity groups could help accelerate diagnosis, suggest preventive measures, and contribute to improved patient care.

Keywords: Anaphylaxis, Wheat allergy, Wheat-induced anaphylaxis, Wheat-dependent exercise-induced anaphylaxis, Omega-5 gliadin

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INTRODUCTION

Wheat is the most common food item consumed by humankind.[1] However, it also acts as a major cause of food allergy,[2] responsible for 37% of food-induced anaphylaxis cases in China,[3] 17.7% in Japan,[4,5] and approximately 15% in Central Europe.[6] Moreover, wheat allergies have been steadily increasing,[7] partly because modern cultivated and varietally selected wheat contains a higher level of gluten and immunogenic epitopes than wheat obtained previously.[8] As an allergen, wheat is more prone to cause anaphylaxis than other foods.[9] Wheat-induced anaphylaxis (WIA), including wheat-dependent exercise-induced anaphylaxis (WDEIA), is potentially fatal and manifests as urticaria, angioedema, and severe allergic reactions such as hypotension or anaphylactic shock.[10,11] WDEIA usually occurs when cofactors, including exercising, alcohol consumption, and nonsteroidal anti-inflammatory drug (NSAID) use,[12,13] occurred within 6 h of wheat ingestion. However, several studies detected no related cofactors.[14,15]

Recently, Kraft et al[6] reported that wheat anaphylaxis in European children differed from that in adults. Little is known about the clinical profiles of WIA among patients at various ages in China, and no predicting indicators for such life-threatening allergic reactions are available. An improved understanding of WIA symptoms in various age/severity groups could help accelerate diagnosis, suggest preventive measures, and contribute to improved patient care. Thus, we analyzed a large cohort of WIA cases (regardless of whether they were cofactor-induced), aiming to explore differences among age groups and severity levels.

METHODS

Patients and study design

This was a retrospective study of 248 patients diagnosed with WIA in a tertiary hospital in China between 2018 and 2022. Patients' data, including sex, age at the first episode, age at diagnosis, residential address, clinical characteristics, laboratory findings, and atopy complications (allergic rhinitis, asthma, other food allergies, or atopic dermatitis), were extracted from the medical records by allergists. The patients were divided into 4 groups per

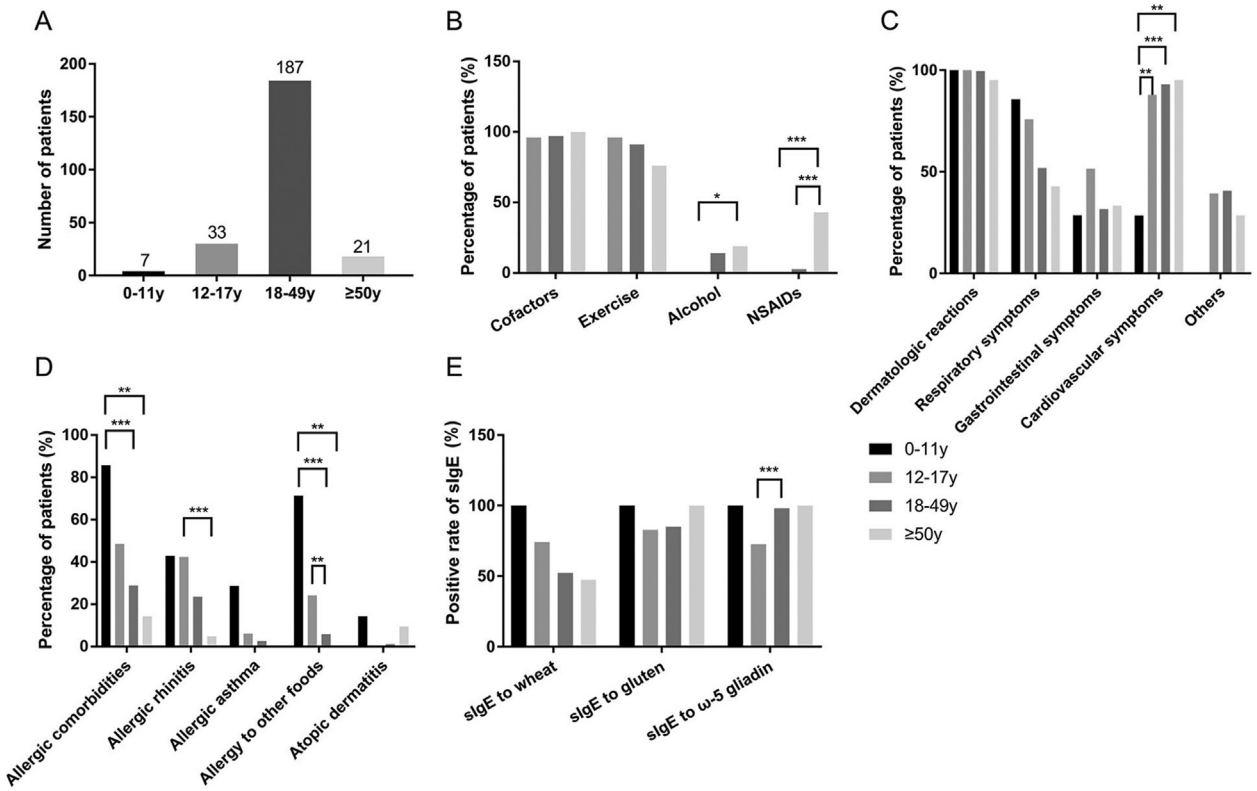

Fig. 1 Characterization of the 248 patients with WIA. WIA, wheat-induced anaphylaxis; sIgE, specific immunoglobulin E. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$

the age at onset: children (0–11 years), adolescents (12–17 years), young adults (18–49 years), and older adults (≥50 years; Fig. 1A).

Diagnostic criteria

WIA was diagnosed if the following criteria were met:[14,16] (1) anaphylaxis manifestation occurred within 6 h of wheat ingestion; (2) specific IgE positivity to wheat, gluten, and/or ω-5 gliadin; and (3) anaphylaxis prevented successfully with a wheat-free diet. Anaphylaxis was defined following the World Allergy Organization (WAO) 2020 criteria[17] as an acute allergic reaction involving more than 2 organ systems or resulting in compromised breathing and/or circulation that can be life threatening. Allergic symptoms were evaluated by allergists according to the patient's medical history, and for children who are unable to describe the symptoms, the medical history is provided by their guardians.

Determination of cofactors

Cofactors were determined based on the patient's medical history. If patients exercise, drink alcohol, or take NSAIDs within 6 h before the occurrence of anaphylaxis,[13,18] cofactors should be highly suspected, which were finally determined by allergy specialists. All types of exercise should be evaluated, including walking, household, running, manual work, sports, and so on.

Severity grading

Anaphylaxis was classified as severe if the patient had respiratory arrest (cyanosis or oxygen saturation ≤92%), hypotension [systolic blood pressure <70 mmHg in infants (1–12 months old), <70 + (2 × age) mmHg in patients aged 1–10 years, and <90 mmHg in other patients], circulatory collapse, confusion, or incontinence.[19] Those without these were defined as having mild-to-moderate anaphylaxis.

Laboratory studies

Levels of total serum IgE and serum-specific IgE against wheat, gluten, and ω-5 gliadin were measured using an ImmunoCAP system (Thermo Scientific, Uppsala, Sweden). Specific IgE result was considered positive at a value >0.35 kU/L.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA). A descriptive analysis was used to characterize the study population. Continuous variables are expressed as medians with their relevant range and were compared using the Wilcoxon–Mann–Whitney or Kruskal–Wallis test. Categorical variables are presented as numbers and percentages and were compared using the chi-square test or Fisher's exact test. Statistical significance was set at $p < 0.05$.

RESULTS

Baseline patient characteristics

This study included 248 patients with WIA, 134 (54%) of whom were male patients. The median age was 34.5 (0.3–68.0) years at the first anaphylaxis episode and 36 (2–69) years at diagnosis. The median time between the first anaphylaxis episode and the WIA diagnosis was 12 (0–312) months. Allergic comorbidities occurred in 31.9% (79/248) of patients, and 10.1% (25/248) of patients had more than one comorbidity, including 25.0% (62/248) with allergic rhinitis, 3.6% (9/248) with asthma, 2.0% (5/248) with atopic dermatitis, and 9.7% (24/248) with an allergy to other foods. The causative foods were seafood (n = 13), fruit (n = 4), tree nuts (n = 3), egg (n = 3), milk (n = 3), peanut (n = 4), soybean (n = 2), and sesame (n = 1).

Clinical features of wheat-induced anaphylaxis

The median number of anaphylactic episodes was 2 (1–10). Of the 239 patients with available data about cofactors, 95.0% (227/239) identified cofactors. The most common cofactor was exercising, followed by alcohol consumption and NSAID use (Table 1).

Table 2 summarizes the symptoms of anaphylaxis; those related to the skin were the most frequent (246/248, 99.2%), followed by the cardiovascular system (225/248, 90.7%), respiratory system (137/248, 55.2%), and gastrointestinal tract (85/248, 34.3%). Urticaria was the most common manifestation (242/248, 97.6%), followed by loss of consciousness (194/248, 78.2%), dyspnea (130/248, 52.4%), hypotension (111/248, 44.8%), and blurred vision (97/248, 39.1%). The positivity rates

General characteristics	Total (n = 248)	Age groups				
		0-11 years (n = 7) [children]	12-17 years (n = 33) [adolescents]	18-49 years (n = 187) [young adults	≥50 years (n = 21) [older adults]	p value
Male sex, n (%)	134 (54)	3 (42.9)	19 (57.6)	96 (51.3)	16 (76.2)	0.149
Duration of anaphylaxis before diagnosis, month, median (range)	12 (0–312)	12 (6–24)	12 (0.23–132)	13.0 (0–312)	13.57 (0.01–84)	0.820
Number of episodes, median (range)	2 (1–>10)	3 (1–5)	2 (1–>10)	2 (1–>10)	2 (1–7)	0.771
Cofactors[a], n (%)	227 (95)	N	32 (96.0)	173 (97.2)	21 (100)	1.000
Exercise, n (%)	211 (88.3)	N	32 (96.0)	162 (91.0)	16 (76.2)	< 0.041
Alcohol consumption, n (%)	29 (12.1)	N	0 (0)	25 (14.0)	4 (19.0)	0.022
NSAID use, n (%)	14 (5.9)	N	0 (0)	5 (2.8)	9 (42.9)	< 0.001
Allergic comorbidities, n (%)	79 (31.9)	6 (85.7)	16 (48.5)	54 (28.9)	3 (14.3)	0.001
Allergic rhinitis, n (%)	62 (25.0)	3 (42.9)	14 (42.4)	44 (23.5)	1 (4.8)	0.010
Allergic asthma, n (%)	9 (3.6)	2 (28.6)	2 (6.1)	5 (2.7)	0 (0)	0.025
Allergy to other foods, n (%)	24 (9.7)	5 (71.4)	8 (24.2)	11 (5.9)	0 (0)	< 0.001
Atopic dermatitis, n (%)	5 (2.0)	1 (14.3)	0 (0)	2 (1.1)	2 (9.5)	0.026
Laboratory examination (median, range, KUA/L)						
Total IgE	242 (16.1–2197)	185 (69.8–1183)	325 (76.1–2036)	246.5 (16.1–2197)	124 (26.3–1170)	0.120
sIgE to wheat[b]	0.53 (0–63.50)	1.46 (0.58–15.50)	0.82 (0–3.83)	0.48 (0–63.5)	0.42 (0–4.12)	0.025
sIgE to gluten[c]	1.73 (0.03–31.2)	0.87 (0.55–2.81)	1.21 (0.24–13.3)	1.95 (0.03–31.2)	1.46 (0.35–8.46)	0.857
sIgE to ω-5 gliadin[d]	7.30 (0–49.4)	7.72 (1.40–9.01)	5.03 (0–21.60)	7.75 (0–41.70)	11.00 (1.63–49.4)	0.241
Rate of positive sIgE (≥0.35 kUA/L), n (%)						
sIgE to wheat[b]	130 (56.3)	7 (100)	23 (74.2)	91/174 (52.3)	9 (47.4)	0.007
sIgE to gluten[c]	203 (86.4)	5 (100)	24 (82.8)	153/180 (85.0)	21 (100)	0.190
sIgE to ω-5 gliadin[d]	185 (95.4)	3 (100)	16 (72.7)	152/155 (98.1)	14 (100)	0.001

Table 1. General characteristics of the 248 patients with WIA in various age groups. *n, number; WIA, wheat-induced anaphylaxis; N, not done; NSAID, nonsteroidal anti-inflammatory drug; sIgE, specific immunoglobulin E. [a]Data missing for 9 in total and 9 in the young adult group. [b]Data missing for 17 in total, 2 in the adolescent group, 13 in the young adult group, and 2 in the older adult group. [c]Data missing for 13 in total, 2 in the children group, 4 in the adolescent group, and 7 in the young adult group. [d]Data missing for 54 in total, 4 in the children group, 11 in the adolescent group, 32 in the young adult group, and 7 in the older adult group*

Clinical manifestations	Total (n = 248)	Age groups				
		0-11 years (n = 7) [children]	12-17 years (n = 33) [adolescents]	18-49 years (n = 187) [young adults]	≥50 years (n = 21) [older adults]	p value
Dermatologic reactions	246 (99.2)	7 (100)	33 (100)	186 (99.5)	20 (95.2)	0.231
Urticaria	242 (97.6)	7 (100)	31 (93.9)	185 (98.9)	19 (90.5)	0.045
Angioedema	60 (24.2)	3 (42.9)	11 (33.3)	44 (23.5)	2 (9.5)	0.148
Respiratory symptoms	137 (55.2)	6 (85.7)	25 (75.8)	97 (51.9)	9 (42.9)	0.013
Dyspnea	130 (52.4)	3 (42.9)	24 (72.7)	94 (50.3)	9 (42.9)	0.072
Throat angioedema	21 (8.5)	0 (0)	7 (21.2)	12 (6.4)	2 (9.5)	0.054
Gastrointestinal symptoms	85 (34.3)	2 (28.6)	17 (51.5)	59 (31.6)	7 (33.3)	0.164
Abdominal pain	36 (14.5)	2 (28.6)	8 (24.2)	23 (12.3)	3 (14.3)	0.173
Diarrhea	11 (4.4)	0 (0)	1 (3)	9 (4.8)	1 (4.8)	1.000
Nausea	26 (10.5)	0 (0)	3 (9.1)	22 (11.8)	1 (4.8)	0.863
Vomiting	56 (22.6)	1 (14.3)	10 (30.3)	39 (20.9)	6 (28.6)	0.535
Cardiovascular symptoms	225 (90.7)	2 (28.57)	29 (87.9)	174 (93.0)	20 (95.2)	< 0.001
Blurred vision	97 (39.1)	1 (14.3)	13 (39.4)	75 (40.1)	8 (38.1)	0.660
Dizziness	40 (16.1)	0 (0)	3 (9.1)	34 (18.2)	3 (14.3)	0.486
Loss of consciousness	194 (78.2)	1 (14.3)	19 (57.6)	155 (82.9)	19 (90.5)	< 0.001
Tachycardia	44 (17.7)	1 (14.3)	5 (15.2)	33 (17.6)	5 (23.8)	0.893
Hypotension	111 (44.8)	0 (0)	14 (42.4)	83 (44.4)	14 (66.7)	0.016
Others	95 (38.3)	0 (0)	13 (39.4)	76 (40.6)	6 (28.6)	0.125
Incontinence	49 (19.8)	0 (0)	4 (12.1)	43 (23.0)	2 (9.5)	0.183
Fatigue	46 (18.5)	0 (0)	7 (21.2)	34 (18.2)	5 (23.8)	0.602
Convulsions	10 (4.0)	0 (0)	1 (3.0)	7 (3.7)	2 (9.5)	0.504
Tinnitus	5 (2.0)	0 (0)	0 (0)	5 (2.7)	0 (0)	1.000
Numbness	5 (2.0)	0 (0)	0 (0)	5 (2.7)	0 (0)	1.000
Recurrent urticaria	101 (81.0)	4 (57.1)	25 (75.8)	155 (82.9)	17 (81)	0.254
Course of urticaria in months, median (range)	48 (0.03-360)	9 (6-24)	24 (1-132)	60 (0.03-360)	72 (9-240)	0.072

Table 2. Clinical manifestations of the 248 patients with WIA in various age groups. *n, number; WIA, wheat-induced anaphylaxis*

of specific IgE to wheat, gluten, and ω-5 gliadin were 56.3% (130/231), 86.4% (203/235), and 95.4% (185/194), respectively.

Clinical features differed among age groups

The first episode occurred at the age of 18–49 years in 187 (75.4%) patients (Fig. 1A). The age groups differed significantly in their clinical features (Table 1).

Cofactors

Compared with adults, children's exercise patterns, drinking habits, and use of NSAIDs were significantly different. Thus, we leave the

comparison of cofactors only between adolescents and adults.

Alcohol was more frequent in older adults (19.0%, 4/21) than in adolescents (0%, 0/33; $p = 0.019$). The frequency of NSAID use in older adults (42.9%, 9/21) was significantly higher than that in adolescents (0%, 0/33; $p < 0.001$), and young adults (2.8%, 5/178; $p < 0.001$; Table 1, Fig. 1B).

Clinical manifestation

Cardiovascular symptoms were less common in children (28.6%, 2/7) than in adolescents (87.9%, 29/33; $p = 0.003$), young adults (93.0%, 174/178; $p < 0.001$), and older adults (95.2%, 20/21; $p = 0.001$). Respiratory symptoms seemed more common in children, but the difference was insignificant. Compared with children, young and older adults had higher rates of loss of consciousness ($p < 0.001$), and older adults also had a higher rate of hypotension ($p = 0.006$; Table 2, Fig. 1C).

Atopic states and specific IgE characteristics

Compared with young and older adults, children had a higher rate of allergic comorbidities (28.9 vs. 85.7%, $p = 0.004$ and 14.3 vs. 85.7%,

Clinical features	Mild-to-moderate anaphylaxis (n = 39)	Severe anaphylaxis (n = 209)	P value
Male sex, n (%)	19 (48.7)	115 (55)	0.468
Onset age of WIA, year, median (range)	27 (0.33–64)	35 (11–68)	0.001
Course of anaphylaxis in months, median (range)	12 (0–168)	13 (0–312)	0.495
Number of episodes, median (range)	2 (1->10)	2 (1->10)	0.425
Cofactors[a], n (%)	30/36 (83.3)	197/203 (97)	0.004
Exercise, n (%)	29/36 (80.6)	182/203 (89.7)	0.155
Alcohol consumption, n (%)	4/26 (11.1)	25/203 (12.3)	1.000
NSAID use, n (%)	0 (0)	14 (6.9)	0.137
Recurrent urticaria, n (%)	30 (76.9)	171 (81.8)	0.474
Course of urticaria in months, median (range)	36 (3–240)	48 (0.03–360)	0.519
Allergic comorbidities, n (%)	19 (48.7)	60 (28.7)	0.014
Allergic rhinitis, n (%)	16 (41)	46 (22)	0.012
Allergic asthma, n (%)	5 (12.8)	4 (1.9)	0.006
Allergy to other foods, n (%)	10 (25.6)	14 (6.7)	<0.001
Atopic dermatitis, n (%)	1 (2.6)	4 (1.9)	0.578
Laboratory examination (median, range, KUA/L)			
Total IgE	292 (25.9–1576)	237 (16.1–2197)	0.962
sIgE to wheat[b]	0.67 (0–35.9)	0.495 (0–63.5)	0.185
sIgE to gluten[c]	1.15 (0.06–31.20)	1.78 (0.03–24.4)	0.332
sIgE to ω-5 gliadin[d]	6.63 (0–41.7)	7.56 (0–49.4)	0.617
Rate of positive sIgE (≥0.35 KUA/L), n (%)			
sIgE to wheat[b]	25/36 (69.4)	105/195 (53.8)	0.083
sIgE to gluten[c]	25/32 (78.1)	178/203 (87.7)	0.164
sIgE to ω-5 gliadin[d]	23/27 (85.2)	162/167 (97.0)	0.023

Table 3. Clinical features of the 248 patients with WIA in various severity groups. *n, number; WIA, wheat-induced anaphylaxis; NSAIDs, nonsteroidal anti-inflammatory drug; sIgE, specific immunoglobulin E. [a]Data missing for 3 with mild-to-moderate anaphylaxis and 6 with severe anaphylaxis. [b]Data missing for 3 with mild-to-moderate anaphylaxis and 14 with severe anaphylaxis. [c]Data missing for 7 with mild-to-moderate anaphylaxis and 6 with severe anaphylaxis. [d]Data missing for 12 with mild-to-moderate anaphylaxis and 42 with severe anaphylaxis*

$p = 0.001$, respectively) and other food allergies (5.9 vs. 71.4%, $p < 0.001$ and 0 vs. 71.4%, $p < 0.001$, respectively; Fig. 1D. The rate of serum-specific IgE positive to ω-5 gliadin was higher for young adults than for adolescents (98.1 vs. 72.7%, $p < 0.001$; Table 1, Fig. 1E).

Clinical profiles of the different severity groups

The included patients were divided into mild-to-moderate or severe anaphylaxis groups, and 84.3% of patients had severe anaphylaxis (Table 3). Age at the first anaphylaxis episode in the severe anaphylaxis group was significantly higher than that in the mild-to-moderate anaphylaxis group ($p = 0.001$) (Fig. 2A). The rate of patients with cofactors in the severe anaphylaxis group was higher than that in the mild-to-moderate anaphylaxis group ($p = 0.004$) (Fig. 2B). The rate of allergic comorbidities in the mild-to-moderate anaphylaxis group was higher than that in the severe anaphylaxis group ($p = 0.014$) (Fig. 2C). A similar pattern was noted for the frequency of allergic rhinitis ($p = 0.014$), allergic asthma ($p = 0.006$), and allergies to other foods ($p < 0.001$). Moreover, the rate of serum-specific IgE positivity to ω-5 gliadin was higher in the severe anaphylaxis group than in the mild-to-moderate anaphylaxis group ($p = 0.023$) (Fig. 2D).

DISCUSSION

The incidence of anaphylaxis is increasing worldwide.[20] Wheat has been reported as the most common food trigger of anaphylaxis in China and the most common trigger for food-dependent exercise-induced anaphylaxis (FDEIA).[3,21,22] Studies in Japan,[23,24] Korea,[25] and Europe[6] have reported similar results. It may partly be because of the high consumption, and high processing of wheat products, which results in a higher level of gluten and immunogenic epitopes.[8] Unlike FDEIA caused by other foods, WDEIA is more common in adults than in children.[10] In line with this, 83.9% of the patients in our study were adults. However, there are limited reports on the clinical characteristics of patients with WIA at various ages. Identifying these differences could greatly assist in precise diagnosis and prevention activities. The demographic features of our patients were similar to those of previous studies; the sex ratio was nearly balanced[26] and most patients were young adults.[27,28] Consistent with published data,[6,26,29] dermatological and cardiovascular symptoms were the most common symptoms in adult patients with WDEIA/WIA, followed by respiratory and gastrointestinal symptoms. Cardiovascular disease was infrequent, whereas skin and respiratory involvement were highly prevalent in children, in line with previous findings.[6,30] The frequency of cardiovascular symptoms was 90.7% and that of loss of consciousness was 78.2%, which is higher than the 2007–2019 European Anaphylaxis Registry data, which reported cardiovascular symptoms and loss of consciousness in 86.7% and 41.0% of the patients, respectively.[6] These differences were possibly because ours was a single-center study based on medical records; therefore, patients with severe cardiovascular involvement were more likely to visit our department than those with mild-to-moderate cases.

In Europe, wheat anaphylaxis in children was found to differ from that in adults.[6] We too observed differences in clinical wheat anaphylaxis symptoms among the age groups. A previous study reported cardiovascular involvement in 86.7% of the participants and respiratory involvement 53.6%.[6] The respective values in children were 14.3 and 96.6%. In line with published data,[6,19] adults with WIA in our study had a higher frequency of cardiovascular symptoms and a lower frequency of respiratory symptoms than did children. The consciousness loss rate was higher in adults than in children ($p < 0.001$), and hypotension was more common in older adults ($p = 0.006$). Dyspnea and abdominal pain are common among adolescents.[19] Similarly, our study showed a higher frequency of dyspnea in adolescents and a higher frequency of abdominal pain both in children and adolescents; however, the difference was statistically insignificant, possibly because our sample was small. Since the clinical manifestations of children are mostly reported by their guardians, which may cause deviation. More studies on WIA in children are needed. This was the first report on WIA characteristics among various age groups in China. Clarifying age-related differences in clinical profiles could

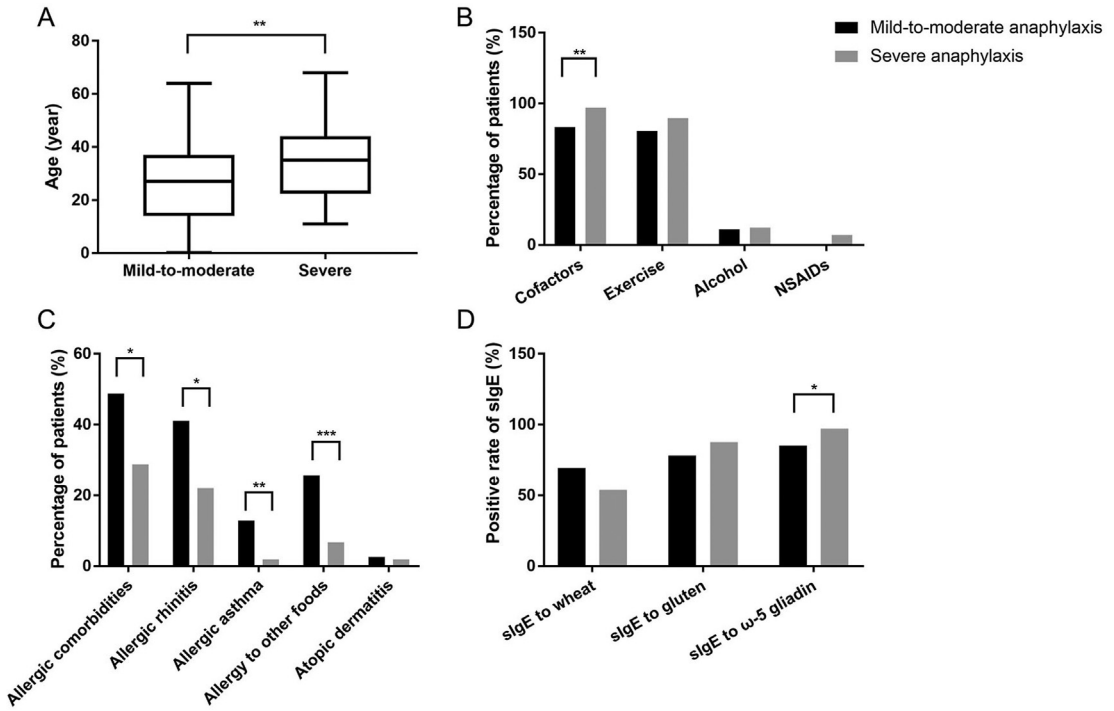

Fig. 2 Characterization of the WIA patients in different severity groups. sIgE, specific immunoglobulin E. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$

facilitate early diagnosis and timely management of potentially life-threatening allergic events.

Augmenting cofactors, including exercise, alcohol consumption, and NSAID use, played important roles in the pathogenesis of WDEIA.[12,31,32] We identified cofactors in 95% (227/239) of our patients, with exercise being a cofactor in 88.3% of the cases (211/239). In line with our study, exercise has been identifies as a cofactor in 82.8–90% of ω-5 gliadin-positive subjects in previous studies.[6,27] These cofactors might lead to increased gastrointestinal mucosal permeability, blood flow redistribution, and transient plasma hyperosmolality, which increase allergen bioavailability and decreased activation threshold of mast cells and basophil.[12,33] The gut microbiome compositions in WDEIA patients were found to be different from those of healthy controls. Meanwhile, a potential association between gut microbial flora and WDEIA development has been described,[34] but the exact mechanism remains elusive. Recently, the possibility of epithelial barrier loss due to microbial dysbiosis, the translocation of commensals and opportunistic pathogens, which trigger the Th2 inflammatory response through microbiome translocation for the pathogenesis of allergic diseases was also proposed.[35] Compared with adolescent, both alcohol and NSAIDs were more likely to be a cofactor in older adult patients ($p = 0.019$, <0.001, respectively). The distinct cofactors in different age groups might be related to lifestyle and complications. This finding suggests that different triggers might be involved, depending on patient age.

Atopic comorbidities were reported in 31.9% of the patients, which in agreement with a recent study that reported atopy in 32.5% of ω-5 gliadin-sensitized subjects.[8] Kraft et al[6] reported that 36.3% of adult patients with wheat allergy had atopic comorbidities, less frequently than in children (78.6%). We found similar differences between age groups, with atopic comorbidity occurring in 28.9% of young adults, 14.3% of older adults, and 85.7% of children with WIA. Other food allergies, especially seafood allergy, were also more common in children than in adults (both age groups; $p < 0.001$).

In the current study, 56.3, 86.4, and 95.4% of the patients were positive for specific IgE to wheat, gluten, and ω-5 gliadin, respectively, similar to the

respective values of 52.7–59%, 76–86.5%, and 98.1–100% reported previously.[14,26] We found that the positive rate of ω-5 gliadin-specific IgE in young adults was higher than in adolescents. Both wheat ω-5 gliadin and gluten are considered major allergens in WIA/WDEIA.[10,24,36,37] Pastorello et al[8] demonstrated that sensitization to ω-5 gliadin was associated with a higher probability of severe reactions, older age, and a higher association with cofactors. A high level of ω-5 gliadin-specific IgE antibodies was identified as a risk factor for persistent wheat allergy.[38] Sensitization to ω-5 gliadin might partly determine the clinical presentation. The significance of the specific IgE profiles in various populations requires further study.

The proportion of patients with severe anaphylaxis in our study was 84.3%, higher than the 55–66% reported in other studies.[6,8] This difference could be because as a monocentric study from a tertiary specialized allergy center, patients with severe anaphylaxis symptoms were more likely to visit our department than those with mild or moderate symptoms. We found that the age of onset was significantly higher in patients with severe anaphylaxis. Therefore, special attention should be paid to these patients. Cofactors were more common in patients with severe anaphylaxis than in those with mild-to-moderate anaphylaxis in our study. Cofactors are significantly associated with systemic reactions[39] and have been well-documented to aggravate or precipitate WDEIA.[10] Compared to that in the mild-to-moderate anaphylaxis group, the severe anaphylaxis group had a lower allergic comorbidity rate. Srisuwatchari et al[40] divided patients with wheat allergy into wheat anaphylaxis or the only skin symptoms group, and they found that patients with WIA showed a lower frequency of atopic dermatitis than those with only skin symptoms. Delays in symptom recognition and anaphylaxis treatment have been associated with more severe outcomes.[41] WIA patients without other allergic comorbidities may have an insufficient understanding of allergic reactions, and when mild anaphylaxis occurs, it is not intervened timely, thus developing into severe anaphylaxis. Moreover, the positive rate of ω-5 gliadin was higher in patients with severe anaphylaxis. Several studies have demonstrated that sensitization to ω-5 gliadin was associated with a higher probability of severe reactions, and IgE specific to ω-5 gliadin can predict the outcome of food challenges.[8,42] Hence, parameters, such as the age at onset, cofactors, and ω-5 gliadin-specific IgE, may be relevant for predicting anaphylactic severity in WIA.

The strength of our study is the large cohort, which comprised 248 patients with WIA from China. It is also the first study to investigate the clinical profiles of Chinese patients at various ages of onset. The occurrence of anaphylaxis in WIA patients may be delayed more than 30 min after wheat ingestion and requires the presence of promoting factors; therefore, WIA might be underestimated. Patients with urticaria or mild dyspnea may be misdiagnosed as having only urticaria. Patients with undeniable anaphylactic symptoms, such as the combination of urticaria and loss of consciousness, have a higher probability of referral to an allergist. As a monocentric study from a tertiary specialized allergy center, the proportion of severe cases may have been more than average in other clinics; therefore, outpatients were regularly included to reduce selection deviation. The other limitations of the study include its retrospective nature and possibility of recall bias. Prospective research is therefore necessary in the future. Moreover, our hospital caters primarily to adults; non-adult patients were less likely to visit our department, which may have led to an underestimation of the WIA incidence in children and adolescents. The number of pediatric patients with WIA was relatively small, indicating the need for further research on the characteristics of WIA in children.

CONCLUSIONS

This study showed that clinical profiles of patients with WIA are different among various onset age/severity groups. WIA in children show higher frequency of atopic disorders (allergic rhinitis, asthma, other food allergies, or atopic dermatitis) than that in adolescents and adults. Other food allergies, especially seafood, were highly common in children. Both alcohol and NSAID use was most common in older adults. Cardiovascular symptoms were uncommon in children, loss of consciousness was more common in adults than children and

adolescents, and hypotension was most common in older adults. Compared with patients with mild-to-moderate WIA, those with severe WIA were characterized by a higher age of onset, greater frequency of cofactors, lower rate of allergic comorbidities, and a higher positive rate of ω-5 gliadin-specific IgE. Hence, these parameters might help predict the severity of anaphylactic episodes in patients with WIA. Recognizing these differences could help physicians reach an early diagnosis and exert timely prevention measures.

Abbreviations
WIA, wheat-induced anaphylaxis; WDEIA, Wheat-dependent exercise-induced anaphylaxis; NSAIDs, Non-steroidal Anti-inflammatory Drugs; ω-5 gliadin, Omega-5 gliadin; FDEIA, food-dependent exercise-induced anaphylaxis.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions
Zhirong Du: Conception of the work, analysis of data, and drafting the work. LL, JL, YYX, LC: Acquisition of data for the work. JY: Supervision of the project, and final approval of the version to be published.

Ethics approval
This study was approved by the ethics committee of Peking Union Medical College Hospital.

Authors' consent for publication
All authors have approved the final manuscript and approved of the submission to World Allergy Organization Journal.

Competing interests
None of the authors have any competing interests related to this study.

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