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Original Article

Analysis of food-specific IgE, IgG, and IgG4 antibodies in children with allergic diseases

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Abstract: Objective: To assess the clinical value of food-specific IgE (sIgE), IgG (sIgG), and IgG4 (sIgG4) in the diagnostic evaluation of allergic diseases in children. Methods: A total of 149 pediatric patients with allergic diseases were retrospectively enrolled and categorized into three groups based on their predominant clinical manifestations: digestive symptoms, skin symptoms, and respiratory symptoms. Ninety-six age-matched healthy children were included as the control group. Serum total IgE and food-specific sIgE, sIgG, and sIgG4 levels were measured simultaneously. Results: The overall positivity rates of food-specific sIgG and sIgG4 in the case group were significantly higher than those of sIgE ($P<0.05$). Substantial agreement was observed between sIgG and sIgG4 ($0.4<\kappa<0.75$), whereas both showed poor concordance with sIgE ($\kappa<0.4$). Among all food allergens, milk and eggs exhibited the highest positivity rates for sIgE, sIgG, and sIgG4. sIgE positivity was mainly concentrated in Grades I-II, while sIgG and sIgG4 were more frequently detected in Grades II-III. Across disease subgroups, total IgE levels were highest in children with respiratory symptoms. The positivity rates of sIgE in the digestive, skin, and respiratory groups were 69.4%, 44.0%, and 58.0%, respectively ($P<0.05$). For distinguishing allergic cases from healthy controls, sIgG demonstrated the best discriminatory performance (Youden index $J=0.612$), followed by sIgG4 ($J=0.394$), whereas sIgE showed relatively lower discriminative ability. Analysis of antibody grade distribution revealed that sIgG ≥ Grade II was most common for egg, milk, and wheat allergens (85.1%, 71.2%, and 69.0%, respectively). Similarly, sIgG4 levels were frequently elevated for milk and egg allergens (78.4% and 78.2%). In contrast, sIgE ≥ Grade II was most prominent for shrimp (57.7%). Conclusion: Food-related adverse reactions in children may involve distinct immune mechanisms. Comprehensive interpretation of sIgE, sIgG, and sIgG4 profiles is recommended in the clinical assessment of pediatric allergic diseases. Among these biomarkers, sIgG and sIgG4 may provide additional reference values for management of food allergies, particularly when antigen exposure is chronic or long-term.

Keywords: Allergic diseases, food-specific IgE antibodies, food-specific IgG antibodies, food-specific IgG4 antibodies

Introduction

Allergic diseases are characterized by abnormal immune responses triggered by allergen exposure and commonly manifest as allergic asthma, allergic rhinitis, and food allergy. According to the World Health Organization estimates, approximately 40% of the global population is affected by allergic rhinitis, while the prevalence of food allergy ranges from 4% to 10% [1]. Children are particularly susceptible due to the immaturity of their immune systems, which not only threatens normal growth and development but also markedly impairs quality of life. Epidemiological studies indicate that food allergens are among the most frequent triggers of allergic disorders in pediatric populations [2].

IgE-mediated food allergy is the most widely recognized and well-established clinical phenotype. However, in practice, some children present mainly with chronic or recurrent digestive tract, skin and respiratory symptoms; and negative sIgE cannot completely exclude food-related adverse reactions. There are also children whose symptoms significantly improve after dietary adjustments. Relying solely on sIgE cannot explain all clinical phenotypes [3]. In contrast, delayed-type reactions that may be

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associated with immunoglobulin G (IgG) and its subclass immunoglobulin G4 (IgG4) have been reported in some patients; however, their clinical relevance remains controversial, and no consensus has been reached [3, 4]. To date, research on the concurrent assessment of food-specific IgE, IgG, and IgG4 in children with allergic diseases remains limited, and available findings are inconsistent.

Previous studies have focused mainly on a single antibody type, and systematic comparisons of the positive rates, intensity distributions, and consistency of sIgE, sIgG, and sIgG4 in food in children with allergic diseases have been relatively limited. There are relatively few studies that include healthy children as controls, quantitatively assess the ability of the three types of antibodies to distinguish "children vs. healthy", and conduct stratified analysis in combination with different clinical phenotypes (digestive tract, skin, respiratory tract). These deficiencies have to some extent restricted the transformation of laboratory results into individualized dietary management and classification diagnoses and treatment strategies.

Therefore, this study retrospectively enrolled 149 children with allergic diseases and 96 healthy children in the same period as the control group. The serum total IgE and the levels of sIgE, sIgG and sIgG4 of 8 common food allergens were detected. By comparing the positive rates and the distribution of medium and high grades between the case group and the control group, the efficacy of the three types of antibodies for differentiating diseases from health states was evaluated. The consistency and characteristic patterns in different foods and different clinical phenotypes was analyzed, in order to provide actionable evidence for the combined interpretation of food-specific IgE, IgG, and IgG4 in children's allergic diseases.

Materials and methods

Clinical data collection

A total of 149 children with allergic diseases who presented to our hospital between November 2024 and May 2025 were enrolled. The patients ranged in age from 0 to 14 years and were clinically diagnosed according to the classification and diagnostic criteria for allergic diseases outlined in Zhu Futang Practical Pediatrics (8th edition). The study was approved by the Ethics Committee of the People's Hospital of Guangxi Zhuang Autonomous Region.

Inclusion criteria: (1) Children presenting with allergic manifestations involving the skin, gastrointestinal tract, or respiratory tract, including atopic dermatitis, urticaria, eczema, allergic rhinitis, asthma, constipation, diarrhea, or gastrointestinal dysfunction; (2) Each patient exhibited predominant symptoms affecting only one organ system without overlap; (3) No use of medications that may influence study outcomes.

Exclusion criteria: (1) Presence of congenital diseases; (2) Severe systemic infectious diseases; (3) Concurrent serious internal medical conditions; (4) Incomplete medical history or clinical data. Based on the primary system involved, patients were categorized into three groups: digestive system (n=49), skin system (n=50), and respiratory system (n=50). Additionally, 96 children undergoing routine physical examination during the same period, with no history or symptoms of allergic disease, were recruited as the healthy control group (48 males and 48 females).

Sample size design

This study adopted a retrospective case-control design. The primary effect size was defined as the difference in the proportion of food-specific sIgE positivity (≥ Grade I) for any tested food between the case group and the healthy control group. Based on preliminary data from our institution and findings reported in similar populations, conservative assumptions were applied: the expected positivity rate in the case group was set at p_1=0.45, and that in the control group at p_0=0.25. Given that multiple comparisons involving major serological indicators were planned (i.e., total sIgE, total sIgG, and total sIgG4, each compared against key food allergens-approximately four comparisons in total), the type I error rate was adjusted using the family-wise error rate approach. A two-sided adjusted $\alpha' \approx 0.012$ was determined according to the Bonferroni correction. The statistical power was set at 1-β=0.90, and the case-to-control ratio was predetermined as $k=n_1/n_0 \approx 1.55$. Using the unequal-sample-size two-proportion comparison method (Fleiss' normal

approximation), the minimum required sample size was estimated to be approximately $n_1 \approx 149$ for the case group and $n_0 \approx 96$ for the control group. In the present study, 149 cases and 96 controls were ultimately included, fully meeting the theoretical sample size requirements.

Instruments and reagents

sIgG and sIgG4 levels were measured using the fully automated Sharay 4000 chemiluminescence analyzer (Xieguang, Sichuan, China), while total IgE and sIgE were assessed with the fully automated HOB 6500 chemiluminescence analyzer (HOB, Suzhou, China). All reagents were manufacturer-matched assay kits provided with the corresponding instruments.

Sample collection

Residual clinical serum samples (1.0-1.5 mL) from children with allergic diseases were collected and stored at -80°C prior to testing.

Laboratory testing

Serum levels of total IgE, food-specific IgE (sIgE), food-specific IgG (sIgG), and food-specific IgG4 (sIgG4) antibodies were simultaneously analyzed using chemiluminescence immunoassays. Eight common food allergens were tested: egg white, milk, beef, cod, soybean, wheat, shrimp, and crab.

Interpretation criteria

Interpretation of antibody levels followed the manufacturer's instructions: (1) Total IgE: <50 IU/mL, negative. (2) sIgE: <0.35 IU/mL, negative; 0.35-0.70 IU/mL, Grade I (low sensitization risk); 0.71-3.50 IU/mL, Grade II (moderate sensitization risk); 3.51-17.50 IU/mL, Grade III (marked sensitization risk); 17.51-50.0 IU/mL, Grade IV (high sensitization risk); 50.0-100.0 IU/mL, Grade V (very high sensitization risk). (3) sIgG: <50 U/mL, negative; 50-100 U/mL, Grade I (mild sensitization risk); 100-200 U/mL, Grade II (moderate sensitization risk); >200 U/mL, Grade III (high sensitization risk). (4) sIgG4: <50 U/mL, negative; 50-200 U/mL, Grade I (mild sensitization risk); 200-400 U/mL, Grade II (moderate sensitization risk); >400 U/mL, Grade III (high sensitization risk).

Statistical analysis

Total IgE levels, positivity rates of food-specific sIgE, sIgG, and sIgG4, and the overall positivity for each antibody type were calculated for all disease groups. Overall positivity was defined as the proportion of patients with at least one positive result among the eight tested food allergens. Data were analyzed using SPSS version 26.0. Continuous variables were expressed as median (P25, P75), whereas categorical variables were summarized as frequency or percentage. Between-group comparisons were performed using the χ^2 test, the McNemar test, or the independent-sample K-M test. Agreement among sIgE, sIgG, and sIgG4 was assessed using the Kappa statistic, with Kappa <0.4 indicating poor agreement. Using case/control status as the reference, diagnostic indices - including sensitivity, specificity, Youden index (J = sensitivity + specificity - 1), odds ratio (OR), and relative risk (RR) with 95% confidence intervals (CIs) - were calculated for sIgE, sIgG, and sIgG4. Based on the antibody grading criteria, ≥ Grade II was defined as a moderate-to-high response, and the distribution of such responses for major food allergens (milk, egg, wheat, and shrimp) were analyzed to evaluate intensity patterns. Pairwise comparisons of overall positivity rates among the gastrointestinal, dermatological, and respiratory groups were conducted using RR and corresponding 95% CIs. Statistical significance was set at $P<0.05$.

Results

Baseline characteristics

A total of 149 children with allergic diseases and 96 healthy controls were included. Gender distribution was as follows: digestive system group, 25 males and 24 females; skin system group, 24 males and 26 females; respiratory system group, 31 males and 19 females; and control group, 48 males and 48 females.

Age data were expressed as median (P25, P75). Detailed results are presented in **Table 1**.

Comparison of total IgE levels among disease groups and healthy controls

Total IgE levels differed significantly among the four groups ($P<0.05$). The median (IQR) total IgE levels were: digestive system group (n=

Table 1. Clinical characteristics of 149 patients

Group	n	Age	Z	P
		Median (P25, P75)		
Digestive system group			-0.101	0.920
Male	25	4 (2, 7.5)		
Female	24	4 (2, 6.7.5)		
Total	49	4 (2, 7)		
Skin system group			-1.226	0.220
Male	24	9 (4, 12)		
Female	26	11.5 (5, 14)		
Total	50	9.5 (4.75, 14)		
Respiratory system group			-1.759	0.079
Male	31	6 (3, 8)		
Female	19	3 (2, 6)		
Total	50	5.5 (3, 8)		
Healthy control			-1.159	0.247
Male	48	7 (5, 7)		
Female	48	6 (5, 7)		
Total	96	6 (5, 7)		

49), 59.11 IU/ml (15.45-161.16 IU/ml); skin system group (n=50), 79.32 IU/ml (23.02-506.76 IU/ml); respiratory system group (n=50), 150.98 IU/ml (45.10-450.25 IU/ml); and healthy controls (n=96), 39.67 IU/ml (10.75-94.55 IU/ml). Among all groups, the respiratory system group showed the highest median IgE level, while the healthy control group showed the lowest (P<0.05) (**Table 2**).

Comparison of sIgE, sIgG, and sIgG4 positivity rates between disease and healthy groups

The positivity rates of sIgE, sIgG, and sIgG4 were compared between the disease group (n=149) and the healthy control group (n=96). Significant differences were observed for all three antibody types between the two groups (all P<0.001) (**Table 3**).

Positivity rates and consistency analysis of sIgE, sIgG, and sIgG4

As shown in **Table 4**, the overall positivity rates among the 149 children with allergic diseases were 45.6% for sIgE, 68.5% for sIgG, and 61.1% for sIgG4, with statistically significant differences (P<0.05). For the eight tested foods, positivity rates varied significantly, with sIgG and sIgG4 generally higher than sIgE. The two most frequently positive foods were milk (44.3%) and egg (30.4%) for sIgE; egg (58.4%) and milk (49.0%) for sIgG; and milk (65.1%) and egg (36.9%) for sIgG4.

Figure 1 illustrates the distribution of specific antibody responses across the eight food allergens. sIgE positivity was highest for shrimp and crab (83.4% and 57.1%, respectively). For sIgG, the highest proportions were observed for beef (79.1%) and milk (41.2%), while sIgG4 positivity was most prominent for soybean (77.4%) and cod (68.7%).

Consistency analysis (**Table 4**) revealed poor agreement between sIgE and both sIgG and sIgG4 for overall positivity rates (Kappa <0.4, P<0.001). A weak agreement was observed between sIgG and sIgG4 (Kappa =0.438, P<0.001). For food-specific comparisons, sIgE vs. sIgG: poor agreement was observed only for egg and cod (Kappa <0.4, P<0.05), with no significant concordance for the other foods. For sIgE vs. sIgG4: poor agreement was noted for egg, soybean, milk, and beef (Kappa <0.4, P<0.05), with no concordance for the remaining items. sIgG vs. sIgG4: poor agreement was found for egg, milk, and wheat (Kappa <0.4, P<0.001), again with no concordance for other foods.

Distribution of positivity rates and antibody grades for sIgE, sIgG, and sIgG4

Among the 149 children with allergic diseases, food-specific sIgE positivity was primarily concentrated in grades 1-2, reflecting mild to moderate sensitization. For sIgG, positivity for egg, milk, and wheat was mainly distributed in grades 2-3, indicating a moderate to high sensitization risk, while the remaining foods were predominantly confined to grade 1. Similarly, sIgG4 positivity for egg and milk was mainly observed in grades 2-3, while other foods were mostly distributed at grade 1. Detailed results are presented in **Tables 5**-**7**.

Comparison of sIgE, sIgG, and sIgG4 positivity rates among symptom-based groups

For sIgE, the overall positivity rates in the digestive system, skin, and respiratory groups were

Table 2. Comparison of total IgE levels among disease groups and healthy controls

Median (P25, P75)				Inter-group comparison	Z	P
Healthy control	Digestive system group	Skin sgroup	Respiratory system group			
39.67 (10.75, 94.55)	59.11 (15.45-161.16)	79.32 (23.02, 506.76)	150.98 (45.10, 450.25)	Healthy vs. Digestive system	2.701	0.007**
				Healthy vs. Skin system	3.471	0.001**
				Healthy vs. Respiratory system	5.694	0.000***
				Digestive system vs. Skin system	-0.653	0.514
				Digestive system vs. Respiratory system	-2.581	0.010*
				Skin system vs. Respiratory system	-1.938	0.053
H		10.181				
P		0.011				

Note: *P<0.05, **P<0.01, ***P<0.001.

Table 3. Comparison of sIgE, sIgG and sIgG4 positivity between the case group and healthy controls

Antibody	Positive cases in the disease group, n (%)	Positive cases in healthy group, n (%)	χ^2	*P*
sIgE	68/45.6	6/6.3	73.372	<0.001***
sIgG	102/68.5	7/7.3	130.298	<0.001***
sIgG4	91/61.1	22/22.9	48.439	<0.001***

Note: ***P<0.001.

Table 4. Positivity rates and consistency analysis of sIgE, sIgG and sIgG4 in 149 patients

Food	Positive cases, n (%)			sIgE vs. sIgG				sIgE vs. sIgG4				sIgG vs. sIgG4			
	sIgE	sIgG	sIgG4	McNemar		Kappa		McNemar		Kappa		McNemar		Kappa	
				χ^2	*P*	k	*P*	χ^2	*P*	k	*P*	χ^2	*P*	k	*P*
Egg	45/30.2	87/58.4	55/36.9	30.414	<0.001***	0.270	<0.001***	2.000	0.203	0.249	0.002**	18.963	<0.001***	0.306	<0.001***
Cod	8/5.4	18/32.2	7/4.7	5.000	0.041*	0.169	0.024*	0.077	1.000	0.087	0.287	5.261	0.035	0.013	0.854
Soybean	11/7.4	34/22.8	5/3.4	15.114	<0.001***	0.124	0.065	3.000	0.146	0.213	0.005**	21.564	<0.001***	-0.062	0.216
Milk	66/44.3	73/49.0	97/65.1	0.778	0.450	0.152	0.062	17.473	<0.001***	0.286	<0.001***	11.077	0.001***	0.306	<0.001***
Beef	2/1.4	2/1.3	13/8.7	0.000	1.000	-0.014	0.868	9.308	0.003**	0.113	0.038	8.067	0.007**	-0.024	0.660
Shrimp	26/17.6	4/2.7	1/0.7	16.133	<0.001***	-0.049	0.349	23.148	<0.001***	-0.013	0.643	1.800	0.375	-0.011	0.868
Wheat	20/13.4	71/48.0	22/14.8	34.797	<0.001***	0.038	0.525	0.000	1.000***	0.146	0.076	45.302	<0.001***	0.236	<0.001***
Crab	12/8.1	7/4.7	2/1.3	1.316	0.359	-0.064	0.421	7.143	0.013	-0.024	0.672	2.778	0.180	-0.021	0.752
Total positive	68/45.6	102/68.5	91/61.1	21.356	<0.001***	0.297	<0.001***	18.234	<0.001***	0.371	<0.001***	12.500	0.001***	0.438	<0.001***

Note: *P<0.05, **P<0.01, ***P<0.001.

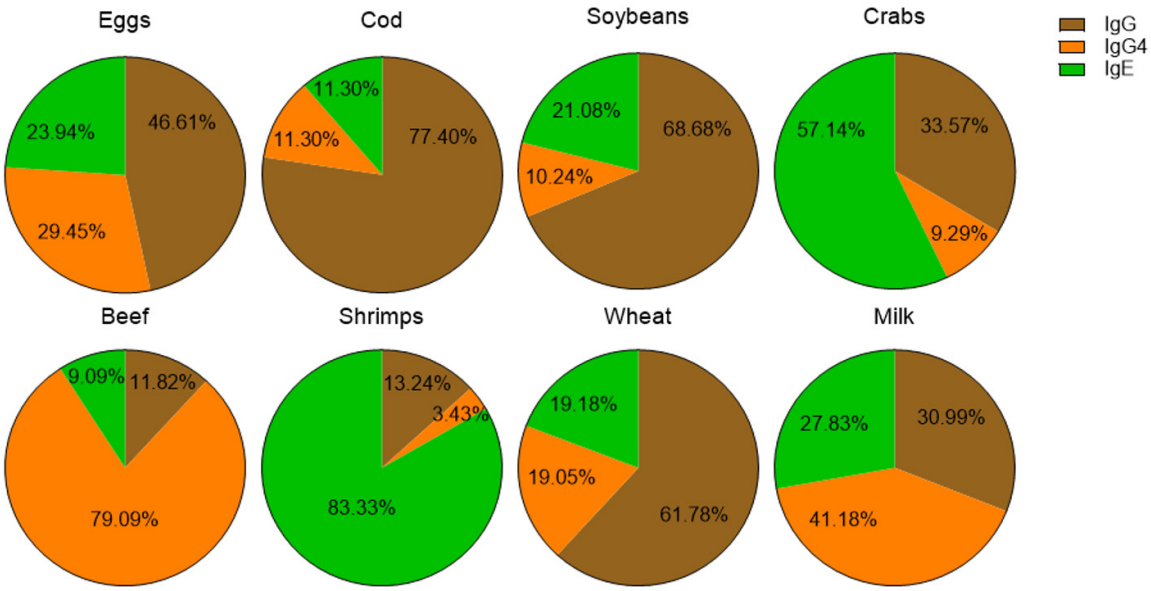

Figure 1. Proportional distribution of sIgE, sIgG, and sIgG4 antibodies across eight common allergenic foods.

Table 5. Positivity grades and distribution of sIgE antibodies in 149 patients

Food	Grade I, n (%)	Grade II, n (%)	Grade III, n (%)	Grade IV, n (%)	Total
Egg	14 (31.1)	24 (53.3)	3 (6.7)	4 (8.9%)	45
Cod	5 (62.5)	1 (12.5)	2 (25%)	0	8
Soybean	5 (45.5)	5 (45.5)	1 (9%)	0	11
Milk	21 (31.8)	39 (59.1)	6 (9.1)	0	66
Beef	1 (50%)	1 (50%)	0	0	2
Shrimp	11 (42.3%)	11 (42.3%)	3 (11.6%)	1 (3.8%)	26
Wheat	15 (7.5%)	3 (15%)	2 (10%)	0	20
Crab	3 (25%)	8 (66.7%)	1 (8.33%)	0	12

Table 6. Positivity grades and distribution of sIgG antibodies in 149 patients

Food	Grade I, n (%)	Grade II, n (%)	Grade III, n (%)	Total
Egg	13 (14.9%)	32 (36.8%)	42 (48.3%)	87
Cod	14 (77.8%)	3 (16.6%)	1 (5.6%)	18
Soybean	14 (41.2%)	17 (50%)	3 (8.8%)	34
Milk	21 (28.7%)	29 (39.7%)	23 (31.6%)	73
Beef	1 (50%)	0	1 (50%)	2
Shrimp	2 (50%)	2 (50%)	0	4
Wheat	22 (31%)	42 (59.2%)	7 (9.8%)	71
Crab	6 (85.7%)	1 (14.3%)	0	7

69.4%, 44.0%, and 58.0%, respectively, with significant differences ($P<0.01$). In the digestive system group, milk, egg, and shrimp exhibited the highest sIgE positivity (57.1%, 42.6%, and 26.0%, respectively), with all showing significant differences compared with the other two groups ($P<0.01$). In both the skin and respiratory groups, the three most frequently positive foods were egg, milk, and wheat. For sIgG, the overall positivity rates were 89.8%, 72%, and 82% in the digestive system, skin system, and respiratory system groups, respectively

Table 7. Positivity grades and distribution of sIgG4 antibodies in 149 patients

Food	Grade I, n (%)	Grade II, n (%)	Grade III, n (%)	Total
Egg	12 (21.8%)	19 (34.6%)	24 (43.6%)	55
Cod	2 (28.6%)	2 (28.6%)	3 (42.8%)	7
Soybean	3 (60%)	2 (40%)	0	5
Milk	21 (21.6%)	10 (10.4%)	66 (68%)	97
Beef	11 (84.6%)	0	2 (15.4%)	13
Shrimp	1 (100%)	0	0	1
Wheat	17 (77.3%)	3 (13.6%)	2 (9.1%)	22
Crab	21 (100%)	0	0	2

(P>0.05). Across all three groups, egg, milk, and wheat showed the highest positivity. For sIgG4, the overall positivity rates were 59.2%, 66%, and 80% in the digestive system, skin system, and respiratory system groups, respectively, with no significant differences (P>0.05). In all groups, the top three foods were milk, egg, and wheat. Results are presented in **Table 8**.

Diagnostic performance of sIgE, sIgG, and sIgG4 in distinguishing cases from healthy controls

Using a positive/negative classification to differentiate patients from healthy controls, diagnostic indices including sensitivity (proportion of patients testing positive), specificity (proportion of controls testing negative), odds ratio (OR), relative risk (RR), and Youden index (J = sensitivity + specificity - 1) were calculated. Among the three antibody types, sIgG demonstrated the highest discriminative performance (sensitivity 68.5%, specificity 92.7%, J=0.612, OR=27.59, RR=9.39), followed by sIgE, while sIgG4 showed relatively lower performance. Results are presented in **Table 9**.

Proportion of moderate-to-high positivity (≥ Grade II) for major foods

For sIgG, the highest proportions of moderate-to-high responses (≥ Grade II) were observed for egg, milk, and wheat (85.1%, 71.2%, and 69.0%, respectively). For sIgG4, milk and egg also exhibited relatively high proportions (78.4% and 78.2%, respectively). For sIgE, shrimp showed the most prominent ≥ Grade II response (57.7%). Results are presented in **Table 10**.

Comparison of overall positivity rates of the three antibodies across clinical phenotypes

The overall sIgE positivity rate was significantly higher in the digestive system group, compared with the skin group (RR=1.62, 95% CI 1.13-2.33). For sIgG, the digestive system group demonstrated a nominally higher positivity than the skin group (RR=1.25). Regarding sIgG4, the respiratory group had a higher positivity rate compared with the digestive system group (RR=1.35). Detailed results are presented in **Table 11**.

Discussion

Food-induced allergies are defined as adverse reactions to food proteins, presenting with a spectrum of clinical manifestations including gastrointestinal dysfunction, urticaria, and airway inflammation [5]. Allergic reactions are classified into three types: IgE-mediated, non-IgE-mediated, and mixed mechanisms [6]. While IgE-mediated type I hypersensitivity has been considered the predominant pathway in allergic diseases, IgG-mediated chronic food allergies are increasingly recognized. Evidence indicates that IgG can trigger immediate immune responses by mast cell activation, similar to IgE, and can also form allergen-immune complexes that promote the release of inflammatory mediators, leading to chronic tissue damage [7, 8]. As a subclass of IgG antibodies, IgG4 exhibits unique molecular and biological properties, and its clinical significance in allergic diseases remains controversial. Some studies suggest that food-specific IgG4 (sIgG4) plays a tolerogenic role in allergen-specific immunotherapy, acting as a protective antibody [9]. However, other research had reported a significant association between elevated food

Table 8. Comparison of sIgE, sIgG and sIgG4 positivity rates across allergic symptom-based groups

Food	sIgE positive cases (n, %)			χ^2	*P*	sIgG positive cases (n, %)			χ^2	*P*	sIgG4 positive cases (n, %)			χ^2	*P*
	Digestive system group	Skin system group	Respiratory system group			Digestive system group	Skin system group	Respiratory system group			Digestive system group	Skin system group	Respiratory system group		
Egg	21/42.0	9/18.4	15/30.6	6.533	0.038*	25/51.0	26/52.0	36/72.0	5.748	0.056	7/14.3	19/38.0	29/58.0	20.346	<0.001***
Cod	2/4.1	0	6/12.0	7.221	0.027*	4/8.2	4/8.0	10/20.0	4.444	0.108	2/4.1	2/4.0	3/6.0	0.285	0.867
Soybean	4/8.2	1/0.2	5/10.0	2.718	0.257	12/24.5	7/14.0	15/30.0	3.750	0.153	0	3/6.0	2/4.0	2.843	0.241
Milk	28/57.1	12/24.5	26/52.0	12.249	0.002**	25/51.0	20/40.0	28/56.0	2.681	0.262	29/59.2	29/58.0	39/78.0	5.527	0.063
Beef	0	0	2/4.0	3.974	0.137	1/2.0	1/2.0	0	2.014	0.365	4/8.2	3/6.0	6/12.0	1.159	0.560
Shrimp	13/26.0	4/8.2	9/13.4	6.469	0.035*	1/2.0	0	3/6.0	3.561	0.169	0	1/2.0	0	1.993	0.369
Wheat	4/8.2	7/14.3	11/22.0	3.763	0.152	24/49.0	18/36.0	29/58.0	4.902	0.086	5/10.2	6/12.0	11/22.0	3.193	0.203
Crab	2/4.1	2/4.1	8/16.0	6.312	0.043*	2/4.1	0	5/10.0	5.646	0.059	1/2.0	1/2.0	0	1.024	0.599
Total positive	35/69.4	22/44.0	29/58.0	9.231	0.010*	44/89.8	36/72.0	41/82.0	5.435	0.066	29/59.2	33/66.0	40/80.0	5.176	0.075

Note: *P<0.05, **P<0.01, ***P<0.001.

Table 9. Diagnostic performance of sIgE, sIgG, and sIgG4 in distinguishing cases from healthy controls

Antibody	Case (Positive/Negative)	Healthy (Positive/Negative)	Sensitivity (95% CI)	Specificity (95% CI)	Youden's J	OR (95% CI)	RR (95% CI)
sIgE	68/81	6/90	45.6% (37.9-53.6)	93.8% (87.0-97.1)	0.394	12.59 (5.19-30.57)	7.30 (3.30-16.16)
sIgG	102/47	7/89	68.5% (60.6-75.4)	92.7% (85.7-96.4)	0.612	27.59 (11.87-64.13)	9.39 (4.56-19.32)
sIgG4	91/58	22/74	61.1% (53.1-68.5)	77.1% (67.7-84.4)	0.382	5.28 (2.96-9.41)	2.67 (1.81-3.93)

Table 10. Proportion of moderate-to-high responses (Grade ≥ II) for eight food allergens

Food	sIgE ≥ II (cases/ positive, total %)	sIgG ≥ II (cases/ positive, total %)	sIgG4 ≥ II (cases/ positive, total %)
Milk	45/66 (68.2%)	52/73 (71.2%)	76/97 (78.4%)
Egg	31/45 (68.9%)	74/87 (85.1%)	43/55 (78.2%)
Wheat	5/20 (25.0%)	49/71 (69.0%)	5/22 (22.7%)
Shrimp	15/26 (57.7%)	2/4 (50.0%)	0/1 (0.0%)
Cod	3/8 (37.5%)	4/18 (22.2%)	5/7 (71.4%)
Soybean	6/11 (54.5%)	20/34 (58.8%)	2/5 (40.0%)
Beef	1/2 (50.0%)	1/2 (50.0%)	2/13 (15.4%)
Crab	9/12 (75.0%)	1/7 (14.3%)	0/2 (0.0%)

IgG4 levels and allergic inflammatory symptoms in affected patients [10]. These findings underscore the need for controlled studies to clarify the interrelationships and clinical utility of sIgE, sIgG, and sIgG4 in pediatric allergic diseases. From a clinical perspective, understanding these immune pathways is essential for guiding testing strategies according to the patient's clinical phenotype. For individuals with suspected immediate-type reactions, such as perioral pruritus, urticaria, wheezing, or a history of anaphylaxis, priority should be given to sIgE measurement or skin testing. In contrast, patients with predominantly chronic gastrointestinal or dermatological symptoms and prolonged disease courses may benefit from complementary sIgG and sIgG4 evaluations, alongside medical history and nutritional assessment, to identify evidence of long-term allergen exposure. Importantly, laboratory results should always be interpreted in the context of clinical follow-up or standardized elimination-challenge testing, to prevent unnecessarily restrictive dietary interventions based solely on IgG or IgG4 findings.

In the 149 pediatric patients included in this study, the overall positivity rates of sIgE, sIgG, and sIgG4 were 45.6%, 68.5%, and 61.1%, respectively, all significantly higher than those observed in the healthy control group. Significant differences were also noted among the three antibody types. Across the eight tested foods, most sIgE, sIgG, and sIgG4 positivity rates differed significantly. Consistency analysis revealed poor agreement between sIgE and both sIgG and sIgG4 (Kappa <0.4), with some individual foods showing no concordance. These findings support the coexistence of IgE-mediated and non-IgE-mediated immune mechanisms in pediatric allergic diseases, consistent with previous reports by Yin et al. [11]. The overall consistency between sIgG4 and sIgG was weak (Kappa =0.438), whereas concordance for individual foods was often poor or absent, indicating that sIgG cannot substitute for sIgG4 testing and that each assay provides distinct clinical information. As a subclass of IgG, IgG4 constitutes approximately 5% of total IgG, and many chronic allergic responses may be mediated by IgG4 or other IgG subclasses involved in immune regulation [12]. These findings suggest that adverse reactions to foods can be mediated through multiple immune pathways, highlighting the value of combined assessment of sIgE, sIgG, and sIgG4 in the clinical evaluation of pediatric allergic diseases. From a clinical perspective, interpretation should follow the principle of "complementary rather than substitutive". A positive sIgE result in the presence of corresponding immediate-type symptoms supports an IgE-mediated allergy risk, guiding prompt management and strict allergen avoidance. Conversely, in cases where sIgE is negative but symptoms persist in a temporally related manner to food intake, positive sIgG or sIgG4 findings may indicate relevant exposure. In such cases, physician- and dietitian-guided time-limited elimination-reintroduction trials are appropriate, with changes in clinical symptoms serving as the primary basis for decision-making. This approach helps minimize missed diagnoses and avoid inappropriate interventions.

The study further observed that sIgG and sIgG4 positivity rates were generally higher than those of sIgE. Moreover, sIgE responses were mostly mild, concentrated at grades - I-II, whereas sIgG and sIgG4 responses to common allergenic foods were primarily distributed at grades - II-III, representing moderate-to-high sensitization. These findings suggest that sIgG and sIgG4 may play a more critical role in chronic food allergies in children, consistent with the observations reported by Yang et al. [13]. In this study, symptom duration ranged

Table 11. Comparison of total positive rates of sIgE, sIgG, and sIgG4 across clinical phenotypes

Comparison (former vs. latter)	Positive rate of the former (%)	Positive proportion of the latter (%)	Absolute difference (%)	RR (95% CI)
Total positive rate of sIgE				
Digestive vs. Skin	35/49 (71.4%)	22/50 (44.0%)	27.4	1.62 (1.13-2.33)
Respiratory vs. Skin	29/50 (58.0%)	22/50 (44.0%)	14	1.32 (0.89-1.95)
Digestive vs. Respiratory	35/49 (71.4%)	29/50 (58.0%)	13.4	1.23 (0.92-1.65)
Total positive rate of sIgG				
Digestive vs. Skin	44/49 (89.8%)	36/50 (72.0%)	17.8	1.25 (1.02-1.52)
Respiratory vs. Skin	41/50 (82.0%)	36/50 (72.0%)	10	1.14 (0.92-1.41)
Digestive vs. Respiratory	44/49 (89.8%)	41/50 (82.0%)	7.8	1.10 (0.93-1.29)
Total positive rate of sIgG4				
Respiratory vs. Skin	40/50 (80.0%)	33/50 (66.0%)	14	1.21 (0.95-1.54)
Respiratory vs. Digestive	40/50 (80.0%)	29/49 (59.2%)	20.8	1.35 (1.03-1.77)
Skin vs Digestive	33/50 (66.0%)	29/49 (59.2%)	6.8	1.11 (0.83-1.22)

from 2 weeks to 6 months. Previous research has shown that prolonged antigen exposure can shift B-cell responses from IgE-dominant to IgG-dominant production [14]. Accordingly, sIgE-mediated immediate reactions are unlikely to serve as the primary triggers of chronic allergic manifestations in children. Clinical evidence also indicates that dietary interventions guided by sIgG and sIgG4 results can help alleviate related symptoms [15]. Therefore, in children presenting predominantly with chronic or recurrent symptoms, such as abdominal pain, bloating, or exacerbation of chronic eczema, elevated sIgG/sIgG4 levels can inform the prioritization of targeted dietary interventions. Short-term elimination should initially focus on foods associated with the highest exposure and antibody titers, with outcomes assessed primarily through symptom relief, growth indices (weight and height), and quality of life. Nutritional risks should be evaluated concurrently, and follow-up reassessments scheduled to prevent energy or micronutrient deficiencies arising from prolonged, broad-spectrum dietary restrictions.

As shown in **Table 4**, the top three sIgE-positive foods were milk, egg, and shrimp, whereas sIgG and sIgG4 positivity were most frequently observed for milk, egg, and wheat. Milk and eggs are major dietary protein sources for children and are among the most common food allergens [16]. In this study, all three antibodies showed high positivity for these foods, suggesting their involvement in both immediate- and delayed-type immune responses and highlighting their potential role in symptom development. By contrast, beef showed low positivity across all three antibodies, likely reflecting its lower consumption frequency in this population. **Figure 1** further illustrates that sIgE positivity was particularly high for shrimp and crab, accounting for 83.4% and 57.1%, respectively, indicating predominantly IgE-mediated immediate reactions. Consistent with previous reports, seafood allergy is typically IgE-mediated, partly due to high histamine content, with tolerance development in preschool children occurring in only approximately 3.4% of cases [17]. Clinically, children with positive results for milk or egg and corresponding symptoms should be managed for immediate-type reactions, including education on epinephrine auto-injector use and risk stratification based on sIgE levels and prior reaction history, alongside appropriate nutritional substitutions. For predominantly sIgE-mediated shrimp allergy, strict avoidance and reintroduction under medical supervision in an emergency-prepared setting are recommended. In contrast, wheat, which showed higher sIgG/sIgG4 positivity, can be managed using a time-limited elimination-reintroduction protocol, with causal associations assessed through symptom monitoring.

In subgroup analyses stratified by digestive, skin, and respiratory symptoms, no significant differences were observed in sIgG or sIgG4 positivity among the groups; however, sIgE positivity differed significantly, with rates of 69.4%, 44.0%, and 58.0% in the digestive system, skin, and respiratory system groups,

respectively. Notably, sIgE positivity for major allergenic foods, such as milk, egg, and shrimp, was highest in the digestive system group (57.1%, 42.6%, and 26.0%, respectively). This pattern reflects the natural course of pediatric food allergies, in which initial gastrointestinal sensitization often precedes the development of tolerance or other allergic manifestations [18]. Therefore, IgE antibodies to major allergens are more likely to directly elicit gastrointestinal symptoms compared with dermatologic or respiratory presentations. Although the skin group exhibited relatively high sIgE positivity, the respiratory system group demonstrated the highest total IgE levels, indicating concurrent IgE-mediated responses to inhalant allergens. Current studies on food-specific sIgE, sIgG, and sIgG4 rarely stratify results by clinical phenotype, limiting comparative insights and highlighting the need for larger, phenotype-specific investigations. Clinically, the phenotype-stratified findings from this study can guide tailored management: for children with predominant gastrointestinal symptoms, priority should be given to sIgE assessment for milk, egg, and shrimp, with early intervention; for children with respiratory symptoms and elevated total IgE, concurrent screening for inhalant allergens is recommended to prevent unnecessary food restrictions; and for the skin group, combined interpretation of sIgE and sIgG/IgG4 is advised to address both immediate triggers and long-term exposures, thereby enhancing intervention precision and reducing ineffective dietary limitations.

In this cohort, sIgG demonstrated superior discriminative performance compared to sIgE and sIgG4 (Youden's J: 0.612 vs. 0.394 and 0.382), more accurately reflecting long-term or repeated exposure responses associated with disease status. Analysis of intensity distribution revealed the highest proportion of sIgG ≥ II-grade responses for egg, milk, and wheat (85.1%, 71.2%, and 69.0%, respectively), while sIgG4 levels were also elevated for milk and egg (78.4% and 78.2%). By contrast, shrimp responses were predominantly sIgE-mediated (≥ II-grade 57.7%), consistent with clinical observations of immediate hypersensitivity to seafood and both immediate and delayed reactions to milk and egg. Phenotype-stratified pairwise comparisons revealed that the digestive system group had higher overall sIgE positivity than the skin group (RR=1.62, 95% CI 1.13-2.33), whereas the respiratory system group exhibited higher sIgG4 levels than the digestive system group (RR=1.35, 95% CI 1.03-1.77). These comparisons were not adjusted for multiple testing and should be considered exploratory; confirmation in larger, prospective studies is warranted. In clinical practice, patient history remains central, and interpretation of sIgE, sIgG, and sIgG4 should be stratified by phenotype. Application should be restricted to time-limited elimination diets and/or standardized challenge tests, as IgG/IgG4 results alone are not recommended for diagnostic decision-making, to avoid unnecessary prolonged or broad-spectrum dietary restrictions.

In pediatric clinical practice in China, children aged 0-14 years represent the primary population covered by both clinical services and research. In this study, pediatric patients aged 1-14 years were included, based on sample availability and ethical approval requirements. It should be noted that age-stratified analyses were not performed, which constituted a limitation of the study. Previous immunologic and epidemiologic evidence indicated that immune system maturity, the introduction and evolution of complementary foods and overall dietary structure, environmental exposures, and hormonal changes (e.g., transitions from preschool and school age to early adolescence) can influence the spectrum and phenotypic expression of food-specific antibodies. These factors may result in age-dependent differences in the detection rates and intensity distribution of sIgE, sIgG, and sIgG4. Therefore, future studies should incorporate age-stratified analyses (e.g., 1-<3 years, 3-<6 years, 6-<12 years, and 12-14 years) with larger sample sizes. Multivariate adjustments and sensitivity analyses should also be conducted, accounting for key confounders such as feeding practices, previous allergic history, coexisting inhalant allergen sensitization, prior antiallergic treatment, and recent infections. Such analyses would help clarify the age-specific patterns of food-specific antibody responses and provide more precise guidance for clinical assessment and management in children of different age groups.

Although research on sIgE, sIgG, and sIgG4 in food-related adverse reactions has been expanding, their precise pathogenic roles in

allergic diseases remain incompletely understood, and no consensus has been reached. Our study demonstrates that the expression patterns of these three antibodies vary across different allergic phenotypes, suggesting a need for integrated clinical assessment and management that considers sIgE, sIgG, and sIgG4 together. Future studies should include larger sample sizes to further investigate their therapeutic use and to identify targets for intervention. Based on our findings, we propose a clinical workflow that incorporate a closed loop of "history-phenotype stratification-combined antibody interpretation-short-term intervention-objective reassessment": select tests guided by patient history; jointly interpret the three antibodies according to their complementarity, as indicated by Kappa values; implement time-limited dietary interventions, with symptom improvement and growth indices as primary outcomes; perform challenge tests under medical supervision if necessary; and dynamically update individualized management plans to translate laboratory results into reproducible clinical benefits.

Disclosure of conflict of interest

None.

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