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Investigating allergen-specific IgE distribution and correlations in chronic urticaria: a retrospective study in Shanghai, China

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Abstract

Background Chronic urticaria (CU) is a persistent skin condition characterized by recurring episodes triggered by diverse allergens and a multifaceted causative nature. The present study aimed to retrospectively explore the distribution patterns and correlations of specific IgE (sIgE) antibodies with various allergens among patients with CU.

Methods For this purpose, the present study enrolled 820 patients with CU treated at Shanghai Skin Disease Hospital from July 2020 to September 2023. Serum samples were assessed for allergen sIgE antibodies via an immunodiagnostic assay. Chi-square tests were used to examine the differences in allergen sIgE antibody distribution across the sex and age groups. Spearman's correlation analysis was used to investigate the correlations between different allergens.

Results Among the 820 patients with CU, 705 presented positive results for at least one sIgE antibody. Concerning sex, no significant disparities were observed in food allergen distribution; however, males presented notably higher storage mites and Aspergillus levels than females. Age stratification revealed that adolescents had significantly higher positivity rates for milk, egg yolk, house dust mites, storage mites, cat and dog dander, and timothy grass than adults and elderly patients. The correlation coefficient between house dust mites and storage mites reached 0.81. However, correlations among distinct food allergens mostly remained below 0.3, barring sesame and mixed fruits, which was a weak correlation ($r=0.31$). The correlations between food and inhaled allergens ranged from 0.3 to 0.5, suggesting a relatively weak association.

Conclusions There were no sex disparities in the distribution of ingestible allergens, yet adolescents presented higher positivity rates than the other age groups. The associations among food allergens, as well as food and inhaled allergens, were relatively weak.

Trial registration Retrospectively registered.

Keywords Chronic spontaneous urticarial, sIgE, Food allergens, Inhaled allergens, Correlations

Background

Chronic urticaria (CU) is a persistent dermatological condition marked by recurrent transient wheals and possible vascular edema, lasting at least 6 weeks. The pathogenesis of CU remains unclear, and it can be triggered by various factors, such as environmental stimuli, drugs, temperature changes (hot or cold), and physical activity [1]. Parasitic infections have also been proposed as potential triggers for exacerbations of CU [2]. Globally,

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the prevalence of CU ranges from 0.02 to 5% [3]. CU's unpredictable and recurrent nature significantly impairs patients' quality of life. This condition is characterized by unbearable pruritus and a lack of established therapeutic options, resulting in a significant burden of prolonged pharmacotherapy and psychological distress for patients. Therefore, understanding the social and health implications of this condition is crucial.

Immunoglobulin E (IgE) plays a crucial role in the immune system, as the fifth class of IgE acts as a primary mediator in allergic responses and is strongly associated with conditions such as urticaria and asthma [4]. Testing for specific IgE (sIgE) directed against specific allergens has a history spanning several decades [5]. The primary detection methods include skin tests and serum sIgE assessments. Skin tests involve introducing minute amounts of allergens to observe reactions. While rapid and sensitive, this method may cause potential adverse reactions, leading to the development of safer in vitro tests [6]. Standard in vitro assays for IgE detection include immunodiagnostics, ELISA, microarray platforms, and highly sensitive immunoprotein chain reaction (iPCR) [7].

The present study utilized immunodiagnostics to analyze IgE antibodies in 820 patients with CU treated at Shanghai Skin Disease Hospital between July 2020 and September 2023. The main objective of the present study was to investigate the distribution characteristics and correlation analysis of various allergens.

Materials and methods

Patients and samples. All 820 enrolled patients were recruited from the outpatient department of Shanghai Skin Disease Hospital. They had been diagnosed with CU, with a duration exceeding 6 weeks, and had not used corticosteroids or immunosuppressants in the 2 months prior to enrollment. The cohort was stratified by sex and consisted of 293 males and 527 females. The age distribution included three groups: adolescents (1–18 years; average, 13.43 years), adults (19–50 years; average, 31.12 years), and older patients (> 51 years; average, 60.6 years).

Previous research has documented a series of common allergens among the general population in southern China [8]. This method was used as a standard to select 29 common allergens as the focus of the present study. The 29 allergens examined were classified as follows: food allergens, such as egg white, sesame, peanuts, milk, shellfish, beef, fish, wheat, egg yolk, mixed fruits (including peach, apple, mango, lychee, and strawberry), mixed nuts (including cashews, pistachios, hazelnuts, almonds, and walnuts) and inhalant allergens, such as house dust mites, storage mites, tropical mites, cat dander, dog dander, cockroaches, silk, *Aspergillus*, *Candida*, Timothy grass, boxelder, birch, tree pollen 1, tree pollen 2, short ragweed, chickweed, ragweed and *Artemisia*. IgE-mediated food allergy is not a direct cause of chronic urticaria; however, it remains one of the triggers. Over the years, numerous reports have linked food to chronic urticaria; thus, we included common food allergens in the present study. Venous blood samples were collected from outpatients and centrifuged (2150 × g, 25 °C, 15 min) to separate the serum. The sIgE antibodies were detected via an immunoassay kit and a MEDIWISS Analytic GmbH allergen detection device, which were acquired from MEDIWISS Analytic GmbH. The sIgE antibody values were categorized as degree 0 (< 0.35 IU/ml), degree 1 (0.35–0.69 IU/ml), degree 2 (0.70–3.4 IU/ml), degree 3 (3.50–17.4 IU/ml), degree 4 (17.5–49.9 IU/ml), degree 5 (50–100 IU/ml) or degree 6 (> 100 IU/ml).

Statistical analysis. Statistical analyses were performed via MedCalc 19.0.4 (MEDIWISS Analytic GmbH) and GraphPad Prism 8 software (Dotmatics). The Chi-square test was used to investigate the differences in the distributions of allergen sIgE across the sex and age groups. Spearman correlation analysis was employed to explore potential correlations between various allergens. A correlation coefficient of $r < 0.3$ indicated no correlation, $r \geq 0.3$ or $r < 0.5$ implied a weak correlation, $r \geq 0.5$ or $r < 0.8$ signified a moderate correlation, and $r \geq 0.8$ or $r < 1$ denoted a strong correlation. A value of $P < 0.05$ was considered to indicate statistically significant differences.

Results

Among the 820 patients with CU, 705 tested positive for sIgE (with at least one degree > 0), resulting in a positivity rate of 85.96%. Patients who tested negative for allergen-specific IgE do not have a distribution of allergen-specific IgE; thus, they were excluded from the study. Among the sIgE-positive individuals, 255 were male (36.17%), and 450 were female (63.83%). The age distribution of the positive cases included 97 adolescents (13.76%), 312 adults (44.26%), and 296 older individuals (41.98%). The demographic characteristics of the patients are presented in Table 1.

To compare the distribution across various allergen levels, patients who tested positive for allergies were stratified by allergen type. Both food and inhalant allergens presented relatively high concentrations of positive reactions at levels 1 and 2, as depicted in Figs. 1 and 2. The prevalence of level 1 and 2 allergens was significantly greater than that of allergens with a level ≥ 3, and the difference was statistically significant ($P < 0.001$).

The distribution of sIgE antibodies across diverse sex and age groups was subsequently statistically analyzed. Within the sex-based comparison, no statistically significant differences were noted in the distribution of

Table 1 Patient demographic characteristics

Characteristics	Positive ($n=705$)	Negative ($n=115$)
Sex, *n* (%)		
Male	255(36.2)	38(33.04)
Female	450(63.8)	77(66.96)
Age (years), *n* (%)		
1–18	97(13.76)	8(6.96)
19–50	312(44.26)	52(45.22)
>51	296(41.99)	55(47.83)
Other diseases, *n* (%)		
(+)	326(46.24)	30(26.09)
(–)	379(53.76)	85(73.91)
Ethnicity (Han Chinese), *n* (%)	705(100)	115(100)
Residence (Urban areas), *n* (%)	705(100)	115(100)

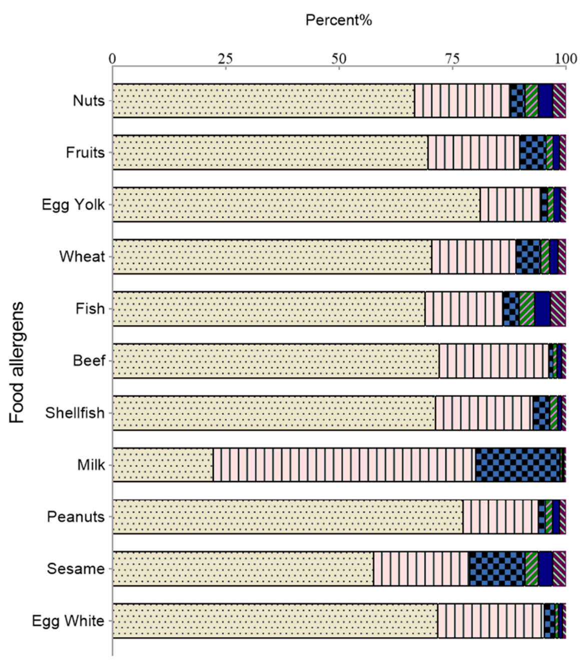

Fig. 1 The distribution of positive grades in food allergens

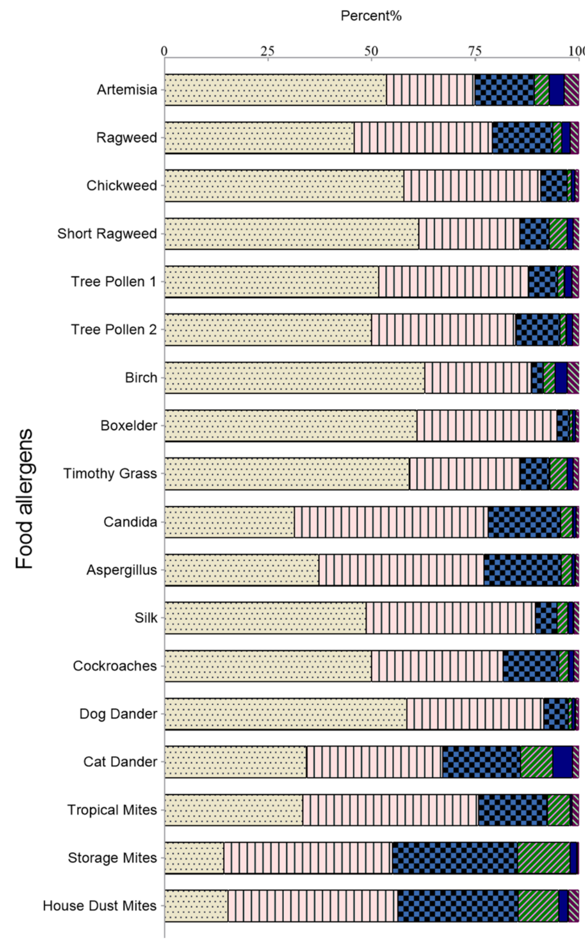

Fig. 2 The distribution of positive grades in inhalant allergens

food allergens (Table 2). There were slight variations in the distribution of inhalant allergens. Among the males, the positivity rates for dust mites (36.86%) and *Aspergillus fumigatus* (18.82%) were notably greater than those for the females, indicating statistically significant differences (Table 2). For patients across different age groups, the positivity rates for milk, egg yolk, house dust mites, storage mites, cat dander, dog dander, and timothy grass were significantly greater in adolescents than in adults and elderly patients (Table 3). Moreover, regardless of sex or age, milk consistently presented the highest positivity rate, followed closely by egg whites.

Additionally, simultaneous positivity was observed for multiple sIgE antibodies among the positive cohort, as depicted in Fig. 3. Excluding patients with single positive responses, the majority of patients predominantly exhibited simultaneous positive reactions to two items (15.74%), three items (17.02%) and four items (13.48%). Patients who tested positive for five to seven items accounted for ~ 25.82% of the total. This prompted the authors to conduct a correlation analysis among the 29 allergens, as illustrated in Fig. 4. Notably, the correlation coefficients among the food allergens predominantly remained < 0.3, apart from a modest correlation between sesame and fruits ($r=0.31$, $P<0.001$). Concerning the correlations between food and inhalant allergens, the coefficients for tree pollen type 1, tree pollen type 2, short ragweed, and sesame ranged between 0.3 and 0.5, indicating that a weak correlation was statistically significant. Among the inhalant allergens, a notably strong correlation was detected between house dust mites and

Table 2 Distribution of sIgE in different sex groups of food- and inhalable allergens

	Male ($n=255$)	Female ($n=450$)	P value
Food allergens			
Egg white	41 (16.08)	80 (17.78)	0.4026
Sesame	12 (4.71)	18 (4)	0.4738
Peanuts	25 (9.8)	37 (8.22)	0.1969
Milk	71 (27.84)	146 (32.44)	0.4058
Shellfish	45 (17.65)	64 (14.22)	0.0753
Beef	44 (17.25)	56 (12.44)	0.4585
Fish	9 (3.53)	16 (3.56)	0.0521
Wheat	18 (7.06)	33 (7.33)	0.8805
Egg yolk	25 (9.8)	46 (10.22)	0.0941
Fruits	22 (8.63)	44 (9.78)	0.4687
Nuts	11 (4.31)	18 (4)	0.1171
Inhalable allergens			
House dust mites	103 (40.39)	59 (13.11)	0.4606
Storage mites	94 (36.86)	15 (3.33)	0.0472*
Tropical mites	75 (29.41)	43 (9.56)	0.3083
Cat dander	24 (9.41)	28 (6.22)	0.4234
Dog dander	49 (19.22)	46 (10.22)	0.3139
Cockroaches	30 (11.76)	39 (8.67)	0.1712
Silk	34 (13.33)	16 (3.56)	0.2205
Aspergillus	48 (18.82)	37 (8.22)	0.015*
Candida	42 (16.47)	80 (17.78)	0.6974
Timothy grass	23 (9.02)	46 (10.22)	0.2433
Boxelder	50 (19.61)	80 (17.78)	0.4167
Birch	17 (6.67)	15 (3.33)	0.1549
Tree pollen 1	18 (7.06)	37 (8.22)	0.2744
Tree pollen 2	21 (8.24)	43 (9.56)	0.3321
Short ragweed	29 (11.37)	39 (8.67)	0.1686
Chickweed	48 (18.82)	59 (13.11)	0.0779
Ragweed	19 (7.45)	28 (6.22)	0.22
Artemisia	9 (3.53)	16 (3.56)	0.3589

The values are represented as N, number (%)

* $P < 0.05$; ** $P < 0.01$

storage mites ($r=0.81$, $P<0.001$), whereas the correlations between house dust mites, storage mites, and tropical rat mites were relatively weak ($r=0.42$, $P<0.001$; $r=0.41$, $P<0.001$). Furthermore, the correlation coefficients between tree pollen (boxelder, birch, tree pollen 1 and tree pollen 2) and grass (Timothy grass, short ragweed, chickweed, ragweed, and *Artemisia*) ranged between 0.3 and 0.5, indicating a weak yet statistically significant correlation.

Discussion

CU is not a single, well-defined disease, but rather an umbrella term that encompasses a variety of clinical phenotypes. Research on chronic urticaria has been inconsistent due to the unclear pathogenesis, with the possibility of multiple underlying endotypes involved [9]. Establishing clearly defined phenotypes and endotypes is essential to predict the prognosis and treatment response [10, 11]. Patients with CU can be classified based on their phenotypes and endotypes according to different clinical presentations and immune mechanisms. Phenotypes refer to classifications based on observable clinical characteristics, such as treatment response, disease duration and severity, and types of allergens, while endotypes categorize patients into multiple pathological subgroups based on their distinct immune response mechanisms.

Researchers have proposed two distinct endotypes for CU based on key pathogenic mechanisms: Type I (autoallergic) and Type IIb (autoimmune). Type I CU is primarily driven by IgE-mediated activation of mast cells, while Type IIb CU is mediated by IgG autoantibodies that act primarily on FcεRI or IgE bound to FcεRI, leading to mast cell activation [12]. Notably, evidence suggests that patients with Type I CU may develop IgG antibodies against FcεRI or IgE over time, indicating that Type I CU may serve as a risk factor for the development of Type IIb disease [13]. Therefore, the detection of IgE levels becomes particularly important, as it is one of the key biomarkers in chronic urticaria research, but it can be influenced by factors such as gender and age.

We measured sIgE levels in patient sera via an immunoassay kit and categorized the sIgE intensity levels for different allergens. A retrospective analysis was conducted to compare the distribution differences in gender and age between food allergy phenotypes and secondary food allergen phenotypes (inhalant allergen phenotypes). This analysis helps reveal the differences in allergen exposure among different populations, providing important insights for allergen avoidance strategies and contributing to the prevention and treatment of chronic urticaria.

In the present study involving 820 patients, 705 tested positive for sIgE antibodies, yielding an 85.96% positivity rate. However, the overall positivity intensity was low, with most cases falling into the first and second levels. According to the reagent guidelines, the estimated sIgE antibody concentrations ranged from 0.35 to 3.40 IU/ml. This finding was consistent with a previous study [14], indicating that lower sIgE antibody concentrations are typical in patients with CU. The study limitations precluded a comprehensive explanation of this trend, necessitating additional analysis and research using more extensive datasets.

Milk components, such as casein, α-lactalbumin, β-lactoglobulin, bovine serum albumin, and lactoferrin, may induce milk allergies [15]. Previous studies have indicated that milk has the highest positivity rate for ingested allergens [16, 17]. The present study confirmed

Table 3 Distribution of sIgE in different age groups of food- and inhalable allergens

	Adolescents ($n=97$)	Adults ($n=312$)	Olders ($n=296$)	P value
Food Allergens				
Egg white	22 (22.68)	53 (16.99)	46 (15.54)	0.1420
Sesame	3 (3.09)	11 (3.53)	16 (5.41)	0.7913
Peanuts	7 (7.22)	20 (6.41)	35 (11.82)	0.0656
Milk	50 (51.55)	98 (31.41)	69 (23.31)	0.0001**
Shellfish	19 (19.59)	44 (14.1)	46 (15.54)	0.6977
Beef	20 (20.62)	45 (14.42)	35 (11.82)	0.1374
Fish	1 (1.03)	10 (3.21)	14 (4.73)	0.3300
Wheat	9 (9.28)	20 (6.41)	22 (7.43)	0.8290
Egg yolk	16 (16.49)	32 (10.26)	23 (7.77)	0.0154*
Fruits	9 (9.28)	33 (10.58)	24 (8.11)	0.4493
Nuts	5 (5.15)	7 (2.24)	17 (5.74)	0.2271
Inhalable Allergens				
House dust mites	44 (45.36)	126(40.3)	96(32.43)	0.0005**
Storage mites	43 (44.33)	114(36.5)	78(26.35)	0.0158 *
Tropical mites	50 (51.55)	102(32.6)	84(28.38)	0.0576
Cat dander	20 (20.62)	28(8.97)	15(5.07)	0.0003**
Dog dander	32 (32.99)	50(16.03)	34(11.49)	0.0003**
Cockroaches	9 (9.28)	35(11.22)	36(12.16)	0.6511
Silk	12 (12.37)	34(10.9)	28(9.46)	0.8386
Aspergillus	9 (9.28)	41(13.14)	67(22.64)	0.5477
Candida	24 (24.74)	48(15.38)	64(21.62)	0.0555
Timothy grass	11 (11.34)	30 (9.62)	28 (9.46)	0.0001**
Boxelder	18 (18.56)	49 (15.71)	63 (21.28)	0.5359
Birch	5 (5.15)	12 (3.85)	15 (5.07)	0.3398
Tree pollen 1	8 (8.25)	25 (8.01)	22 (7.43)	0.3744
Tree pollen 2	8 (8.25)	35 (11.22)	21 (7.09)	0.1029
Short ragweed	10 (10.31)	30 (9.62)	28 (9.46)	0.9936
Chickweed	17 (17.53)	48 (15.38)	42 (14.19)	0.6942
Ragweed	10 (10.31)	15 (4.81)	22 (7.43)	0.1656
Artemisia	4 (4.12)	9 (2.88)	12 (4.05)	0.9335

The values are represented as N, number (%)

* $P<0.05$; **$P<0.01$

this trend, with milk exhibiting the highest positivity rate across the sex and age groups. No statistically significant differences in food allergen sIgE antibody distributions were observed between the sexes. Some researchers have suggested that sex hormones may affect the incidence of CU, usually more significant in females than in males [18, 19]; however, comprehensive data on sex-specific IgE positivity for ingestible allergens are limited. The present study obtained a definitive finding: there was no correlation between food allergen distribution and sex in patients with CU.

In previous studies, house dust mites have emerged as one of the most prevalent allergens causing allergies. House dust mites contain a variety of allergens, among which Dermatophagoides pteronyssinus and Dermatophagoides farinae are the two most common mites that cause allergic diseases in humans [20–22]. Storage mites, reported globally as major allergens in dust samples, include two common types: Blomia tropicalis and Tyrophagus putrescentiae. House dust and storage mites exhibit extensive cross-reactivity, leading to simultaneous positivity for both [23, 24]. The present study demonstrated that males had positive rates consistent with previous findings [20–22] for both house dust mites and storage mites, whereas females had a significantly lower positive rate for storage mites, at merely 3%. This disparity may be attributed to differences in regional and demographic lifestyles. Research has also indicated that the

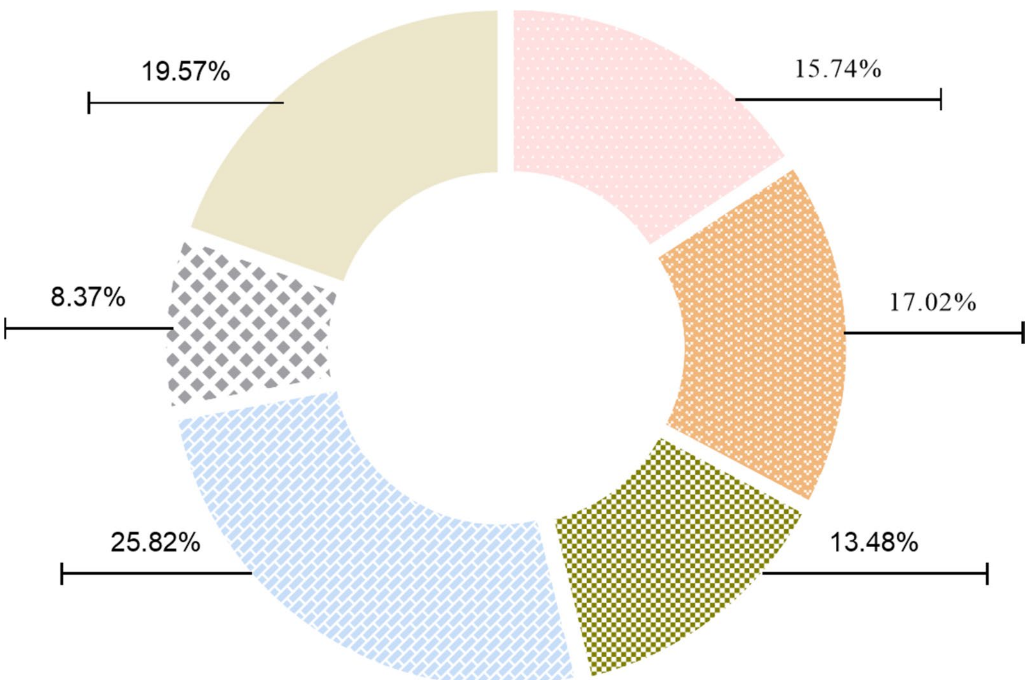

Fig. 3 The distribution of simultaneous positive items

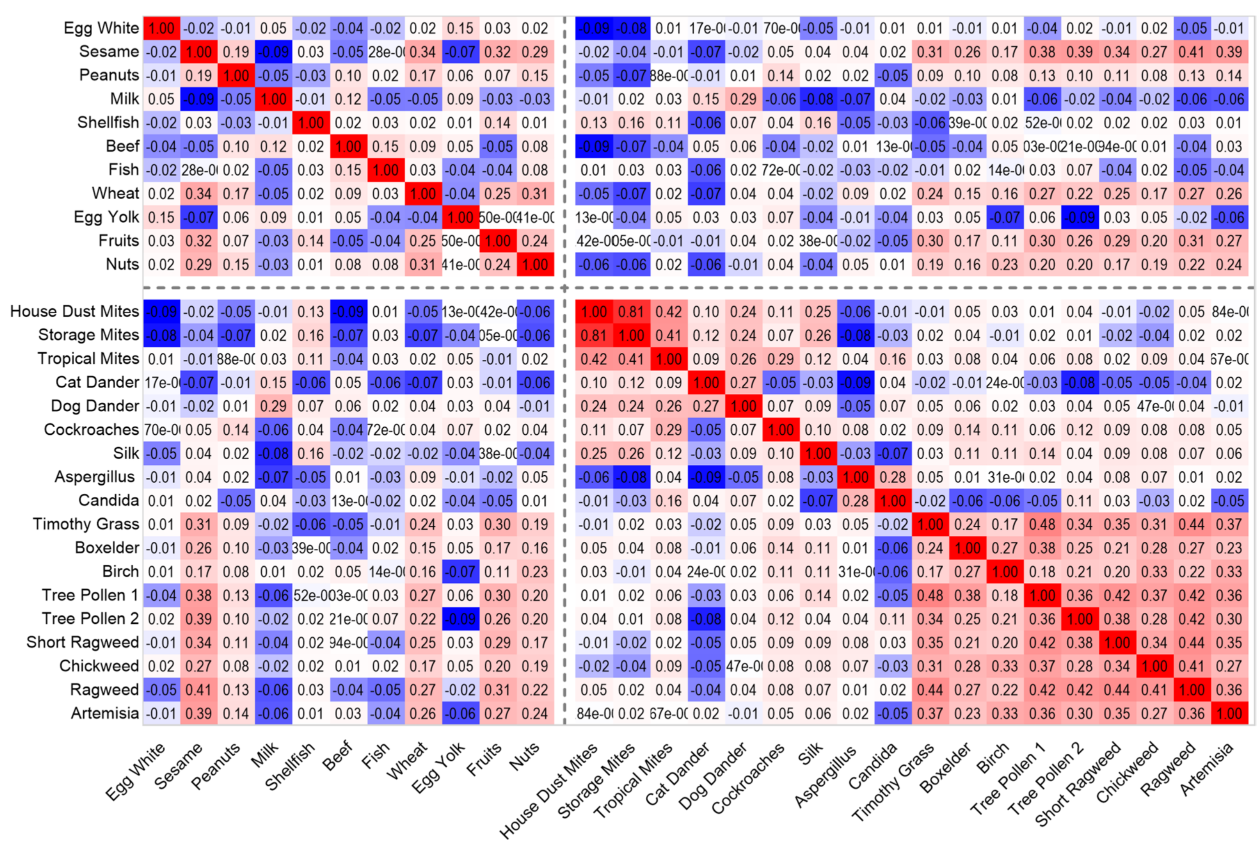

Fig. 4 The correlation analysis among the 29 allergens

positivity rate of storage mites is indeed higher among males than females [25].

The positivity rates of milk and egg yolk allergens differed significantly across age groups, highest in adolescents, followed by adults, and lowest in elderly individuals, indicating a statistically significant trend. Beef and egg whites are prevalent food allergens; eggs are the second most common dietary allergen after milk. Jeffrey et al. [26] reported a frequent co-allergic response between beef and milk. Their study revealed high prevalence rates for both egg and beef allergies, particularly in adolescents, compared with adults and elderly individuals. Although not statistically significant, the literature indicates that dietary proteins elicit a more robust immune response in children than adults, which may account for the higher prevalence of food allergies among adolescents [27]. Across different age groups, both house dust mites and storage mites exhibited substantial prevalence, with marked variations. Similarly, cat and dog dander, as well as timothy grass, follow a pattern akin to dietary allergens, with adolescents displaying the highest positivity rates, which decrease with age. Research suggests that CU is increasing in adolescents but remains stable in adults [28]. This trend may be due to the increased sensitivity of adolescents to allergens compared with that of adults.

The present study revealed that 80.43% of the patients tested positive for two or more allergens concurrently. Notably, three patterns of coexisting allergens were observed: sensitivity to multiple ingested allergens, sensitivity to both ingested and inhaled allergens, and sensitivity to several inhaled allergens. Cross-reactivity, the immune response to one antigen that simultaneously triggers reactions against antigens from disparate sources, is the principal reason behind the concurrent sensitivity to multiple allergens. This process involves an antibody binding to two or more allergens, triggering cross-reactive hypersensitivity reactions [29, 30]. Previous studies have explored the associations between various allergens via comprehensive correlation analyses [31].

Additionally, extensive literature has documented cross-reactivity across a range of allergies, including interactions among food allergens, between food and airborne allergens, and airborne allergens [32–35]. In the present study, a conspicuous correlation among inhaled allergens was evident. The correlation coefficient between indoor dust mites and storage mites was as high as 0.81, attributed to the highly homologous sequences of allergens Der p2 and Der f2 in house dust mites and those of lep d2 in storage mites. Extensive cross-reactivity exists between house dust mites and storage mites [24, 36]. Moreover, there is a discernible connection between tree pollen and grass allergens, as previous scholarly discussions have posited that plants within the same genus or family may have a common or akin ancestor, leading to shared antigens and potential cross-reactivity [33].

In the present study, an interesting finding emerged: a minimal correlation was observed among ingestible allergens or between ingestible and inhalable allergens. This contrasts with the literature, which suggests connections, for example, between timothy grass and fruits, strong reactions between house dust mites and shrimp, and notable cross-reactivity among various food allergens, such as peanuts and tree nuts, fish and shellfish [32–35, 37]. However, the present study consistently revealed low correlation coefficients among these allergens. The observed differences may be related to the population of patients with CU. The pathological condition of patients with CU may influence the cross-reactivity among different allergens. The present study obtained novel results through data analysis; however, our study was limited by its retrospective nature, which may introduce selection bias, and the relatively small sample size, which may affect the generalizability of our findings to a broader population. Although sIgE has shown potential in identifying allergic responses, its sensitivity and specificity in diagnosing chronic urticaria require further validation in multicenter prospective studies.

Conclusions

Patients with CU exhibit relatively high rates of sIgE antibodies, although the intensity of positivity was generally low. Notably, compared with adults and elderly individuals, adolescents consistently presented higher rates of sIgE positivity. There were no sex disparities in the distribution of ingestible allergens, and the correlations between ingestible allergens and between ingestible allergens and inhalable allergens were relatively weak.

Abbreviations

CU	Chronic urticaria
sIgE	Specific IgE
IgE	Immunoglobulin E
iPCR	Immunoprotein chain reaction

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Author contributions

All the authors listed participated in the design of the study and conducted the study. Jiaqin Zhang and Yijie Tang drafted the manuscript and performed the statistical analysis of the study. All of the authors read and approved the final manuscript.

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None.

Availability of data and materials

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The Medical Ethics Committee of Shanghai Skin Disease Hospital, Tongji University (Shanghai, China) approved the current study. The ethical approval number: SSDH-IEC-SG-057–4.1

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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