# A Multi-centre Analysis of Serum IgE Levels in Atopic Dermatitis

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## Abstract

**Objective:** To assess the characteristics of total immunoglobulin E (IgE) and allergen-specific IgE (sIgE) to 20 common allergens in 154 patients with atopic dermatitis (AD). To assess the correlation of clinical food allergy with positive food allergens' sIgE results. We further discuss the significance of IgE as a potential biomarker for AD disease severity. **Methods:** A total of 154 AD patients were collected from 15 hospitals nationwide in China from 2019 to 2021. Serum IgE was measured using reverse-enzyme immuno capture test (REAST). Patients were required to have at least one positive sIgE (N ≥ 0.35 IU/mL). Patients were divided into groups according to gender, age, disease severity, and region. SPSS 26.0 software was used for statistical analysis. **Results:** Compared with adolescent and adult, AD in infancy and childhood showed significantly higher frequencies of positive sIgE to food allergens, including egg, cow milk, and wheat (P < 0.01). However, adolescent and adult AD showed significantly higher frequencies of positive sIgE to inhaled allergens, dermatophagoides farinae, and house dust mite. In addition, sIgE in different sexes were different. Compared with women, men showed higher frequencies of positive allergen-specific IgE level to wheat, dermatophagoides farinae, and house dust mite. The most common food allergens with elevated sIgE levels were egg (71%), cow milk (39%) and wheat (32%). However, AD patients reported seafood, including crab, shrimp, and fish, as the most frequent food allergens which aggravate their disease in their daily life. Only 18 (12%) patients reported definite correlation of clinical practice with positive food allergens' IgE results. Among 154 sIgE-positive patients, 99 patients had an increase of total IgE (≥60 IU/ml). TotalIgE (tIgE) levels were significantly different between mild (193 ± 239 IU/mL), moderate (170 ± 202 IU/mL), and severe (375 ± 343 IU/mL) forms of AD patients (P < 0.01). AD patients with accompanied allergic diseases showed significantly higher tIgE levels than those without accompanied allergic symptoms (280 ± 286 IU/mL vs 194 ± 248 IU/mL). **Conclusion:** Neither sIgE nor tIgE levels can be used to evaluate the condition or severity of AD. AD patients with accompanied allergic diseases showed significantly higher tIgE levels than those without accompanied allergic symptoms. Infantile AD patients are more allergic to food, while adolescents and adults are more allergic to environmental antigens. IgE tests must be interpreted by combining with clinical history to avoid unnecessary food avoidance. Early food allergen introduction for infants may be promising for the prevention of food allergies.

**KEY WORDS:** Allergen, atopic dermatitis, biomarker, IgE

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## Introduction

Atopic dermatitis (AD), also known as atopic eczema, is a chronic inflammatory disease characterized by eczematous eruptions, which are recurrent and itchy.[1] The overall prevalence rate of AD has increased over the past few decades, approximately 10–20% in children and 1–3% in adults.[2] Because of severe pruritus, most of AD patients suffer from various mental problems, such as sleep disturbance, depression, and anxiety.[3] The etiology of AD involves multiple complex factors, including genetic predisposition, skin barrier dysfunction, immune imbalance, and altered skin microbiome.[4,5] Immune imbalance plays a central role in the pathogenesis of AD.[6] Clinical features of AD vary in different ages, genetic backgrounds, races, and regions.[7]

Elucidation of the mechanisms underlying AD is significant for the development of novel therapeutic strategies.[8] AD is considered a cutaneous manifestation of a systemic disease characterized by increased serum

immunoglobulin E (IgE) levels and eosinophils in peripheral blood and clinically p by asthma, allergic rhinitis, and food allergy.[9,10] The IgE is produced through the adaptive immunity. Exposure to specific allergens initiates B-cell proliferation and overproduction of specific IgE, which contributes to the development of many allergic diseases.[11] Re-exposure to specific allergens activates the IgE-dependent inflammatory cascade. An allergen is broadly defined as any molecule that induces IgE production and binds IgE antibodies.[12] AD patients frequently exhibit high levels of total serum IgE and allergen-specific IgE. Recent studies have categorized AD into two subtypes: the IgE-high, extrinsic subtype and the IgE-normal, intrinsic subtype. These subtypes differ in the level of serum tIgE level, sIgE level, and response to allergens in skin prick tests. . Environmental and food allergens are causative for extrinsic AD but not intrinsic AD. It is estimated that 10–45% cases of eczema are intrinsic AD. Allergen-specific IgE (sIgE) detection is crucial for the treatment and prevention of AD. The distribution pattern of allergens in AD patients varies in different races, genetics,  and geographic backgrounds and is affected by diet.[13] It is crucial to characterize and clinically correlate  the various allergen since increased IgE levels may be encountered in people without clinical allergic diseases.

Food allergies have been implicated in about 40% of children with moderate-to-severe AD.[14] Many AD parents make efforts in food avoidance. It was reported that more than 70% of AD children had been subject to dietary manipulation by their parents.[15] unnecessary food avoidance is  common in China, which may lead to malnutrition. The widely used test methods for food allergy diagnosis involve skin prick tests, allergen-specific IgE, and oral food challenges. Unfortunately, there is  no laboratory test with high sensitivity and specificity to predict food allergy. Many dermatologists still feel challenged when asked to interpret sIgE results with the clinical food allergy. A double-blind, placebo-controlled food challenge (DBPCFC) remains the gold standard for diagnosis of food allergies.

## Patients and Methods

The present study included patients nationwide in China from December 2019 to December 2021. Only Patients with  at least one IgE detection result positive, tIgE (IU/mL) level >60 IU/mL or sIgE test result >0.35 IU/mL were considered. At last, 618 patients with  were recruited. Among them, 154 patients were diagnosed as AD. The diagnosis of AD was based on the Williams criteria of AD. Inclusion criteria:(1) Patients with  AD who satisfied  the Williams criteria. Exclusion criteria: (1) Patients with a history of systemic use of glucocorticoids within 2 weeks; (2) patients with a history of antihistamine use within 3 weeks; (3) patients

with any history of parasitic infection, congenital malformations or severe heart, liver, kidney, and other diseases, and recent respiratory and digestive tract infections; and (4) pregnant or lactating women.

The standardized questionnaire which includes the clinical symptoms, disease duration, and personal or family history was answered by AD patients. The questionnaire and dermatological examination were completed by investigators. Serum samples were taken to measure total IgE and specific IgE levels before treatment. All patients provided  the informed consent. The study was approved by the ethical committee of Beijing Friendship Hospital. AD severity was defined by the eczema area and severity index (EASI) score during patients' first visit. ( Mild severity :  EASI score of <7, moderate :  ≥7 and <21, and severe : ≥21.)

### Total IgE and allergen-specific IgE testing

The present study investigated total and specific serum levels of IgE to 20 most common allergens in 154 AD patients Participants are required to have at least one specific IgE test result positive (>0.35 IU/mL). The total serum IgE and specific IgE antibody levels were measured using reverse-enzyme immuno capture test (REAST by Jiangsu Haooubo Biological Medicine Co. Ltd). Determination of test results: A serum total IgE  level of >60 IU/mL was   determined as positive. Serum allergen-specific IgE level : >0.35 IU/mL was determined as positive. The specific IgE detection types included a total of 20 items, including 10 food allergens (egg, milk, codfish, crab, shrimp, wheat, soybeans, beef, lamb, and peanut) and 10 inhalation allergens (house dust, dermatophagoides farinae, house dust mite, cat epithelium, Alternaria, dog epithelium, artemisia argyi, ragweed, cockroach, and willow).

### Statistical analysis

Statistical analyses were performed using SPSS Statistics 26 (IBM SPSS Inc., Chicago, IL, USA). Data are expressed as means ± SDs (standard deviation). Changes in tIgE values in different AD group were calculated using Student's t-tests or one-way ANOVA. Positive proportion (%) is defined as the percentage of the positive detection to various allergens. The standard Chi-square test is applied to analyze the differences of positive allergen-specific IgE frequencies. $P < 0.05$ was considered statistically significant.

## Results

### Clinical characteristics of 154 AD patients

The general characteristics of AD patients  are illustrated in Table 1. A total of 154 AD patients were included in the study (82 men and 72 women). The mean age of 154 selected patients was 9.53 ± 11.28 years old, with a minimum age of 4 months and a

### Table 1: Clinical characteristic of patients

| Characteristic of Patients | Number of Patients |
|---|---|
| Total number | 154 patients |
| Gender | 82 men, 72 women |
| Average age | 9.53±11.28 |
| Average AD duration | 3.24±4.36 years |
| Average SCORAD | 39 points, s.d. 13.1 points |
| Severity of AD | Mild form 24 (16%) |
| | Moderate form 85 (55%) |
| | Severe form 45 (29%) |
| Family history about atopy | Positive family history 62 patients (40%) |
| | Negative family history 92 patients (60%) |

maximum age of 45 years. The average AD duration was 3.24 ± 4.36 years.

Positive family history about atopy was recorded in 62 patients (40%). AD patients were classified into three subgroups by clinical severity assessment tools, including the EASI, DLQI, and pruritus NRS: mild form, 24 (16%); moderate form, 85 (55%); and severe form 45 (29%). We also analyzed the age differences of serum IgE level in AD patients by classifying them into three groups: infancy (0–2), childhood (2–12), and adolescence and adulthood (12–60).

### Analysis of frequencies of positive allergen-specific IgE

We evaluated the frequencies of positive sIgE to 20 allergen reagents [Table 2]. The most abundant allergens related to AD are egg (70%), cow milk (39%), wheat (32%), house dust (26%), dermatophagoides farinae (24%), and house dust mite (23%). However, allergens including soybean, cat epithelium, shrimp, crab, peanut, alternaria alternate, dog epithelium, artemisia argyi, beef, codfish, ragweed, cockroach, and willow showed a low frequency [Figure 1]. SIgE to mutton has not been found in any AD patients. In addition, sIgE in different sexes were different. Compared with women, men showed higher frequencies of positive allergen-specific IgE level to wheat, dermatophagoides farinae, and house dust mite.

### Allergen-specific IgE frequencies were significantly different in three age groups [Table 3]

We classified AD patients into three3 groups according to age differences: infancy (0–-2, n= = 20), childhood (2–-12, n= = 98), adolescence, and adulthood (12–-60, n= = 36). Pearson Chi-square test was used to analyze the statistical differences between three groups. Compared with adolescent and adult AD, infancy and childhood AD showed significantly higher frequencies of positive sIgE to food allergens, including egg, cow
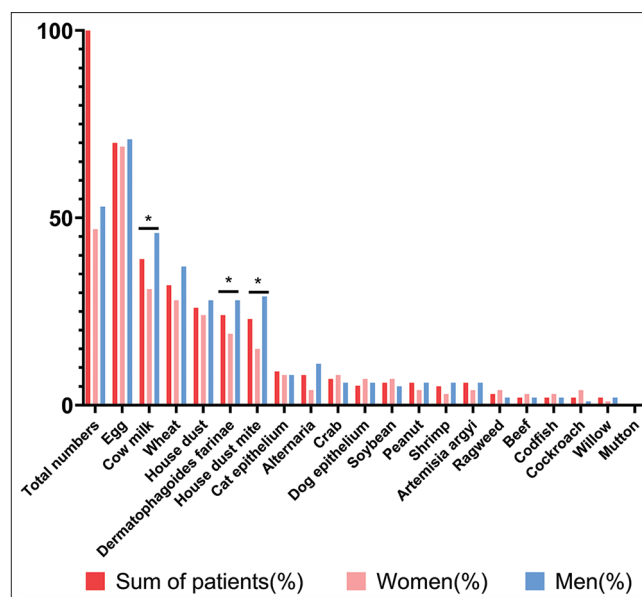


**Figure 1:** Frequencies of positive sIgE to 20 allergen reagents in different genders

milk, and wheat ($P < 0.01$). However, adolescent and adult AD showed significantly higher frequencies of positive specific IgE to inhale allergens, including Dermatophagoides farinae and house dust mite ($P < 0.01$).

### Correlation of clinical manifestations and positive food allergens' IgE results

Among 127 AD patients with positive food allergens' IgE results, only 18 (12%) patients reported definite correlation of clinical practice and positive food allergens' IgE results. That means those AD patients' condition developed or worsened after eating positive food allergens. And 40 (26%) patients reported no correlation of clinical positive food allergies and positive sIgE results. The other 96 (62%) patients reported possibly correlation. The most frequent allergens with the elevated sIgE levels were egg, cow milk, and wheat. However, AD patients reported seafood, including crab, shrimp, and fish, as most frequent food allergens in their daily life, which means they reported history of disease aggravation after eating seafood.

### Differences of serum total IgE levels among different AD groups [Table 4]

Among 154 sIgE-positive patients, 99 (65%) patients had an increase of tIgE (≥60 IU/ml). The mean of serum levels of total IgE in 154 AD patients was 230 ± 267 IU/mL. The mean of total IgE levels was 246 ± 277 IU/mLIn men and 211 ± 256 IU/mL in women. Total IgE levels are similar between men and women. TIgE levels were significantly different between mild (193 ± 239 IU/mL), moderate (170 ± 202 IU/mL), and severe (375 ± 343 IU/mL) forms of AD patients ($P < 0.01$). In

### Table 2: Frequencies of positive allergen-specific IgE in AD patients

| Allergens | Sum of patients (%) | Women (%) | Men (%) | Pearson Chi-square, P |
|---|---|---|---|---|
| Egg | 108 (70) | 50 (69) | 58 (71) | 0.28, 0.60 |
| Cow milk | 60 (39) | 22 (31) | 38 (46) | 2.59, 0.11 |
| Wheat | 50 (32) | 20 (28) | 30 (37) | 4.000, 0.05 |
| House dust | 40 (26) | 17 (24) | 23 (28) | 1.80, 0.18 |
| Dermatophagoides farinae | 37 (24) | 14 (19) | 23 (28) | 4.38, 0.04 |
| House dust mite | 35 (23) | 11 (15) | 24 (29) | 9.66, 0.00 |
| Cat epithelium | 14 (9) | 6 (8) | 8 (8) | - |
| Alternaria | 12 (8) | 3 (4) | 9 (11) | - |
| Crab | 11 (7) | 6 (8) | 5 (6) | - |
| Dog epithelium | 10 (5.2) | 5 (7) | 5 (6) | - |
| Soybean | 9 (6) | 5 (7) | 4 (5) | - |
| Peanut | 9 (6) | 3 (4) | 6 (6) | - |
| Shrimp | 7 (5) | 2 (3) | 5 (6) | - |
| Artemisia argyi | 8 (6) | 3 (4) | 5 (6) | - |
| Ragweed | 5 (3) | 3 (4) | 2 (2) | - |
| Beef | 4 (2) | 2 (3) | 2 (2) | - |
| Codfish | 4 (2) | 2 (3) | 2 (2) | - |
| Cockroach | 4 (2) | 3 (4) | 1 (1) | - |
| Willow | 3 (2) | 1 (1) | 2 (2) | - |
| Mutton | 0 (0) | 0 | 0 | - |
| Total numbers | 154 | 72 (47) | 82 (53) | - |

### Table 3: Age differences of frequency of positive serum-specific IgE in AD patients

| Allergens (%) | Infancy (n=20) | Childhood (n=98) | Adolescence and adulthood (n=36) | Pearson Chi-square, P |
|---|---|---|---|---|
| Egg | 75% | 82% | 36% | 26.31, 0.00 |
| Cow milk | 50% | 45% | 17% | 10.00, 0.01 |
| Wheat | 50% | 38% | 8% | 13.62, 0.00 |
| House dust | 15% | 27% | 31% | 1.66, 0.44 |
| Dermatophagoides farinae | 5% | 18% | 50% | 18.99, 0.00 |
| House dust mite | 10% | 18% | 42% | 10.26, 0.01 |

### Table 4: Differences of serum total IgE level (mean±SD) among different sexes, atopic history, severity, and ages in AD patients

| | Total IgE level (IU/mL) | | | P |
|---|---|---|---|---|
| Sex | Male (n=82) | Female (n=72) | | 0.41 |
| | 246±277 | 211±256 | | |
| Associated allergic diseases | Positive (n=64) | Negative n=90 | | 0.05 |
| | 280±286 | 194±248 | | |
| Severity | Mild (n=24) | Moderate (n=88) | Severe (n=42) | 0.00 |
| | 193±239 | 170±202 | 375±343 | |
| Age | ≤2 (n=20) | 2-12 (n=98) | >12 (n=36) | 0.94 |
| | 212±279 | 235±276 | 230±267 | |

addition, 64 (42%) AD patients reported accompanied symptoms of other allergic diseases (allergic rhinitis, allergic conjunctivitis). Those patients showed significantly higher tIgE levels than those without accompanied allergic symptoms (280 ± 286 IU/mL vs 194 ± 248 IU/mL).

## Discussion

IgE plays a critical role in the pathogenesis of atopic disease. We analyzed the specific IgE antibodies to 20 common allergens in 154 AD patients nationwide of China. The association between IgE and AD has been elucidated in several clinical studies. Food allergy can influence the long-term choice of elimination diets. However, its diagnosis remains challenging.

Most studies showed that egg, milk, wheat, and soy are the leading causes of food allergy in Asian countries.[16-18] Similarly, we reported the highest frequency of food-specific IgE as follows: egg 56.2%, cow milk 34.3% and wheat 32.9%. However, Hon et al.[19] studied 85 AD children in China and observed a totally different food allergy frequency: shrimp 54%, egg whites 43%, and wheat 42%. In Western countries, egg, milk, and peanut are the most common food allergens among young AD children.[20]

Frequencies of positive sIgE were significantly different in three age groups. In our study, compared with

infancy and childhood, adolescent and adult AD showed significantly lower frequencies of positive specific IgE to food allergens, including egg, cow milk, and wheat ($P < 0.01$). In addition, adolescent and adult AD showed significantly higher frequencies of positive specific IgE to inhaled allergens, including Dermatophagoides farinae and house dust mite ($P < 0.01$). Previous researches showed similar findings. . Therefore, it seems that infantile AD patients are more allergic to food, while adults are more allergic to environmental antigens.

In China, AD patients are very concerned about food allergy (FA) and dietary restrictions. However, its diagnosis is challenging. FA is reported in one-third of AD children and particularly in those with moderate-to-severe AD.[21] Two investigations are most widely used to investigate food allergy: the food sIgE in vitro and the skin prick test (SPT) in vivo. However, the double-blind placebo-controlled food challenge is the gold standard for diagnosis of FA. Our study showed that only 22 (16%) patients reported definite correlation of clinical practice and positive food allergen IgE results, which means their diseases developed or worsened after eating positive food allergies. The presence of antigen-specific IgE is called sensitisation and alone does not confirm food allergy since sIgE is often present in the absence of clinical allergy.[22] Most patients reported no significant correlation of clinical practice and positive food allergens' IgE results. The most common food items with the elevated sIgE levels were egg, cow milk, and wheat. However, AD patients reported crab, shrimp, and fish as most frequent food allergens in their daily life. That means seafood is the most common food item leading to AD disease aggravation. Therefore, IgE results must be interpreted in the context of clinical history to avoid unnecessary food avoidance. Elevated sIgE antibodies are markers of sensitisation, not synonymous with being allergic. Individuals may produce sIgE to a given substance without developing allergic symptoms upon exposure to that substance. Elevated sIgEs carry a high rate of false positive results, and negative sIgEs do not completely exclude allergy. It was reported that the negative predictive value of sIgEs is more than 90%, while the specificity is low, only 40–60%.[23] Therefore, IgE results need to be interpreted in the context of other information. FA can be divided into three groups: a) IgE-mediated, b) non-IgE-mediated, or c) combination of both IgE- and non-IgE-mediated features. IgE-mediated FA classically demonstrates clinical symptoms within 2 hours of food intake. Non-IgE-mediated FA can manifest as conditions including AD.[24] Non-IgE-mediated food-induced AD has delayed and subtle onset. Therefore, IgE tests are useless for the majority of non-IgE-mediated allergies.[25,26]

For the relationship between IgE levels and the AD severity, previous studies have proved a correlation between IgE level and AD severity. Kiiski et al.[27]

reported that tIgE level and sIgE levels were significantly associated with the severity of AD. Kam-lun Ellis Hon and his colleagues assessed serum tIgE in 117 AD children (younger than 18 years) and showed that levels of tIgE differed significantly between patients with mild, moderate, and severe disease. There was a significant correlation between increased EASI scores and the tIgE levels in 5000 AD patients in South Korea.[28] In contrast to previous reports, no significant correlations in serum IgE levels were observed with AD severity. There is no significant difference of serum tIgE or sIgE between with mild, moderate, and severe AD. A higher serum IgE level does not predict the severity of AD. Hu et al.[29] found that elevated serum total IgE level was less seen in elderly patients compared with in adolescent and adult patients. Somani et al.[30] also reported that the highest IgE elevation was seen in AD between 10 and 20 years old. However, our results showed serum total IgE levels were similar in the three age groups.

## Limitations

There are several limitations in this study. A limited sample size and possibility of selection bias exist. The study only analysed 20 specific allergens, which may not cover the all the major spectrum of allergens. More data are needed to analyse the correlation of IgE results with laboratory tests, such as increased peripheral eosinophils and basophils. Moreover, follow-up is required to document dynamic changes in allergen sensitisation over an extended period. The data lacked detailed descriptions of clinical features, such as pruritis, flexural dermatitis, xerosis, and perifollicular accentuation.

## Conclusions

Our study provides a comprehensive analysis of both tIgE and sIgE levels in a large cohort of AD patients (n = 154). This allows for a more nuanced understanding of the role of IgE in AD pathogenesis compared to studies focusing solely on tIgE. We demonstrate distinct patterns of sIgE sensitisation across different age groups. Infancy and childhood AD patients exhibit higher sensitisation to food allergens, while adolescents and adults show increased sensitisation to inhalant allergens. This age-specific analysis offers valuable insights for tailoring allergy management strategies. While acknowledging that neither sIgE nor tIgE can definitively assess AD severity, our study highlights the potential of tIgE as a biomarker for disease severity. We observed significantly higher tIgE levels in patients with moderate and severe AD compared to those with mild AD. This finding warrants further investigation to explore the potential of tIgE as a prognostic or therapeutic monitoring tool. We emphasise the importance of interpreting IgE test results in conjunction with clinical history to avoid unnecessary food avoidance. This aligns with current

clinical practice guidelines and reinforces the need for a holistic approach to allergy management. Our findings suggest that early food allergen introduction for infants may be promising for the prevention of FA. This aligns with emerging research on the role of early exposure in immune development and allergy prevention. We believe that our manuscript provides valuable insights into the characteristics of IgE in AD patients and the findings will be of interest to researchers and clinicians working in the area of allergy and immunology.

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### Conflicts of interest
There are no conflicts of interest.

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