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The Skin Prick Test Response after Allergen Immunotherapy in Different Levels of tIgE Children with Mite Sensitive Asthma/Rhinitis in South China

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ABSTRACT

Background: At present, the biomarkers which can predict the clinical efficacy of allergen immunotherapy (AIT) are still much debated. IgE levels are often related to allergic severity. Therefore, this study aimed at relating total IgE (tIgE) levels with the efficacy of AIT assessed by symptoms and drug score and skin prick test (SPT) response. **Methods:** We evaluated 81 allergic children who had received house-dust mite (HDM) subcutaneous immunotherapy for three years. According to the tIgE levels before treatment, all children were divided into high value, medium value and low value group. Each group according to sIgE/tIgE ratio was divided into subgroups. The efficacy of AIT is assessed by symptoms and drug score. By comparing changes in the grade of SPT in each group, the response of AIT are evaluated. **Results:** The SPT grade changes to determine efficacy had a high degree of consistency with symptoms and drug score judgment (sensitivity 89.7%, specificity 78.3%, Kappa = 0.670, $P < 0.001$). Compared to ineffective cases, the effective cases had lower tIgE ($P <$

0.001) and higher ratio of sIgE/tIgE ($P < 0.001$). The grades of SPT declined the most in the low value group (low value group vs. medium value group, $P < 0.05$; low value group vs. high value group, $P < 0.001$; medium value group vs. high value group, $P < 0.05$). *Conclusions:* The SPT grade change can be used for efficacy evaluation. Children with lower level of tIgE and higher ratio of sIgE/tIgE that obtain a more satisfactory effect.

Key Words:

Asthma; Allergen immunotherapy; Efficacy; Skin prick test; Total IgE

Introduction

Allergen immunotherapy (AIT) is a recognized way of treating IgE-mediated allergic disease repeatedly verified for efficacy and safety by double blind placebo-controlled studies.¹⁻³ The efficacy of AIT is mainly assessed by the clinical symptom improvements and drug reductions. In addition, the skin prick test end point was significantly reduced after treatment and there was a significant correlation between the skin prick test end point and symptom scores in grass pollen-induced rhinitis.⁴ Moreover, the wheal size of the SPT and symptom changes in nasal provocation test were statistically correlated.⁵ Skin prick test can be used to judge the allergen and evaluate allergy severity in children with atopic dermatitis.⁶

However, not all allergic patients can benefit from AIT. In addition, there is no good biomarkers being found to predict the clinical efficacy of AIT. Since AIT is an expensive and prolonged treatment, it is crucial to find an available marker to predict responders. Theoretically IgE-mediated inflammation produced by exposure to allergens is the main characteristic of asthma and rhinitis. Thus, the production of IgE is known as a stamped mark of allergy. Previously, studies have reported that total IgE (tIgE) levels were related to asthma severity.^{7,8} Recently, several studies have shown that tIgE level can be used as a biomarker to predict the clinical efficacy of AIT.^{9,10}

Therefore, in this study, we aimed to relate tIgE levels with the efficacy of AIT assessed by symptoms and drug score and SPT response.

Results

Study Population and Basic Characteristics

We enrolled 81 pediatric patients (59 males and 22 females) who met the inclusion criteria for house dust mite allergy associated asthma and rhinitis. Their median age was 7 years. From all of them, 19 patients were diagnosed with asthma alone, 5 were diagnosed with rhinitis

alone and 57 were rhinitis combined with asthma. Pretherapeutic basic characteristics are listed in Table 1.

Differences in patient characteristics before and after treatments of AIT

The paired-sample t test, χ^2 test and nonparametric Wilcoxon test were used to compare the differences before and after AIT. We found that, after treatment, tIgE level increased ($P < 0.001$), blood eosinophil count and sIgE/tIgE ratio decreased ($P = 0.003$ and $P < 0.001$), skin prick test significantly improved ($P < 0.001$). There was no statistical difference observed in pulmonary function parameters and Dp-specific IgE (sIgE) level, as it showed in Table 1.

Difference in parameters before treatment between patients with and without an effective response to AIT

As shown in Table 2, the treatment judging by symptoms and drug scores was effective for 58 (71%) of patients and ineffective for 23 (28%). Compared with cases with ineffective responses those with effective responses had lower tIgE ($P < 0.001$) and sIgE ($P = 0.011$), higher sIgE/tIgE ratio ($P < 0.001$) and lower level of blood eosinophil count ($P = 0.020$). In terms of efficacy judgments, 52 patients were judged to be effective both in SPT grade changes and symptoms and drug score, and 18 cases were ineffective in either of the two judgements above. However, there were 6 cases being judged as effective in terms of the symptoms and drug score but ineffective judged from the SPT grade changes, and 5 cases being considered to be valid by through SPT grade changes judgement but invalid by symptoms and drug score judgment. Through the consistency test of efficacy judgements, we found that the SPT grade changes to determine efficacy had a high degree of consistency with symptoms and drug score judgment (sensitivity 89.7%, specificity 78.3%, Kappa = 0.670, $P < 0.001$; Table 3).

The sensitivity and specificity got from calculating ROC curves for tIgE, sIgE levels, sIgE/tIgE ratios, blood eosinophil count (Fig. 1). The AUC was 0.806 for tIgE levels (95% CI 0.703–0.885), 0.730 for sIgE/tIgE ratio (95%CI 0.620–0.823), 0.676 for sIgE levels (95%CI 0.563–0.776), and 0.666 for blood eosinophil count (95%CI 0.663–0.767). Our ROC analysis shows that tIgE lower than 610 kU/l and sIgE/tIgE ratio greater than 15.0% have the best sensitivity and specificity for predicting a valid response to AIT. Comparing each AUC, as shown in Table 4, there was a significant difference between tIgE with sIgE ($P = 0.011$), and also with blood eosinophil count ($P = 0.037$). No statistical difference was found between tIgE with sIgE/tIgE ratio ($P = 0.136$), neither between sIgE/tIgE ratio with sIgE ($P = 0.551$), sIgE with blood eosinophil count ($P = 0.902$), and sIgE/tIgE ratio with blood eosinophil count ($P = 0.422$).

According to the tIgE levels before treatment, all patients were divided into low value group (tIgE $\leq$ 130 kU/l), medium value group (tIgE $>$ 130 kU/l and tIgE $<$ 540kU/l) and high value group (tIgE $\geq$ 540 kU/l), then each group was divided into two subgroups according to the sIgE/tIgE ratio, at the cut-off value of 15.0%. We found that the skin prick test grade of three groups were all significantly declined after treatment (low value group, $P < 0.001$; medium value group, $P < 0.001$; high value group, $P < 0.001$). As shown in Fig. 2, when compared with each other, the low value group was superior to the medium value group and high value group (low value group vs. medium value group, $P < 0.05$; low value group vs. high value group, $P < 0.001$), and the medium value group is superior to high value group (medium value group vs. high value group, $P < 0.05$). However, when compared subgroups, statistically significant of the change of skin prick test grade in different ratio of sIgE/tIgE was only found in high value group ($P = 0.036$; Table 5).

Discussion

AIT has been used as a tolerance-inducing therapy for allergic diseases for more than 100 years and is effective in improving the symptoms and reducing concomitant drugs of asthma and allergic rhinitis in children. Our study showed that the clinical symptoms and concomitant drug were reduced in 58 child patients after treatment, and their skin prick test were significantly improved. Moreover, the SPT grade changes to determine the efficacy had a high degree of consistency with the symptom and drug score judgment, which suggest it can be used for efficacy evaluation.

However, not all allergic patients can benefit from AIT, it has been reported that AIT is effective at about 80%.^{14,15} As a result of the high cost, the long treatment period, and poor patient compliance in particular, it would be extremely useful in clinical practice to find a biomarker to predict the response of AIT, but it should be reliable, available and easy to carry out. In this study we found that tIgE levels $<$ 610 kU/l, sIgE/tIgE ratio $>$ 15.0%, sIgE levels $<$ 76.7 kU/l and blood eosinophil count $<$ $0.49 \times 10^9/l$ were related to an effective clinical response to AIT. We proved that the tIgE is better than both sIgE level and peripheral blood eosinophil count in predicting the clinical response to AIT by pairwise comparisons of ROC curves. Research had shown that IgE plays a central role from the very start of the allergic disease and throughout its continuum.¹⁶ High serum IgE levels correlate with asthma severity despite of different ages or populations.^{7,17,18} According to the value of tIgE before treatment, we grouped the children and found that the skin prick test grades of children in the low value group changed most obviously, suggesting that low tIgE level obtain a more satisfactory effect. Previous evidence showed that IgE had a indirect influence on the persistence of the inflammation, and in addition, it was associated with an increased airway hyperresponsiveness and an accelerated decrease in lung function.^{19,20} Patients with allergic diseases in vivo IgE, IL-4, IL-5, EOS significantly increased, some of them have mild or no

clinical symptoms, while others have obvious or severe allergic symptoms. It is considered that the former have normal or up-regulated Treg cell function, while Treg cell function is inhibited or reduced in number in the latter. In this study, we found that tIgE increased after treatment, but the clinical symptoms were relieved. Studies show that this increase in tIgE is transient and decreases gradually over months or years after AIT. And this decrease in tIgE does not relate to improvement of clinical symptoms.²¹

Previous studies have indicated that the sIgE or sIgE/tIgE ratio can be used as predictors to predict the clinical efficacy of AIT,^{22,23} which were not exactly consistent with our result. But it was inappropriate to make a simple comparison because the age compositions of our study were different from them. In theory, the level of serum Dp-specific IgE is a reflection of the extent of exposure to HDM. Thus, it is convincing that the higher the sIgE/tIgE ratio is, the more clinical relevance will be with HDM for an individual. Similarly, the more clinical relevance of HDM in AIT, the more successful AIT will be. However, we found only a higher ratio of sIgE/tIgE in the high value group obtained better efficacy, while in the other two groups showed no difference, implying that tIgE has a greater impact on the efficacy.

Confusingly, there was no significant corresponding increase in sIgE after treatment in our study, which may be attributed to the upper limit of the measurement of sIgE: patients had already been in a very high level of sIgE before AIT.

Our study showed that the levels of peripheral blood eosinophil decreased after AIT. And comparing to the effective response cases, there was a higher level of blood eosinophil count before treatment in those with an ineffective response to AIT. However, the sensitivity and specificity of blood eosinophil counts predicting the curative effect are not high. The reason for this is that the eosinophilia in sputum or tissue or luminal appears to be the most accurate and clinically relevant.²⁴ There was no statistical difference in lung function parameters, which may be attributed to the control of asthma in most children before AIT, but PC20 significantly improved after AIT as we found in another article.²⁵

In this study, we analyzed the relationship between serum parameters before AIT and AIT efficacy, which provided a reference for selecting the appropriate patients for AIT. However, it is not clear whether serum parameters after AIT is related to the clinical symptoms. In addition, we used the changes of SPT grade to make a qualitative assessment of AIT efficacy, but whether the size of its diameter can be used to quantitatively assess the efficacy of AIT is not yet known. These are the directions of our research in the future.

The limitation of our study was the SPT readout and the symptom and medication scores are very subjective. It was a retrospective study without control for clinical observations so that conclusions would not be very safe. However, we believe these limitations do not significantly confuse the main results of our study.

In conclusion, skin prick test significantly improved after AIT, its change in grade had a high degree of consistency with the symptom and drug score judgment, which suggested it can be used for efficacy evaluation. Children with lower tIgE levels and higher sIgE/tIgE ratio obtain a more satisfactory effect. Serum total IgE could be considered as a good predictor for clinical efficacy of AIT.

Materials and methods

This study is a retrospective study; we analyzed 81 children with allergic asthma and/or rhinitis sensitised to mite allergens who underwent 3-year standardized-quality subcutaneous immunotherapy from February 2009 to February 2014 at Asthma and Allergy Immunotherapy Center of The Second Affiliated Hospital & Yuying Children's Hospital of Wenzhou Medical University, China. All child patients met the criteria for persistent mild asthma and/or allergic rhinitis according to GINA and ARIA guidelines.^{11,12} Sensitization of allergens was confirmed by presencing a positive skin prick test response to *Dermatophagoides pteronyssinus* (Dp; ALK-ALBELLLO AS, Hørsholm, Denmark) and had Dp-specific IgE (sIgE) against Dp >0.35 ku/l (UniCAP, Pharmacia Diagnostics, Uppsala, Sweden). According to the international guidelines,¹³ none of the patients had a contraindication to AIT. Serum tIgE, sIgE, eosinophil count, skin prick test, and lung function were measured before and after treatment. Patients were divided into three groups depending on the tIgE level before treatment (low value group as tIgE ≤130 ku/l, medium value group as tIgE >130 ku/l and tIgE <540 ku/l and high value group as tIgE ≥540 ku/l). Each group was then divided into two subgroups at the cut-off point of the sIgE/tIgE ratio of 15.0%. The study was approved by the Ethics Committee of University Hospital. The parents of each children were informed and signed the consent.

Blood Eosinophil Counts

The peripheral blood was took from every patient before and after AIT. The blood eosinophils absolute count was detected by a fully automated hematology analyzer (Mindray, Shenzhen, China), and the value $\leq 0.45 \times 10^9/l$ was considered normal.

Serum tIgE and sIgE levels

Serum tIgE and sIgE were measured by fluoroimmunoassay technique (UniCAP, Pharmacia Diagnostics, Uppsala, Sweden). The tIgE was measured in the range of 2 ku/l to 2,500 ku/l. Similarly, sIgE levels were determined in the range of 0.35 kua/l to 100 kua/l. And sIgE value is divided into 7 grades, from 0 to 6: <0.35 kua/l (grade 0), ≥ 0.35 kua/l and <0.70 kua/l (grade 1), ≥ 0.7 kua/l and <3.5 kua/l (grade 2), ≥ 3.5 kua/l and <17.5 kua/l (grade 3), ≥ 17.5 kua/l and <50.0 kua/l (grade 4), ≥ 50 kua/l and <100 kua/l (grade 5), ≥ 100 kua/l (grade 6). Furthermore, we use the following formula to calculate the Dp-specific IgE and tIgE ratio: $\text{sIgE/tIgE ratio} = (\text{sIgE/tIgE}) \times 100$.

Skin Prick Test

The skin prick agent is produced by an assassination (R) SO (ALK-ABELLO AS), including Dp, Df, tree and weed pollens, cat and dog epithelia, streptomyces and cockroach, a total of 10 kinds of standard inhalation allergen point thorn liquid. Physiological saline was used as a negative control and histamine solution (10mg/ml) as a positive control. We observed the response fifteen minutes after application, and the average of the largest diameter and its perpendicular diameter of the wheal were recorded. It is determined positive reaction that the response is at least 3mm greater than the negative control. We calculate the ratio of allergen wheal diameter divide by the histamine wheal diameter to get the skin index value, and the grades of SPT for each allergen are determined by the skin index values: ≤ 0.5 (1+), > 0.5 and ≤ 1.0 (2+), > 1.0 and ≤ 2.0 (3+) and > 2.0 (4+).

Lung Functions

Lung function was measured by JAEGER MasterScope Body automated system before and after the immunotherapy. The percentage of predicted value as the present of the result.

Evaluation of AIT efficacy

The effective AIT was based on the improvement of clinical symptoms (alleviation in nasal and pulmonary symptoms) and the reduction of concomitant drugs (eg, inhaled glucocorticoids and inhaled short-acting β_2 -agonist). The efficacy of AIT was considered to be effective response if the dose of concomitant drug was decreased to 25% of before treatment and symptoms became well-controlled after treatment. We defined the grade of skin prick test that is at least one grade lower than before treatment as an effective response to treatment. By comparing changes in the grade of SPT in each group, the efficacy of AIT were evaluated.

Statistical Analysis

Statistical analysis was carried out by statistics softwares (SPSS version 17 and Medcalc 15). We use the arithmetic mean and the 95% confidence interval to represent normally distributed data. Abnormally distributed data were expressed as the geometric mean and the 95% CI after logarithmic transformation, or expressed as the median (IQR). Normal distribution was assessed using the Kolmogorov-Smirnov test. Group comparison tests were performed using two-sided t test and nonparametric test, and χ^2 test was used to compare categorical variables. Multiple comparisons were compared by using One-way ANOVA test. Recipient Operator Profile (ROC) curve analysis was used to estimate the optimal cutoff value for distinguishing between responders and nonresponders. The Kappa value was used to assess the degree of diagnostic efficacy consistency between the SPT grade changes and symptoms and drug score judgment. For all tests, $P < 0.05$ was considered statistically significant.

Disclosure of potential conflicts of interest

The authors state that they have no conflict of interests.

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Figure 1. ROC curves got from serum tIgE levels (cut off value 610 kU/l; sensitivity 75.9% and specificity 74.0%), serum Der p sIgE/tIgE ratio (cut off value 15.0%; sensitivity 56.9% and specificity 91.3%) , serum sIgE levels (cut off value 76.7 kua/l; sensitivity 67.2% and specificity 69.6%) and blood eosinophil count (cut off value $0.49 \times 10^9/l$; sensitivity 69.0% and specificity 60.9%) by plotting sensitivity to effective AIT versus 100-specificity to ineffective AIT in children with asthma.

Figure 1.

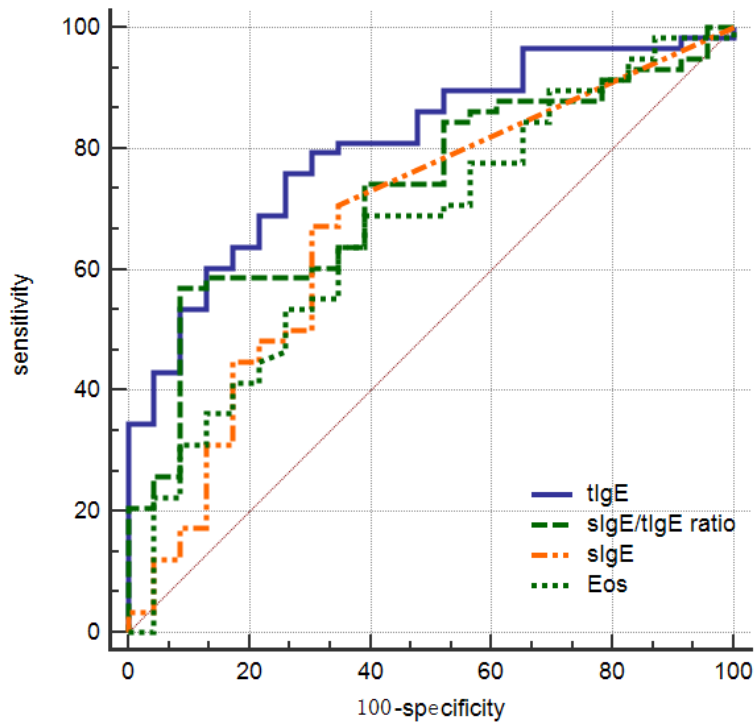


Figure 2. Multiple comparisons between different levels of tIgE (low value group vs. medium value group, $*P < 0.05$; low value group vs. high value group, $**P < 0.001$), and the medium value group is superior to high value group (medium value group vs. high value group, $*P < 0.05$).

Figure 2

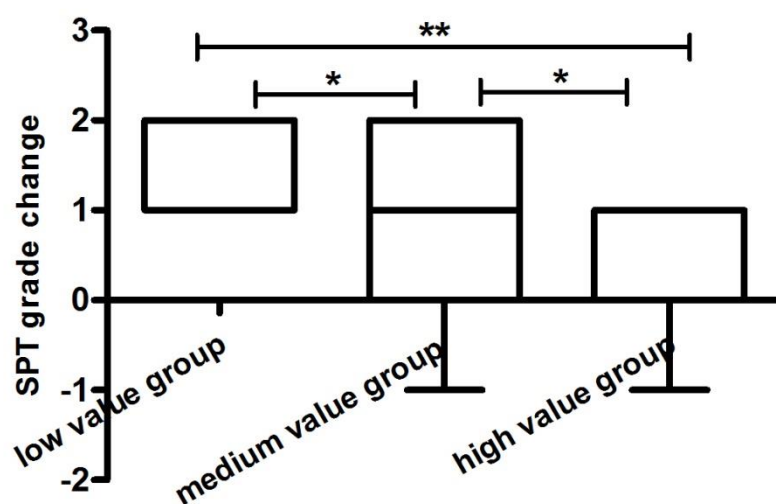


Table 1. Differences in patient characteristics before and after treatments of AIT

Characteristic	All patients		<i>P</i> value
	before treatment	after treatment	
Patients, n	81		
Age, years [*]	7(6–10)		
Males/females, n	59/22		
Height (cm) ^a	125.7(122.4–128.9)		
Weight (kg) [*]	25.0(20.3–34.9)		

BMI [*]	16.3(14.8–18.8)		
Asthma/rhinitis/asthma + rhinitis, n	19/5/57		
Serum tIgE level, kU/l ^b	420.8(331.4–534.2)	661.5(532.0–822.2)	<0.001
Serum sIgE level, kua/l [*]	72.5(31.1–100.0)	70.9(40.0–100.0)	0.684
Blood eosinophil count, cells × 10 ⁹ /l ^a	0.52(0.43–0.60)	0.38(0.33–0.44)	0.003
Serum sIgE/tIgE ratio ^a	16.3(13.8–18.9)	9.8(8.7–10.9)	<0.001
Dp grade(1/2/3/4/5/6), n	0/4/8/17/19/33	0/0/8/21/25/27	0.871
Df grade(1/2/3/4/5/6), n	0/4/8/23/24/22	0/0/11/20/34/16	0.687
Skin Prick Test			
Dp wheal diameter/histamine ^a	1.76(1.61–1.91)	0.95(0.88–1.02)	<0.001
Df wheal diameter/histamine ^a	1.49 (1.32–1.66)	0.81(0.74–0.87)	<0.001
Dp grade(0/1/2/3/4), n	0/1/6/49/25	0/3/47/30/1	<0.001
Df grade(0/1/2/3/4), n	0/3/19/42/17	1/9/61/9/1	<0.001
Provocation test (postive/negative), n	50/31	43/38	0.239
Pulmonary Functions			
FVC,pred ^a	90.5(87.4–93.5)	90.2(87.2–93.3)	0.813
FEV1,%pred ^a	93.3(90.3–96.2)	91.2(88.5–93.9)	0.162
PEF,%pred ^a	92.2(88.4–96.1)	95.4(92.1–98.7)	0.228
FEV1/FVC%,%pred ^a	101.2(99.4–102.9)	100.6(99.0–102.3)	0.226
FEF25–75%,%pred ^a	87.8(82.4–93.1)	84.9(80.3–89.4)	0.195
MEF75%, %pred ^a	87.1(82.7–91.4)	85.9(81.8–89.9)	0.457
MEF50%,%pred ^a	85.7(80.5–90.9)	83.8(79.6–88.1)	0.265
MEF25%,%pred ^a	92.7(86.1–99.4)	88.6(83.0–94.2)	0.068
^a Mean (95% CI)			
^b Geometric mean after logarithmic transformation (95% CI)			
[*] Median (IQR)			

Table 2. Differences *in parameters before treatment* between patients with and without an effective response to AIT

Characteristic	Clinical response		P value
	effective	ineffective	
Patients, n (%)	58(71.6)	23(28.4)	
Age, years*	7(6-9)	7(6-10)	0.941
Males/females, n	39/19	20/3	0.072

BMI [*]	17.5(16.5-18.4)	16.3(14.6-17.6)	0.200
Serum tIgE level, kU/l ^b	294.1(227.6-380.2)	870.8(633.7-1196.5)	<0.001
Serum sIgE level, kua/l [*]	61.1(25.1-100.0)	100.0(56.5-100.0)	0.011
Serum sIgE/tIgE ratio ^a	17.8(14.9-20.8)	9.6(6.8-12.4)	<0.001
Blood eosinophil count, cells × 10 ⁹ /l ^a	0.45(0.37-0.53)	0.65(0.48-0.82)	0.020
Skin Prick Test			
Dp wheal diameter/histamine ^a	1.83(1.65-2.01)	1.58(1.30-1.87)	0.143
Dp grade(0/1/2/3/4), n	0/0/2/36/20	0/1/4/13/5	0.049

^a Mean (95% CI)

^b Geometric mean after logarithmic transformation (95% CI)

^{*}Median (IQR)

Table 3.Consistency of skin prick test with symptoms and drug score judgment

		symptoms and medication score judgment	
		effective	ineffective
Skin prick test	effective	52	5
	ineffective	6	18

Table 4. Comparison the AUC of potential predictors

Potential predictors	AUC	Difference between areas	<i>P</i> value
Serum tIgE	0.806(0.703-0.885)		
Serum sIgE/tIgE ratio	0.730(0.620-0.823)		
Serum sIgE	0.676(0.563-0.776)		
Blood eosinophil count	0.666(0.663-0.767)		
tIgE vs. sIgE		0.130(0.030-0.230)	0.011
tIgE vs. blood eosinophil count		0.140(0.008-0.271)	0.037
tIgE vs. sIgE/tIgE ratio		0.076(-0.024-0.175)	0.136
sIgE/tIgE ratio vs. sIgE		0.054(-0.124-0.233)	0.551
sIgE vs. blood eosinophil count		0.010(-0.145-0.164)	0.902
sIgE/tIgE ratio vs. blood eosinophil count		0.064(-0.092-0.220)	0.422
Figures in parentheses are 95% CI			

Table 5.Comparison of subgroups of different sIgE / tIgE ratios

Group (tIgE, ku/l)	Subgroup (sIgE/tIgE, %)		Z value	P value
	≤15.0, n	>15.0, n		
tIgE ≤130	6	10	-0.630	0.529
tIgE >130 and tIgE <540	10	21	-1.469	0.142
tIgE ≥540	29	5	-2.097	0.036