Profiles of sensitization and comorbidity in asthma patients with markedly increased serum total immunoglobulin E level (>1000 kUA/L)

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Research

Abstract

Background

Immunoglobulin E (IgE) plays an important role in asthma, but a few cases exhibited extremely high levels of serum total IgE. This study aimed to investigate the profiles of complications, severity, and sensitizations in asthma patients with serum total IgE level >1000 kU_A/L.

Methods

We retrospectively analyzed 170 asthma patients with serum total IgE levels >1000 kU_A/L from the in-patient database of First Affiliated Hospital of Guangzhou Medical University from January 2014 to June 2019. Available information including age, gender, body mass index (BMI), diagnosis, results of blood routine, pulmonary function, fractional exhaled nitric oxide (FeNO), induced sputum (if any), IgE (both total and specific) and medication records were analyzed.

Results

About 15% patients had at least one complication, and 78.82% patients were positive for at least one allergen. The top two complications were airway infections (44.71%) and rhinosinusitis (41.18%), followed by hypertension and/or cardiovascular diseases (20.59%) and COPD (12.94%). And in patients without sensitization, rhinosinusitis accounted for the highest proportion over all complications (45.83%). Serum total IgE levels did not differ among patients with different complications. Overall, mites had the highest positive rate (59.4%). In minors, the positive rates of mites (81.25% vs. 54.35%, $P < 0.01$) and food (68.75% vs. 39.86%, $P < 0.01$) were significantly higher than those in adults. Serum total IgE levels were positively correlated to house dust mite specific IgE levels (r=0.23, $P < 0.05$), peripheral blood eosinophil counts (r=0.21, $P < 0.01$) and number of confirmed sIgE positivity (r=0.19, $P < 0.01$) and optimal scaling analysis showed that asthma severity was associated with *A. fumigatus* specific IgE levels.

Conclusions

In asthma patients with markedly increased serum total IgE levels (>1000 kU_A/L), the most common two complications were airway infections and rhinosinusitis despite of sensitization. *A. fumigatus* specific IgE levels were closely associated with total IgE levels and asthma severity.

1. Background

Asthma is a chronic inflammatory disease of the airways with the typical characteristics of reversible airflow limitation and airway hyperresponsiveness (AHR) [1]. Its clinical symptoms vary from individuals, including wheeze, shortness of breath, dyspnea, chest tightness and/or cough. Asthma has been a public health issue over all ages worldwide, affecting 1–18% of the population in different countries, and the economic burden of the disease is still on the rise [2, 3]. Allergic asthma is the most common phenotype [4], in which T helper type 2 inflammation is considered to be the predominant immune response against

the allergens encountered [5]. Antigen presenting cells (APCs) with captured allergen leads to the activation of T helper 2 (Th2) cells, resulting in the secretion of Th2 cytokines such as interleukin-4 (IL-4) and IL-13. Afterwards, B cell is stimulated for immunoglobulin E (IgE) synthesis and secretion. The secreted IgE can not only binds to mast cells, which triggers degranulation, consequently causing allergic symptoms, but binds to APCs and activates more Th2 cells.

In fact, most cases of asthma contributes to IgE-mediated reaction, and the increased levels of total and specific IgE in the peripheral is involved in the onset as well as the chronic phase of the disease [6]. Studies have indicated that elevated serum total IgE levels could occur in atopic and non-atopic asthma patients, and it was associated with the risk of asthma as well as with AHR [7–9]. However, the correlation between IgE level and asthma severity is controversy. Borish L et al.'s study found that children with severe asthma had high serum IgE level, while another did not find a significant association between total IgE levels and disease severity [10, 11]. This can be affected by several factors, such as polysensitization, non-allergenic factors (e.g. infection) and persistent inflammation caused by allergens [12]. Despite of that, anti-IgE treatment has been applied in clinical practice for some cases of poorly controlled moderate-to-severe asthma, which improves asthma related symptoms and reduces severe exacerbations [13, 14].

There are a few patients exhibited extremely high levels of serum total IgE (> 1000 kU_A/L). Conditions like atopic eczema, helminthic infection and rare primary immunodeficiencies can lead to markedly up-regulated total IgE levels (> 1000 kU_A/L) [15]. In some of these cases with sensitization of *Aspergillus fumigatus*, they might develop allergic bronchopulmonary aspergillosis (ABPA) as Th2 immunity against the fungi increased [16, 17]. The prevalence was estimated to be about 6% in chronic cases of asthma, and total IgE > 1000 kU_A/L is considered as one of the diagnostic criteria of ABPA [18, 19]. However, certain amount of asthma patients with total IgE > 1000 kU_A/L do not meet the diagnostic criteria of ABPA. To date, few study has been performed to investigate these asthma cases. In order to better understand the characteristic of these cases, we aimed to analyze the profiles of complications, severity, and sensitizations in asthma patients with serum total IgE > 1000 kU_A/L.

2. Methods

2.1 Study subjects

This is a retrospective analysis of the in-patient database generated by First Affiliated Hospital of Guangzhou Medical University, from January 2014 to June 2019. We screened the database for patients who were clinically diagnosed as asthma and had serum total IgE levels > 1000 kU_A/L (n=202). Patients met the diagnostic criteria of ABPA based on The International Society of Human and Animal Mycology (ISHAM) working group were excluded [18]. A total of 170 asthma patients with total IgE > 1000 kU_A/L were screened out from the database (Figure S1). Among the included subjects, 24 patients had hospitalization records for more than one time during the study period. The data used for analysis was the data of the patients when total IgE >1000 kU_A/L was first recorded among their hospitalizations. None

of the included patients had diagnosis of primary immunodeficiency diseases. Available information of each patient were collected for analysis, including age, gender, body mass index (BMI), diagnosis, results of blood routine, pulmonary function, fractional exhaled nitric oxide (FeNO), induced sputum (if any), IgE (both total and specific) and medication records.

2.2 Diagnosis criteria and disease classification

The diagnosis of asthma was based on the Global Initiative for Asthma (GINA) guidelines, including asthma clinical features of the patient as well as presence of airflow limitation. The diagnosis of chronic obstructive pulmonary disease (COPD) was based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, including presence of clinical features like dyspnea, chronic cough or sputum production and meeting the spirometry standard. The diagnosis of eosinophilic granulomatosis with polyangiitis (EGPA) was based on the criteria developed by Lanham et al., including asthma, peak eripheral blood eosinophil count > 1.5 ×10^9 cells/L and systemic vasculitis involving two or more extrapulmonary organs [20]. The definition of rhinosinusitis was according to the European position paper on Rhinosinusitis and nasal polyps, which contains characterized symptoms, endoscopic signs and CT changes [21]. Cardiovascular diseases (CDVs) included coronary heart disease, cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, congenital heart disease and deep vein thrombosis and pulmonary embolism. Hypertension was diagnosed following WHO's instruction, which is on two different days, the systolic blood pressure readings was ≥ 140 mmHg and/or the diastolic blood pressure readings was ≥ 90 mmHg. The diagnosis of cancer was confirmed via pathological diagnosis of the lesions. Airway infection includes pneumonia, bronchi infections and lung infections caused by microorganisms.

2.3 Grouping

Since some of the complications (e.g. COPD) as well as sensitization profiles (food sensitization may decrease as children grew up [22]) varied from ages, patients were classified into minors (age <18, n=32) and adults (age ≥18, n=138) for our analysis. The assessment of asthma severity was based on the level of treatment required to control symptoms and exacerbations of the past 4 weeks following the instruction of GINA guideline [3]. Briefly, mild asthma is well controlled with Step 1 or Step 2 treatment; moderate asthma is well controlled with Step 3 treatment; severe asthma requires Step 4 or 5 treatment to prevent it from becoming 'uncontrolled', or remains 'uncontrolled' despite this treatment. The severity assessment was recorded in the medical records of each patient by specialists, and those who lacked such information were not available for assessing severity. Among the enrolled patients, 27 (15.88%) were with mild asthma, 68 (40%) were with moderate asthma, 55 (32.35%) were with severe asthma and 20 patients (11.76%) lacked information for asthma severity assessment.

2.4 IgE detection

Serum samples were obtained from venous blood collecting with separation gel containing vacutainer tubes by centrifuged at 3000rpm for 10min. Serum total IgE and specific IgE (including Phadiatop test

[23], allergen mixtures such as house dusts mix (hx2) and specific allergens) were analyzed by ImmunoCAP 1000 system (Thermo Fisher Scientific Inc., California, USA) according to the procedures offered by the manufacture. The tests of patients undergoing were depended on the allergy history of each patient and were prescribed by specialists. A positive result of specific IgE was considered as ≥ 0.35 kU_A/L. For those patients who were positive for Phadiatop or allergen mixtures but did not take further detection of specific IgE of typical allergens, they were considered as sensitized to at least one inhaled allergen or at least one of the mixture allergens, respectively. IgE detection was done during the hospitalization.

2.5 Measurement of lung functions and FeNO

Lung function tests were performed on a computerized spirometer (MasterScreen, Leibnizstrasse, Hoechberg, Germany). The examination parameters included forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), peak expiratory flow (PEF) percentage predictors' parameters (%FVC, %FEV_1 and %PEF) and the FEV_1/FVC ratio. Fractional exhaled nitric oxide (FeNO) measurement (NioxMino, Acerocrine, Sweden) were performed prior to bronchial provocation at a flow rate of 50mL/s using signals fed back for the control.

2.6 Statistical analysis

Parametric quantitative data were expressed as mean ± standard deviation and non-parametric quantitative data were expressed as median (interquartile range). For Parametric quantitative data, ordinary one-way ANOVA was applied for comparison of three groups and student t-test was used for two-group comparison. For non-parametric data, differences of the three groups were analyzed using the non-parametric Kruskall-Wallis test and Mann-Whitney test was used for comparison between two groups. Spearman *rho* test was applied for correlation analysis. Proportions were compared between groups with chi-square tests (c^2). Optimal scaling was carried out with categorical principle component analysis. Statistical analysis was performed with SPSS 22.0 (SPSS, Chicago, IL) and GraphPad Prism 6.0 software (GraphPad Software Inc., San Diego, CA, USA). A value of $P < 0.05$ was considered statistically significant.

3. Results

Characteristics of the study subjects were shown in Table 1. Compared with minors, adults had lower proportion of mild asthma and higher proportion of severe asthma. This resulted in worse lung function results (%FEV_1, FEV_1/FVC and %PEF) in adults. Besides, the number of sIgE positives among minors was higher than that of adults (4 [3, 5] vs. 2 [1, 5], $P < 0.05$).

Table 1
Characteristic of the study population

	Overall (n = 170)	Minors (n = 32)	Adults (n = 138)
Demographic			
Age (years)	43.99 ± 22.52	6.81 ± 3.22	52.34 ± 15.38**
Gender (male/female)	106/64	21/11	85/53
BMI (kg/m^2)	21.52 ± 4.31	16.15 ± 3.23	22.68 ± 3.71**
Asthma severity			
Mild (%)	15.88%	43.75%	7.97%**
Moderate (%)	40.00%	25.00%	43.48%
Severe (%)	32.35%	3.13%	39.13%**
Immunological characteristic			
Total IgE levels (kU$_A$/L)	1438 [1181, 2255]	1541 [1222, 2494]	1459 [1170, 2279]
Specific IgE positive rate (%)	78.82%	29/32	109/138
Number of confirmed sIgE positivity	3 [1, 5]	4 [3, 5]	2 [1, 5]*
Use of corticoids			
OCS (%)	34.12%	0%	42.75%**
ICS (%)	85.88%	78.13%	86.96%
Blood cell counts			
WBC (×10^9 cells/L)	8.39 [6.60, 10.40]	8.56 [6.98, 11.07]	8.20 [6.50, 10.20]
Neutrophil (×10^9 cells/L)	4.50 [3.40, 6.70]	3.75 [2.90, 6.63]	4.80 [3.70, 6.70]
Eosinophil (×10^9 cells/L)	0.32 [0.1, 0.71]	0.44 [0.17, 0.79]	0.30 [0.10, 0.70]
Spirometry			
FVC pred (%)	87.50 [68.35, 99.95]	95.00 [79.12, 111.10]	85.50 [66.75, 96.55]

Age and BMI were given as mean ± standard deviation, other non-parametric quantitative data were given as medians with interquartile range (IQR). BMI: body mass index; OCS: oral corticoid steroid; ICS: inhaled corticoid steroid; WBC: white blood cell; *$P < 0.05$ compared with Minors; **$P < 0.01$ compared with Minors

	Overall (n = 170)	Minors (n = 32)	Adults (n = 138)
FEV_1 pred (%)	67.90 [45.70, 90.00]	94.40 [73.37, 103.90]	63.95 [42.78, 86.93]**
FEV_1/FVC ratio (%)	66.00 [52.66, 75.29]	81.01 [77.99, 88.48]	62.65 [51.15, 71.44]**
PEF pred (%)	72.90 [47.25, 87.02]	82.00 [68.10, 108.00]	69.00 [40.05, 83.15]**
FeNO (ppb)	34.00 [15.00, 64.00]	35.00 [10.50, 57.00]	37.50 [18.50, 68.25]
Induced sputum			
Neutrophil (%)	71.50 [48.75, 87.50]	53.05 [30.31, 86.34]	73.50 [48.75, 87.75]
Eosinophil (%)	5.50 [1.25, 17.09]	10.00 [4.84, 43.81]	5.00 [1.00, 17.09]
Age and BMI were given as mean ± standard deviation, other non-parametric quantitative data were given as medians with interquartile range (IQR). BMI: body mass index; OCS: oral corticoid steroid; ICS: inhaled corticoid steroid; WBC: white blood cell; *$P < 0.05$ compared with Minors; **$P < 0.01$ compared with Minors			

We investigated the complication status in these patients (Table 2). There were 4 patients (2.35%) complicated with conditions that may associate with serum total IgE levels > 1000 kU_A/L, which were helminthic infection (3 cases, 1.76%) and atopic dermatitis (1 cases, 0.59%). In patients complicated with other conditions, airway infections (76 cases, 44.71%) and rhinosinusitis (70 cases, 41.18%) were the most common two complications, followed by hypertension and/or CDVs (35 cases, 20.59%) and COPD (22 cases, 12.94%). We further analyzed the complications in patients who were not sensitized to any detected allergens, and the pattern of complication was similar to the overall study subjects (Table S1).

Table 2
Complication profiles of asthma patients with total IgE level > 1000 kU$_A$/L

Complications	Frequency (n = 170)
Asthma without complications	24 (14.12%)
Complicated with 2 or more conditions	68 (40.00%)
Typical conditions associated with tIgE > 1000 kU$_A$/L	
Helminthic infection	3 (1.76%)
Atopic dermatitis	1 (0.59%)
Other conditions	
Airway infections	76 (44.71%)
Rhinosinusitis	70 (41.18%)
Hypertension and/or CDVs	35 (20.59%)
COPD	22 (12.94%)
Type II diabetes	12 (7.06%)
EGPA	10 (5.88%)
Cancer	4 (2.35%)
ILD	2 (1.18%)
Rheumatoid arthritis	1 (0.59%)
CDVs: cardiovascular diseases; COPD: chronic obstructive pulmonary disease; EGPA: eosinophilic granulomatosis with polyangiitis; ILD: interstitial lung disease.	

The overlaps of complications in minors and adults were shown in Fig. 1. Only two complications were observed in minors and airway infections accounted for the most common complication in the minors group (Fig. 1A), while rhinosinusitis was the most common one in adults (Fig. 1B). In the analysis of serum total IgE levels, we performed the comparisons from various aspects, including age, asthma severity, complications, number of complications, sensitization status and number of confirmed sensitization. No significant differences were found in any of the comparison. (Fig. 2).

In the 134 patients confirmed to be sensitized to at least one allergen, we further analyzed the sensitization patterns. Overall, mites had the highest positive rate (59.41%), followed by food (45.29%), cockroaches (37.06%), molds (24.71%), animal dander (13.53%) and pollens (11.18%) (Fig. 3A). The sensitization patterns varied between minors and adults, where minors had significantly higher positive rates in mites (81.25% vs. 54.35%, $P < 0.01$) and food (68.75% vs. 39.86%, $P < 0.01$) compared with adults (Fig. 3B). Venn diagrams showed the profiles of poly-sensitization. In minors, nearly 90% were sensitized

to at least 2 types of allergens and the majority were sensitized to 2 types of allergens (44.83%), while in adults, the majority were sensitized to 1 type of allergens (26.53%) (Fig. 3C, 3D).

Among the study subjects, serum total IgE levels were positively correlated to house dust mite specific IgE levels (r = 0.23, P< 0.05), peripheral blood eosinophil counts (r = 0.21, P< 0.01) and number of confirmed sIgE positivity (r = 0.19, P< 0.01) (Table S2). Besides, asthma severity was positively correlated to $A.$ $fumigatus$ specific IgE levels (r = 0.200, P< 0.05), but reversely correlated to lung function results (%FVC: r=-0.47, P< 0.01; %FEV$_1$: r=-0.60, P< 0.01; FEV$_1$/FVC: r=-0.51, P< 0.01) (Table S2). Similarly, $A.$ $fumigatus$ specific IgE levels were also negatively associated to some of the lung function results (%FEV$_1$: r=-0.29, P < 0.01; FEV$_1$/FVC: r=-0.34, P< 0.01) (Table S2).

Results from optimal scaling illustrated a close association among lung function results, among peripheral neutrophil counts, percentage of neutrophil in sputum and white blood cell counts, between number of confirmed specific IgE positivity and house dust mite specific IgE, between peripheral eosinophil counts and percentage of eosinophil in sputum, as well as between asthma severity and $A.$ $fumigatus$ specific IgE levels. (Cronbach's α = 93.7%) (Fig. 4).

In the comparison of asthma patients with different severities (Table 3), except for the lung function results, which were worsen as asthma severity increased, younger age was found in mild asthma group compared with moderate and severe group (P< 0.01). Similarly, mild asthma group had lower BMI compared with severe group (P< 0.05). Meanwhile, the peripheral blood neutrophil counts were also increased in moderate and severe asthma group compared with mild group (P< 0.05). Regarding complications, no significant difference was found in number of complications among the three groups (P= 0.09). In the mild group, lower proportion of COPD complication compared with the other two groups (P< 0.05). No statistical significance was found in serum total IgE levels (P= 0.84) and number of confirmed specific IgE positivity (P= 0.73) among the three groups.

Table 3
Comparisons in asthma patients of various severity

	Mild (n = 27)	Moderate (n = 68)	Severe (n = 55)	P value
Demographic				
Age (years)	27.63 ± 25.46	44.41 ± 19.74**	51.29 ± 16.73**	**< 0.001**
Gender (male/female)	13/14	42/26	39/16	0.132
BMI (kg/m^2)	20.00 ± 4.48	21.45 ± 3.94	22.92 ± 3.85**	**0.009**
Spirometry				
FVC pred (%)	106.9 [94.25, 116.70]	88.42 [76.16, 100.10]**†	74.50 [62.20, 91.00]**	**< 0.001**
FEV$_1$ pred (%)	96.05 [93.63, 107.80]	73.76 [52.50, 90.00]**††	50.00[33.60, 65.70]**	**< 0.001**
FEV$_1$/FVC ratio (%)	77.69 [69.49, 86.99]	68.60 [59.00, 79.04]*††	54.26 [41.66, 66.00]**	**< 0.001**
FeNO (ppb)	57 [20, 113]	34 [18.50, 90]	38 [12, 52]	0.369
Blood cell count				
WBC (×10^9 cells/L)	7.73 [6.07, 9.21]	8.53 [6.70, 10.46]	7.80 [6.55, 10.59]	0.388
Eosinophil (×10^9 cells/L)	0.36 [0.22, 0.93]	0.30 [0.03, 0.72]	0.35 [0.10, 0.71]	0.378
Neutrophil (×10^9 cells/L)	3.70 [2.60, 4.75]	4.80 [3.90, 7.00]*	4.30 [3.55, 6.70]*	**0.014**
Induced sputum				
Eosinophil (%)	8.00 [6.00, 48.50]	5.50 [0.94, 20.88]	9.75 [1.75, 17.75]	0.642
Neutrophil (%)	55.60 [34.25, 64.00]	64.50 [45.75, 90.00]	77.50 [49.75, 87.75]	0.198
Immunological characteristic				
Total IgE level (kU$_A$/L)	1457 [1182, 2012]	1545 [1194, 2288]	1718 [1247, 2896]	0.842

Age and BMI were given as mean ± standard deviation, other non-parametric quantitative data were given as medians with interquartile range (IQR). BMI: body mass index; COPD: chronic obstructive pulmonary disease; EGPA: eosinophilic granulomatosis with polyangiitis; CDVs: Cardiovascular diseases. *P< 0.05 compared with mild asthma; **P< 0.01 compared with mild asthma; †P< 0.05 compared with severe asthma; ††P< 0.01 compared with severe asthma

	Mild (n = 27)	Moderate (n = 68)	Severe (n = 55)	P value
Number of confirmed sIgE positivity	3 [1.5, 5]	3 [1, 6]	2 [1, 5.5]	0.726
Complications				
Number of complications	1 [1, 1]	1 [1, 2]	2 [1, 2]	0.090
Airway infection (%)	51.85%	44.12%	30.91%	0.142
Rhinosinusitis (%)	59.26%	45.59%	43.64%	0.910
COPD (%)	0%	13.24%	21.82%	**0.027**
EGPA (%)	0%	8.82%	7.27%	0.291
Type II Diabetes (%)	0%	8.82%	7.27%	0.291
Hypertension and/or CDVs (%)	7.41%	22.06%	21.82%	0.223

Age and BMI were given as mean ± standard deviation, other non-parametric quantitative data were given as medians with interquartile range (IQR). BMI: body mass index; COPD: chronic obstructive pulmonary disease; EGPA: eosinophilic granulomatosis with polyangiitis; CDVs: Cardiovascular diseases. *P< 0.05 compared with mild asthma; **P< 0.01 compared with mild asthma; †P< 0.05 compared with severe asthma; ††P< 0.01 compared with severe asthma

4. Discussion

In this study, we described the profiles of comorbidity and sensitization of a typical group of asthma patients (total IgE > 1000 kU$_A$/L). This is the first study investigating the clinical information in asthma patients with such high level of serum total IgE. Our results demonstrated that in these patients, less than 5% patients were complicated with conditions associated with serum total IgE level > 1000 kU$_A$/L and nearly 80% patients were positive for at least one specific IgE test. Airway infections and rhinosinusitis were accounted for the most popular complications in minors and adults, respectively. Moreover, sensitization to *A. fumigatus* was associated with asthma severity.

In general, elevation of serum total IgE is usually found in allergic diseases. Extremely high level of serum total IgE (> 1000 kU$_A$/L) could attribute to conditions like ABPA, helminthic infection and atopic dermatitis. Patients with ABPA were not included in our study, because it is a different entity of disease that exhibits asthma symptoms and may affects the analysis of IgE in asthma patients. Helminth infection induces strongly Th2-skewed responses in host defense, resulting in mastocytosis, eosinophilia and IgE production [24]. And in atopic dermatitis, the immune deviation towards Th2 and Th22 expansion, which also leads to generation of IgE against both exogenous and self allergens, and the persisting inflammation contributes to markedly elevated IgE level [25, 26].

It has been reported that asthma accounted for 26.1% in patients with serum total IgE level > 1000 kU$_A$/L in a 15-year retrospective analysis [15]. We further investigated the comorbidity of asthma patients with such high IgE level. There were only about 2% patients complicated with helminth infection or atopic dermatitis, and the highest two proportions of complications were airway infection (44.71%) and rhinosinusitis (41.18%). The frequency of patient complicated atopic dermatitis was low in our cohort. As patients complicated atopic dermatitis may not require hospitalization and the included patients were screened from in-patient system, the proportion might be underestimated. In patients without sensitization, only one patient complicated conditions associated with the raised total IgE (helminthic infection). Rihosinusitis and airway infections still accounted for the most common two complications. Asthma patients complicated with rhinitis, whether allergic or non-allergic, or airway infections could lead to elevation of total IgE levels because of chronic inflammation and the reactivity of IgE against microorganisms [27–30]. In addition to infection, air pollutants such as diesel exhaust particles can also impair the integrity of airway epithelium, which promotes infiltration of pathogens via the damaged epithelium, causing inflammation responses [31].Regarding other conditions such as COPD, EGPA, type II diabetes, CVDs and hypertension, studies have also observed up-regulated levels of serum total IgE in these diseases [32–36]. However, whether these diseases could affect total IgE levels remains unclear and the underlining mechanism of IgE overproduction in nonatopic asthma requires further investigation.

In the analysis of sensitization profiles, despite the difference between age groups, mites had the highest positivity overall allergens, followed by food. This may due to our study population, as the top five most sensitized allergens in southern China were house dust mite, cockroach and three types of food allergens [37]. There was no significant difference in total IgE levels between patients with and without sensitization, neither between patients with 1–2 specific IgE sensitization and more than 3 specific IgE sensitization. This suggested that the increase in sensitizations may have less impact on these total IgE level of these patients, because their IgE levels were already high.

Asthma severity is associated with various factors. Although IgE is the primarily responsible for both acute and chronic phase of inflammation characteristic of bronchial asthma, it is not an effective indicator of asthma severity [38]. In our study cohort, the proportion of mild asthma (15.88%) was the lowest, and the average age was younger compared with the other two groups. There are several risk factors of severe asthma, including allergens, environmental and occupational sensitizers, smoking, aspirin sensitivity, behavior and infection [39]. As people grow, they might have higher chance as well as longer duration of exposure to the risk factors above, which could lead to chronic and/or persisted inflammation. Indeed, compared with the mild group, a higher proportion of COPD complications were observed in the moderate and severe groups, and the peripheral blood neutrophil counts were also higher. Evidences showed that non-type 2 inflammation (with/without type 2 inflammation) is likely to contribute to severe asthma, particularly the neutrophilic airway inflammation driven by type 1 responses and IFN-γ [40]. Since there was no significant difference in serum total IgE levels, number of sIgE positivity or eosinophil counts among the three groups, indicating that the type 2 inflammation was at a similar level. Hence, neutrophilic inflammation could be a major factor that increases asthma severity.

Correlation analysis showed associations between serum total IgE levels and house dust mite sIgE levels. Since the majority of our study subjects were positive for mites, the markedly increased total IgE levels may partly attribute to the increase of house dust mite sIgE. Additionally, we found positive correlation between asthma severity and *A. fumigatus* specific IgE levels. There is an entity of worse controlled asthma namely severe asthma with fungal sensitization (SAFS). Patients with SAFS could have similar symptoms as ABPA, even though they did not meet the diagnostic criteria of ABPA. In asthma patients sensitized to fungi, the long lasted inflammation caused by fungi leads to increase of Th2 immune responses, and as a result, the severity of asthma increases, which could even develop ABPA [16, 17]. In fact, our result of optimal scaling also showed that *A. fumigatus* specific IgE levels were related to asthma severity, and both of them were at the opposite site of lung function data in the scale, suggesting a negative correlation between these two sets of parameters. Therefore, management of these asthma patients should be focus on those sensitized to fungal allergens to prevent from developing severe asthma or ABPA.

There were several limitations in our study. First, the inclusion criteria was set as total serum IgE > 1000 kU_A/L, we cannot compare with patients with lower IgE levels. Second, this study was conducted in a single center in Southern China. Thus, our results may not be representable to other populations. Third, the allergen screening may not be comprehensive. However, we have screened for suspicious allergens of each patient based on their medical history and living environment. Last but not least, the cause of the rise of IgE level was not fully explained. Further studies are required to determine the underlining mechanism of markedly increased serum IgE level in asthma patients.

5. Conclusion

In conclusion, in asthma patients with markedly increased serum total IgE levels (> 1000 kU_A/L), the most common two complications were airway infections and rhinosinusitis despite of sensitization status. The majority were sensitized to mite allergens and house dust mite specific IgE levels partly contributed to the remarkably raised total IgE levels. In addition, *A. fumigatus* specific IgE levels were closely associated with total IgE levels and asthma severity.

Abbreviations

IgE
Immunoglobulin E
AHR
airway hyperresponsiveness
APCs
antigen presenting cells
A. fumigatus
Aspergillus fumigatus,
ABPA

allergic bronchopulmonary aspergillosis

BMI

body mass index

FeNO

fractional exhaled nitric oxide

GINA

Global Initiative for Asthma

COPD

chronic obstructive pulmonary disease

EGPA

eosinophilic granulomatosis with polyangiitis

CDVs

Cardiovascular diseases

FVC

forced vital capacity

FEV$_1$

forced expiratory volume in 1 second

PEF

peak expiratory flow

RA

rheumatoid arthritis

SAFS

severe asthma with fungal sensitization

Declarations

7.1 Ethics approval and consent to participate

This study was reviewed and approved by the ethics committee of First affiliated hospital of Guangzhou Medical University (GYFYY-2016-73). The use of human serum samples was in accordance of legislation in China and the wishes of donors, their legal guardians or next of kin, where applicable, who had offered written informed consent to using the serum samples for future unspecified research purposes.

7.2 Consent for publication

Not applicable.

7.3 Availability of data and materials

Not applicable.

7.4 Competing interests

The authors declare that they have no conflicts of interest.

7.6 Authors' contributions

Baoqing Sun conceived and designed the experiments. Ge Wu and Teng Zhang collected and analyzed the data. Ge Wu led the writing. All authors reviewed the manuscript.

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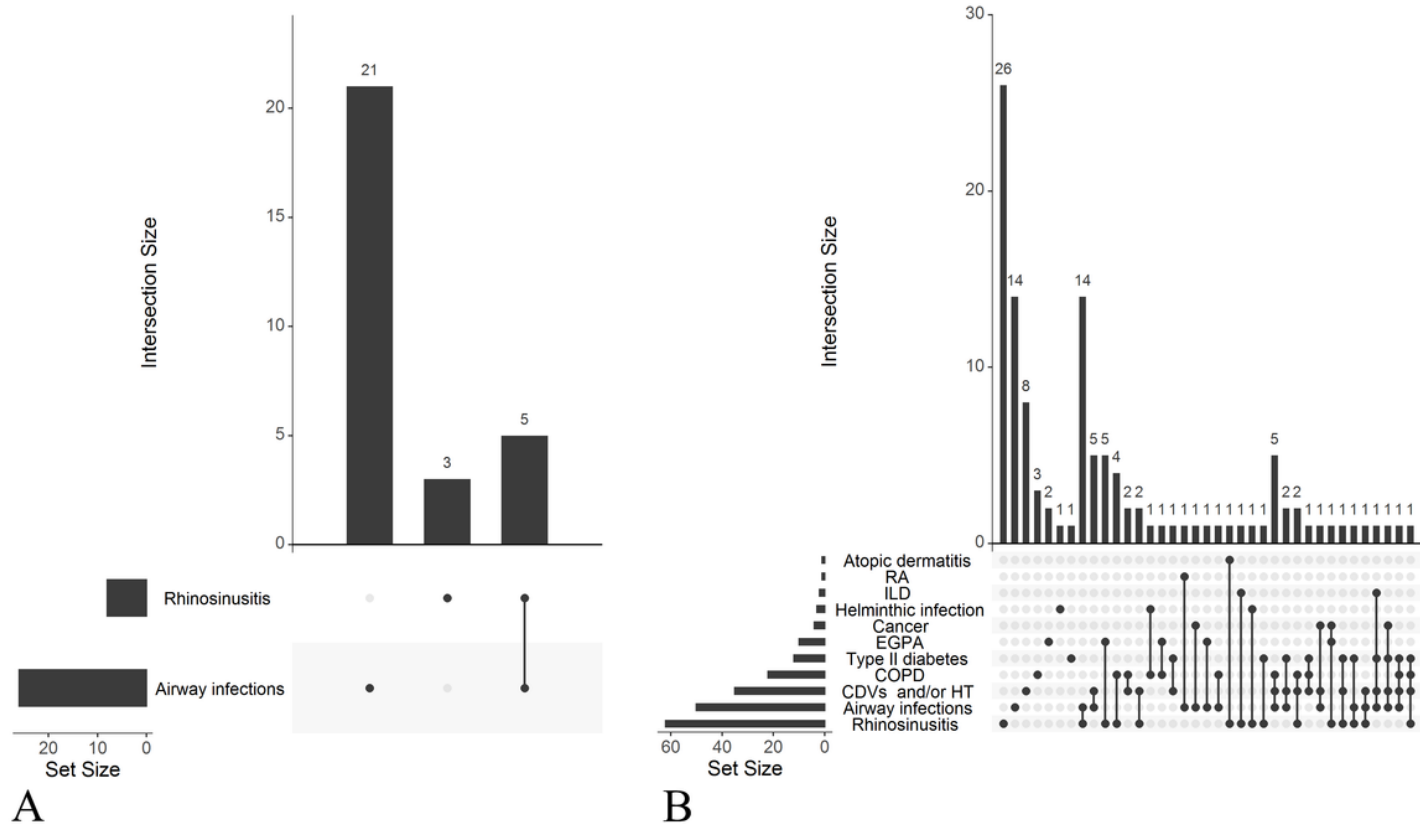
Figures

Figure 1

Complication profiles in (A) minor and (B) adult asthma patients with total IgE >1000 kUA/L. RA: rheumatoid arthritis; ILD: interstitial lung disease; EGPA: eosinophilic granulomatosis with polyangiitis; COPD: chronic obstructive pulmonary disease; CDVs: cardiovascular diseases; HT: hypertension.
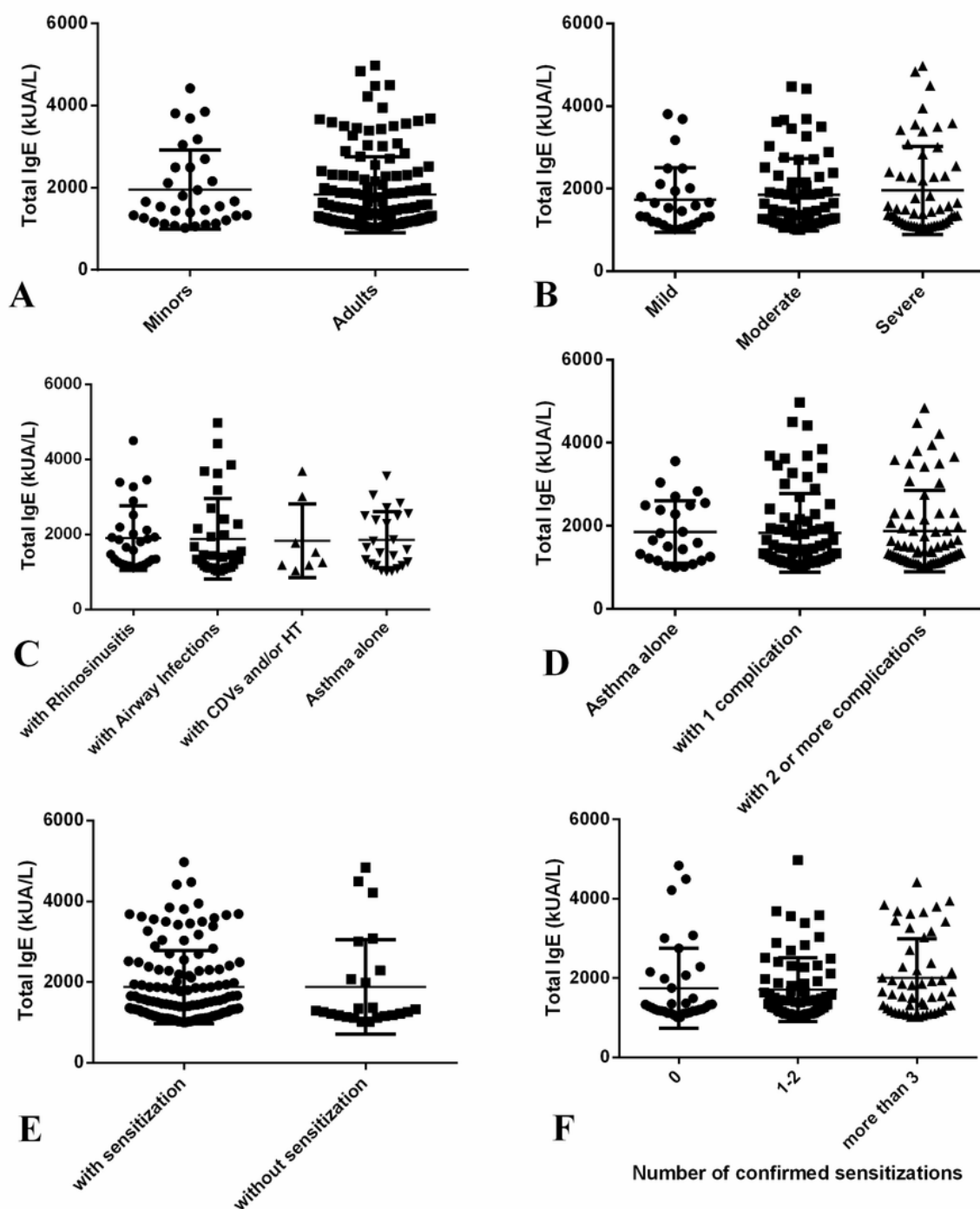
Figure 2

Comparison of serum total IgE levels in (A) minors and adults, (B) patients with different asthma severities, (C) patients with different complications, (D) patients with different number of complications, (E) patients with and without sensitization and (F) patients with different number of sensitizations.
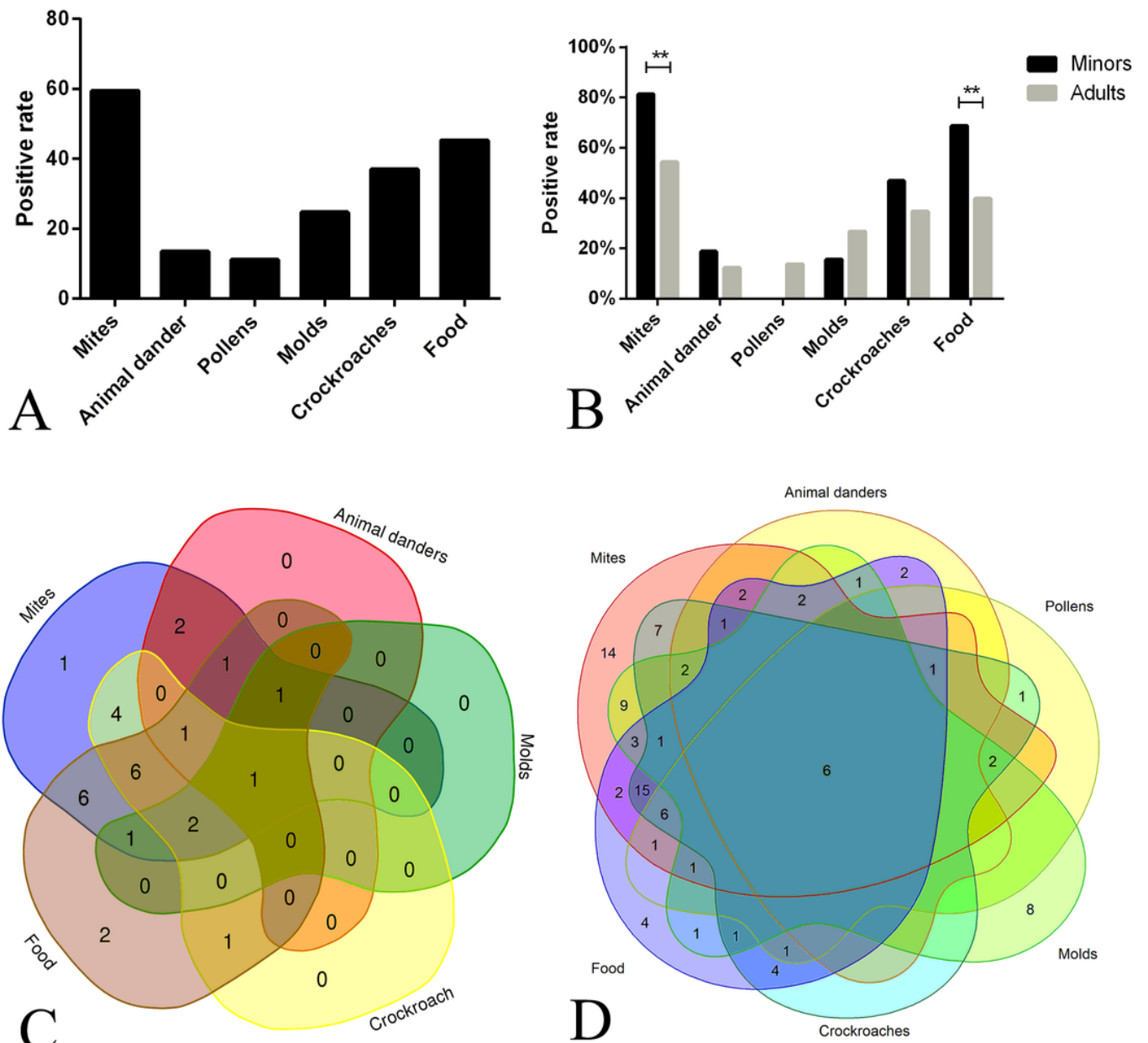
Figure 3

Sensitization profiles of asthma patients with total IgE >1000 kUA/L. (A) positive rates of 6 allergen types overall; (B) comparison of the positive rates of the 6 allergen types in minors and adults; Venn diagram showed the profiles of polysensitization in (C) minors and (D) adults. **P <0.01.
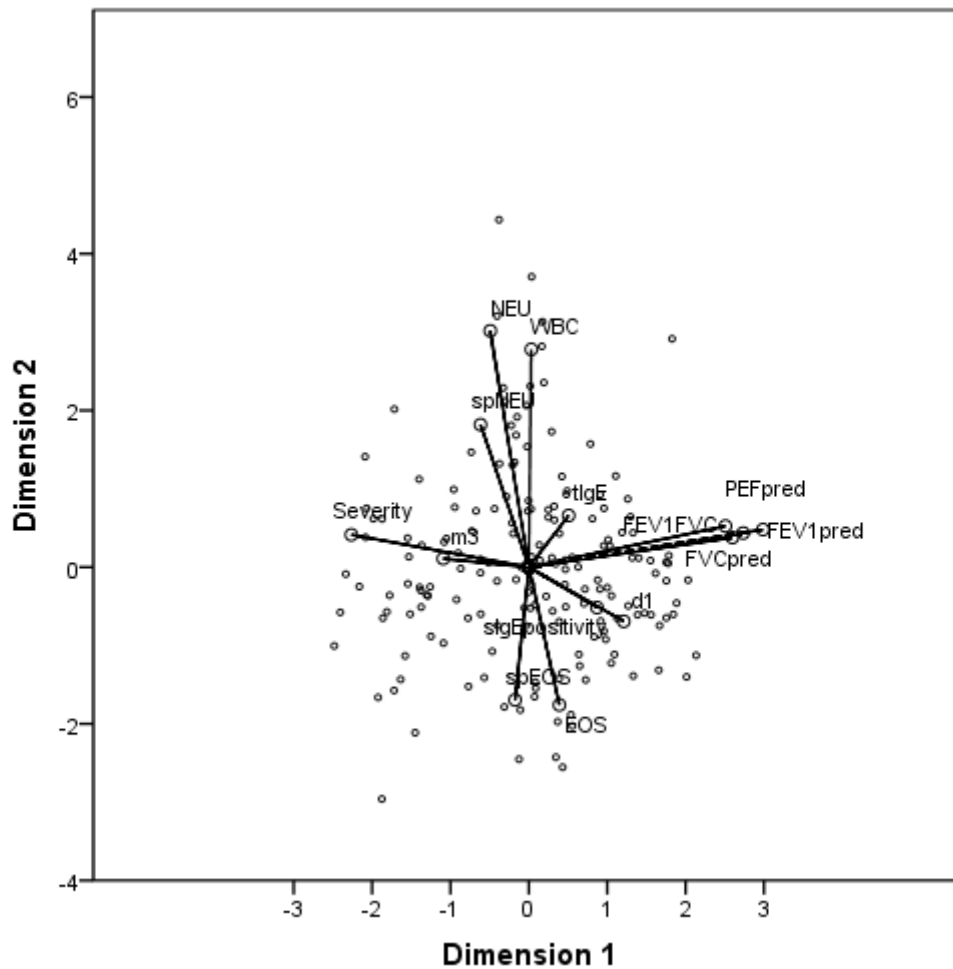
Figure 4

Optimal scale analysis of clinical data in asthma patients with total IgE >1000 kUA/L. A closer distance between the dots indicated a stronger correlation of the corresponding data (Cronbach's α = 93.7%). tIgE: total IgE; d1: house dust mite specific IgE; m3: Aspergillus fumigatus specific IgE; WBC: white blood cell; NEU: peripheral blood neutrophil counts; EOS peripheral eosinophil counts; spNEU: percentage of neutrophil in induced sputum; spEOS: percentage of eosinophil in induced sputum.

Supplementary Files

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