High Dust Mite specific Immunoglobulin E (sIgE): a Promising Indicator of Allergic Rhinitis to Asthma

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Abstract

Background: House dust mites are the most prevalent allergens in patients with asthma and/or rhinitis in China. Cross-sectional data in 2009 have shown that allergic rhinitis often preceded or occurred at the same time as asthma in patients which was used to investigate the association of serum specific immunoglobulin E (sIgE) levels to house dust mite with the onset of asthma in patients with allergic rhinitis.

Methods: 321 patients with allergic rhinitis were face-to-face interviewed and underwent sIgE tests to house dust mite. The temporal sequence of allergic rhinitis and asthma was documented. Univariate analysis, multinomial logistic regression, and Kaplan-Meier survival analysis were performed.

Results: Of the 321 participants, 213 (66.4%) had asthma, which occurred after or simultaneously with rhinitis, and 108 (33.6%) suffered from allergic rhinitis only. After controlling basic parameters, factors correlated to sIgE, and essential factors considered by clinical allergists, the risk of developing asthma always increased with the levels of sIgE to house dust mite in all four models ($p < 0.01$). In Kaplan–Meier analysis, in the first ten years with allergy rhinitis, a high sIgE level represented a high probability of the coexistence of allergic rhinitis and asthma ($p < 0.01$). For house dust mite sIgE level 5-6, 5 years Rhinitis-Asthma Conversion Rate (RACR) had reached almost 70%.

Conclusion: High-level house dust mite sIgE can exist as an indicator of rhinitis to asthma. It provides a theoretical basis for early intervention in patients with high sIgE levels in order to prevent asthma. This assessment and intervention should be performed at the early stage of rhinitis.

Background

Allergic rhinitis is a costly and highly prevalent chronic disease now.[1]More seriously, many of the patients with allergic rhinitis also suffer from asthma. The presence of rhinitis is an increased risk factor for the development of asthma. [2] However, despite the increasing awareness of the pathogenesis of asthma and the range of drugs available for treatment, asthma is still a significant cause of mortality for all ages.[3] Therefore, predicting whether asthma can occur early in the discovery of allergic symptoms is an important measure to reduce accidental death, the severe health hazards caused by asthma to patients, and the enormous economic burden on society. This prediction requires some accurate biomarkers.

House dust mites are an unsurpassed cause of atopic sensitization and allergic illness throughout the world, including rhinitis and asthma. Li et al. concluded that house dust mites were the most prevalent allergens in patients with asthma and/or rhinitis in China. [4]However, there are few biomarkers with higher clinical applicability for the development of allergic rhinitis into allergic asthma. Through our retrospective study, it was indicated that high dust mite sIgE value is an indicator of the development of allergic rhinitis to asthma.

The discovery of this asthma indicator could provide the possibility of asthma prevention. If the clinician discovers the indication and guides the patient during the stage of allergic rhinitis, the patient will avoid developing allergic rhinitis into severe asthma. Asthma is prevalent but mostly undiagnosed and undertreated in China. Given the rising trend of asthma in China, it has caused a severe socio-economic burden. [5, 6] The prevention of asthma based on rhinitis not only maintains the health of patients but also reduces the social and economic burden.

Methods

Ethics

The Institutional Review Board of Peking Union Medical College Hospital approved the study. Verbal informed consent was obtained from each patient and the parents of all participating children. All the evaluated parameters were obtained from the routine examination of the allergy department. The researchers adhered to the voluntary principle of participants and paid attention to protecting the privacy of participants.

Population

A cross-sectional study of 393 patients with allergies was conducted (Fig. 1). The participants comprised of children and adults (6–76 years old) from North China and had nasal allergies with/without asthma. A thorough medical history taken by senior allergists detailed their history of asthma, cough, allergic rhinitis, their parental history of allergies, drug allergies, food allergies, and living environment. The temporal sequence of allergic rhinitis and asthma and the use of asthma medications were reviewed. All participants underwent intradermal skin tests (IDT) to inhaled allergens (house dust mites, *Artemisia*, *Humulus*, *Juniper*, *Sycamore*, *Ash*, *Alternaria*, *Cladosporium*, cat hair, dog hair), and sIgE tests to house dust mite.

Case selection

The selection excluded 10 patients without rhinitis and asthma, and 62 patients with asthma only. 321 patients with rhinitis but with/without asthma were retained. In the 321 patients with allergic rhinitis, 108 had only allergic rhinitis when they were interviewed in 2009, and 213 had both allergic rhinitis and asthma. The individuals involved in the analysis meet the following criteria: All suffer from allergic rhinitis; Recurrent nasal itching, sneezing, rhinorrhea, and hyperemia; Clearly living environment; Clearly with or without allergic asthma; All sIgE serum tests of house dust mites were conducted; All kinds of inhaled allergens are tested for the skin.

Definitions

Allergic rhinitis (AR) is a hypersensitivity reaction caused when inhaled particles contact the nasal mucosa and induce an immunoglobulin E (IgE)-mediated inflammatory response, which is often accompanied by ocular pruritus, redness and/or lacrimation.[7]

The diagnosis of allergic rhinitis was made on clinical grounds based upon the presence of characteristic symptoms (i.e., paroxysms of sneezing, rhinorrhea, nasal obstruction, nasal itching, postnasal drip, cough, irritability, and fatigue), a suggestive clinical history (including the presence of risk factors), and supportive findings on physical examination. Besides, a positive skin test for inhaled allergens confirmed that the patient's symptoms were related to the allergies.

Asthma was defined by allergist in the 2009 cross-sectional survey when the participants had a history of recurrent dyspnoea, wheezing or cough episodes, positive airway reversibility testing (FEV1 increasing > = 12% and 200 mL after inhalation of 400 mg of salbutamol or treatment with inhaled glucocorticoid or anti-leukotriene drugs for 4–8 weeks).[8]

Measurement of serum specific IgE

sIgE was measured using ImmunoCAP (Phadia1000, Thermofisher Scientific). sIgE with a value of 0.35 kU/L or more (0.35-100kU/L) were considered sIgE-positive. sIgE were divided into six degrees: Class 1: values ≥ 0.35–0.7 kU/L, Class 2: values ≥ 0.7–3.5 kU/L, Class 3: values ≥ 3.5–17.5 kU/L, Class 4: values ≥ 17.5–50 kU/L, Class 5 : values ≥ 50–100 kU/L, and Class 6: values ≥ 100 kU/L.

Intradermal skin test (IDT)

IDT was performed with commercial allergen extracts (Xinhualian ®, Beijing) according to a standard protocol. Experienced nurses performed IDT. The allergists read the IDT results. Intradermal tests were performed using a series of common aeroallergens, including house dust mites, Artemisia, Humulus, Juniper, Sycamore, Ash, Alternaria, Cladosporium, cat hair, dog hair. For positive and negative controls, we used histamine chlorhydrate at 0.1 mg/mL and 0.9% saline solution. Skin reactions were interpreted at 15 minutes after skin testing and found to be positive when the diameter of the wheal was > 5 mm with local erythema. The following grading system was used according to the criteria that our department established[9]:

1. Wheal < 5 mm and no or small erythema = negative
2. Wheal 5–10 mm and small erythema = 1+
3. Wheal 10–15 mm and erythema > 10 mm = 2+
4. Wheal > 15 mm and erythema > 10 mm or with pseudopod formation = 3+
5. Local response as grade 3+, accompanying with systemic allergic reaction = 4+

Statistical analysis

Univariate analysis was performed to estimate Crude Odd Ratios (OR value), and a significance value of 0.05 was used to generate a 95% confidence interval (95% CI). Logistic regression analysis was used to analyze the effect of house dust mite sIgE levels on patients with asthma based on allergic rhinitis. Four models were established for regression analysis, and adjusted OR values were obtained. In model 1, only house dust mite sIgE was involved. In model 2, based on sIgE, age at visiting clinics and gender were added. In model 3, food allergy and living environment were added, whose p values with sIgE were

smaller than 0.05 in the Pearson correlation test. Drug allergy, allergic rhinitis duration, family allergy history, and having pets in the family were added into model 4 based on model 3. The new parameters were factors often considered by clinical allergists.

Kaplan-Meier survival function model was used to estimate the survival rate of asthma based on allergic rhinitis. The time range for the group with both rhinitis and asthma is from the first allergic rhinitis attack to the first asthma attack. For the group with rhinitis only, the time range is from the first allergic rhinitis attack to the time when patients came to our hospital. The survival function analysis was used to obtain the zero to five years Rhinitis-Asthma Conversion Rate (RACR) of rhinitis patients at different house dust mite sIgE levels.

Logistic regression analysis was used to analyze the confonding and interaction of house dust mite sIgE and other allergens. The diagnosis of patients allergic to other allergens mainly comes from intradermal tests. The analysis was performed with SPSS version 25 for MAC (SPSS Inc., Chicago, IL, USA).

Results

Based on the asthma status of 321 participants, 213 (66.4%) had both allergic rhinitis and asthma, 108(33.6%) had allergic rhinitis alone. Of the asthmatics, asthma preceded allergic rhinitis in 16 participants. Allergic rhinitis occurred at the same time as asthma in 100 participants and occurred before asthma in 97 participants.

A comparison of baseline characteristics between asthmatics and non-asthmatics was shown in Table 1. In the univariate analysis, factors with significant differences between the two groups include allergic rhinitis duration, living environment, and house dust mite sIgE. When patients suffered from allergic rhinitis for more than ten years, there was a significant difference in frequency between the two groups ($p < 0.01$). It was indicated that asthma based on allergic rhinitis might have a strong relationship with the duration of allergic rhinitis. The frequency of bungalow as their living environment in the asthmatic group was 30.0%, compared with 14.2% in the non-asthmatic group ($p < 0.01$). The frequency of levels 5 to 6 of sIgE to house dust mite in the asthmatic group was 21.6%, compared with only 9.3% in the non-asthmatic group ($p < 0.01$).

Table 1
Baseline characteristics of participants with and without asthma. Abbreviations: AR, allergic rhinitis; OR, odds ratio; SD, standard deviation;CI, confidence interval.

	AR with asthma(n = 213)	AR alone(n = 108)	crude OR estimates (95% CI)	P value
Female, n (%)	126(59.2%)	60(55.6%)	1.159(0.726−1.849)	0.537
Age at visiting clinics, year, mean (SD)	35.35(14.982)	32.28(15.665)	1.013(0.998−1.029)	0.089
AR duration (years), n (%)				
1−5	68(31.9%)	53(49.1%)		
6−10	65(30.5%)	35(32.4%)	1.447(0.839−2.498)	0.183
11−15	49(23.0%)	13(12.0%)	2.938(1.446−5.970)	0.002
>=16	31(14.6%)	7(6.5%)	3.452(1.410−8.450)	0.005
Living environment				
Storied building	147(70.0%)	91(85.8%)		
Bungalow	63(30.0%)	15(14.2%)	2.600(1.398−4.837)	0.002
Drug allergy, n (%)	44(20.7%)	14(13.0%)	1.748(0.911−3.356)	0.090
Food allergy, n (%)	29(9.0%)	15(4.7%)	0.977(0.499−1.912)	0.946
Family allergy history, n (%)	54(25.4%)	32(29.6%)	0.807(0.482−1.351)	0.414
Having pets in family, n (%)	31(14.6%)	8(7.4%)	2.129(0.943−4.808)	0.064
sIgE to house dust mite, n (%)				
0	48(22.5%)	33(30.6%)		
1−2	48(22.5%)	32(29.6%)	1.031(0.549−1.936)	0.924
3−4	71(33.3%)	33(30.6%)	1.479(0.807−2.711)	0.204
5−6	46(21.6%)	10(9.3%)	3.163(1.400-7.144)	0.005

Logistic regression showed four models after controlling different parameters, including basic parameters such as gender and age, factors correlated to sIgE, and essential factors considered by clinical allergists (Table 2). In all the four models, sIgE to house dust mite was significantly and associated with the onset of asthma in patients with allergic rhinitis (p < 0.01). Besides, living environment, drug allergy, allergic rhinitis duration were also risk factors for asthma attacks (p < 0.05).

Table 2
Logistic regression of the effect of sIgE levels on the onset of asthma. Abbreviations: AR, allergic rhinitis; OR, odds ratio.

	P value	Adjusted OR
Model 1		
sIgE to house dust mite	0.004	1.390(1.108−1.744)
Model 2		
sIgE to house dust mite	0.001	1.466(1.160−1.852)
Female	1.000	1.000(0.611−1.637)
Age at visiting clinics	0.027	1.019(1.002−1.036)
Model 3		
sIgE to house dust mite	0.004	1.425(1.119−1.815)
Female	0.94	0.981(0.591−1.628)
Age at visiting clinics	0.034	1.018(1.001−1.036)
Food allergy	0.995	0.998(0.496−2.005)
Living environment	0.007	2.402(1.276−4.520)
Model 4		
sIgE to house dust mite	0.006	1.427(1.109−1.838)
Female	0.774	0.926(0.548−1.564)
Age at visiting clinics	0.625	1.005(0.986−1.024)
Food allergy	0.648	0.842(0.403−1.760)
Living environment	0.004	2.598(1.355−4.982)
Having pets in family, n (%)	0.056	2.329(0.977−5.551)
Drug allergy, n (%)	0.019	2.401(1.156−4.987)
Family allergy history, n (%)	0.273	0.725(0.408−1.289)
AR duration, n (%)	0.001	1.593(1.197−2.120)

The Kaplan-Meier model was then applied to analyze the relationship between the progression of allergic rhinitis to asthma and sIgE levels (Fig. 2). Considering the sample size and avoiding excessive stratification, sIgE levels were represented as three degrees. In the first ten years, a low level of sIgE represented a low probability of the coexistence of allergic rhinitis and asthma ($p < 0.01$). A high sIgE level represented a high probability of the coexistence of allergic rhinitis and asthma ($p < 0.01$). Because of the

influence of allergic rhinitis duration and sample size of long duration with AR, survival curve crosses appeared after ten years.

The Rhinitis-Asthma Conversion Rate (RACR) of 0 to 5 years at various levels of sIgE levels were shown in Table 3. For each year with allergic rhinitis, RACR increased as the increase of house dust mite sIgE level. Furthermore, for each sIgE level, RACR also increased as the allergic rhinitis duration increase. For house dust mite sIgE level 5–6, 5 years RACR had reached almost 70%. It was worth noting that for the high-level house dust mite sIgE patients when the symptoms of allergic rhinitis first appeared, their RACR had exceeded 50%. It might be necessary for clinical allergists to intervene with the patients as soon as possible if high house dust mite sIgE was detected.

Table 3
The Rhinitis-Asthma Conversion Rate (RACR) of 0 to 5 years at various levels of sIgE levels

	0 year RACR	1 year RACR	2 years RACR	3 years RACR	4 years RACR	5 years RACR
Level 0	22.4%	26.3%	29.0%	36.0%	40.3%	47.0%
Level 1–2	26.7%	30.7%	36.0%	43.3%	43.3%	48.8%
Level 3–4	40.2%	44.3%	46.4%	51.0%	54.7%	54.7%
Level 5–6	51.1%	55.3%	61.7%	63.8%	63.8%	69.9%

Table 4
Analysis of the confounding and interaction of house dust mite sIgE and other allergens.

		crude OR estimates (95% CI)	P value
Artemisia	Allergic (n = 124)	1.409(0.907−2.187)	0.127
	Non allergic(n = 170)	1.476(1.052−2.071)	0.024
Humulus	Allergic (n = 67)	1.328(0.744−2.368)	0.337
	Non allergic (n = 215)	1.423(1.081−1.873)	0.012
Sabina vulgaris	Allergic (n = 34)	1.827(0.701−4.760)	0.218
	Non allergic (n = 241)	1.378(1.068−1779)	0.014
Parasol	Allergic (n = 24)	1.667(0.527−5.305)	0.387
	Non allergic (n = 240)	1.495(1.151−1.942)	0.003
Pewter	Allergic (n-=23)	1.702(0.499−5.805)	0.396
	Non allergic (n = 240)	1.368(1.061−1.764)	0.016
Streptomyces alternatus	Allergic (n-21)	1.033(0.403−2.649)	0.945
	Non allergic (n = 251)	1.411(1.091−1.824)	0.009
Cladosporium	Allergic (n = 16)	1.062(0.273−4.130)	0.931
	Non allergic (n = 253)	1.416(1.100-1.824)	0.007
Car hair	Allergic (n = 10)		0.998
	Non allergic (n = 249)	1.471(1.135−1.908)	0.004
Dog hair	Allergic (n = 14)		0.998
	Non allergic (n = 83)	1.452(0.936−2.252)	0.096

Logistic regression analysis excluded the possibility of other allergens as confounding factors or interaction factors. The patients allergic to other allergens were divided into two groups, allergic group, and non-allergic group. In the p < 0.05 groups, crude ORs were similar to OR = 1.390 in sIgE ANOVA analysis. However, in many groups, this comparison could not be finished because of the small sample size.

Discussion

Allergy to house dust mite is a high-risk factor for rhinitis and asthma. Shaaban et al. put forward that allergic rhinitis with sensitization to dust mite increased the risk of asthma independently of other allergens. [10] By our retrospective study, we further proposed that high house dust mite sIgE value was

an indicator of the development of allergic rhinitis to asthma. Moreover, the cumulative incidence of rhinitis patients converted to asthma within five years under different dust mite sIgE levels was also presented.

In terms of sample selection, we ensured the universality of the study. In the case selection, the non-rhinitis and non-asthma patients and the only asthma patients were excluded. Allergen types were not taken into consideration into the exclusion criteria, which made sure the universality of our study. Besides, the confounding and interaction analysis proved that house dust mite sIgE was an independent high-risk factor.

The participants in this study were from the specialty practice in Peking Union Medical College Hospital. The Allergy Department of Peking Union Medical College Hospital is a national diagnostic center for allergic diseases. Therefore, the participants were patients who were different from those in community hospitals. These patients had received treatment and might not satisfied with the treatments. It could be understood why asthma patients were more than only rhinitis patients.

A possible explanation of high sIgE as an indicator is the systemic propagation of inflammation from the nasal to the bronchial mucosa. [11, 12] In the study by Inal et al., They showed that even before the onset of clinical symptoms, nasal allergen challenge could increase markers of eosinophil inflammation in the upper and lower respiratory tract of children who are sensitive to mites. [13] As the duration of rhinitis increases, the cumulative damage to the upper and lower respiratory tract might be a high-risk factor in inducing asthma. Besides, it was broadly proved that IgE is associated with allergic inflammation. [14–17] Moreover, there were already some drugs targeting IgE for asthma in the research and development stage. [16, 18] However, furthermore studies are still needed to clarify the possible mechanism.

High house dust mite sIgE value may become a biomarker for allergists to assess the possibility of rhinitis to asthma. This assessment and intervention should be performed at the early stage of rhinitis. Because zero to five years Rhinitis-Asthma Conversion Rate (RACR) increased with the progress of rhinitis, especially in high-level sIgE (Table 3). It is worth mentioning that house dust mites are allergens commonly screened by allergy patients in northern China. [19] Detecting house dust mite sIgE level does not bring the extra cost to the patient, nor does it bring redundancy to the doctor's diagnostic steps. Serum IgE test not only provides a reference for clinical allergists to diagnose allergen type and severity of the allergy but also alludes to high-risk allergic diseases. [20]Quantification of the high risk, including sIgE and concluding an evaluation form, might provide the possibility of preventing asthma in the future. The quantification can bring better operability for asthma prevention for clinicians. A large number of population-based studies are needed to carry out in the future.

Conclusions

In conclusion, our study proved that high-level house dust mite sIgE could exist as an indicator of rhinitis to asthma. It provides a theoretical basis for early intervention in patients with high sIgE levels in order to prevent asthma. Furthermore, the asthma prediction is independent of other allergens. The retrospective

study also strengthened the relationship between allergic rhinitis and asthma, which might be explained by subsequent allergen exposure and systemic propagation.

Declarations

Ethics approval and consent to participate

The Institutional Review Board of Peking Union Medical College Hospital approved the study. Verbal informed consent was obtained from each patient and the parents of all participating children. All the evaluated parameters were obtained from the routine examination of the allergy department. The researchers adhered to the voluntary principle of participants and paid attention to protecting the privacy of participants.

Consent for publication

All authors read and approved the manuscript.

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Competing interests

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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Authors' contributions

Rui Tang conceived and designed the study. Xiaohong Lyu analyzed the data and wrote the paper. Yuelun Zhang and Shi Chen revised and improved statistical methods. Hong Li was responsible for the study concept. All the authors reviewed and edited the manuscript. All authors read and approved the manuscript.

Acknowledgements

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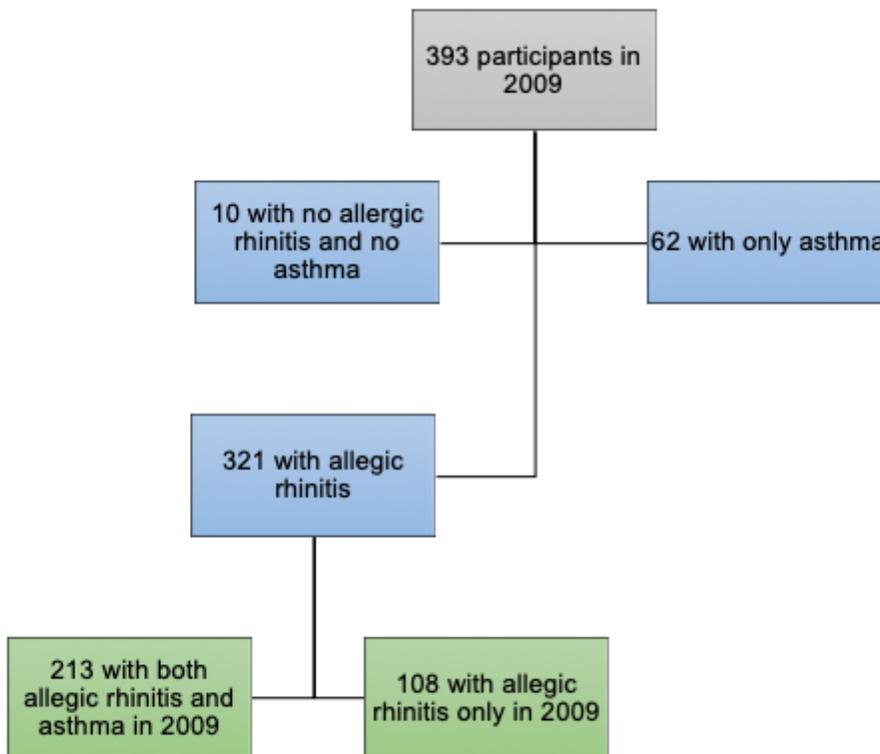
Figures

Figure 1

A schematic illustrates the enrollment and follow-up of participants in the study
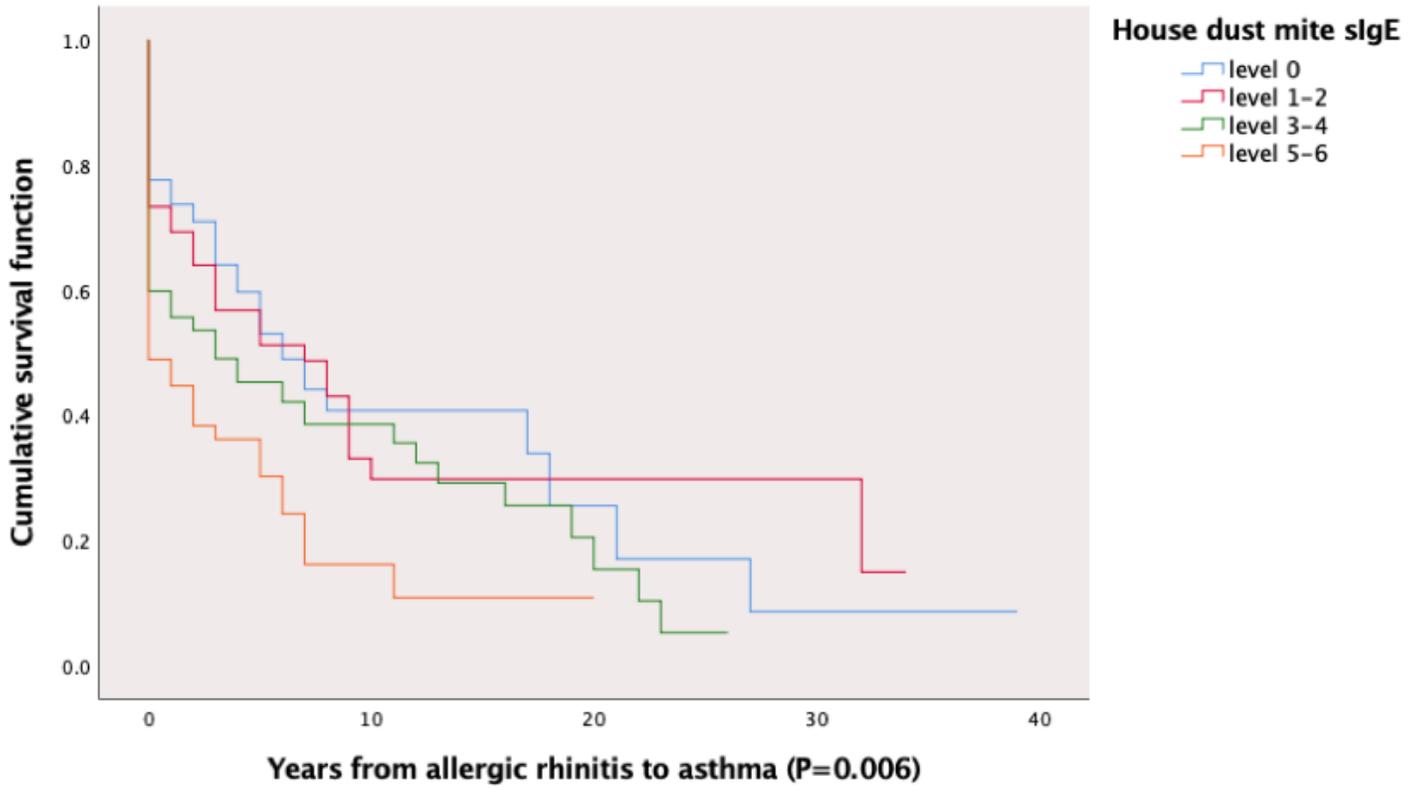
Figure 2

House dust mite sIgE levels and cumulative survival rate of rhinitis to asthma.