

Optimal cutoff values of allergen-specific immunoglobulin E to house dust mites and animal dander based on skin-prick test results: Analysis in 16,209 patients with allergic rhinitis

Sang Duk Hong, M.D.,¹ Gwanghui Ryu, M.D.,¹ Min Young Seo, M.D.,¹ Jong In Jeong, M.D.,² Hyo Yeol Kim, M.D., Ph.D.,¹ Seung-Kyu Chung, M.D., Ph.D.,¹ and Hun-Jong Dhong, M.D., Ph.D.¹

ABSTRACT

Background: The most common tests for allergen sensitization in patients with allergic rhinitis are the skin-prick test (SPT) and an *in vitro* test to detect serum specific immunoglobulin E (sIgE). However, *in vitro* allergen test results were interpreted dichotomically as positive or negative at a threshold of 0.35 kU/L of sIgE, regardless of the patient characteristics or antigen types.

Objective: The purpose of this study was to determine the cutoff value for sIgE in house-dust mites and animal dander, and to analyze differences in cutoff value according to age and gender.

Methods: A total of 16,209 patients with more than one allergic rhinitis symptom who underwent both SPT and serum sIgE testing were retrospectively evaluated between March 2008 and May 2012. There were 9374 male (57.8%) and 6835 female (42.2%) patients. The mean age was 31.8 years (range, 2–89 years). The criterion standard for allergen sensitization was defined as a wheal of >3 mm or an allergen-to-histamine ratio of ≥ 1 in SPT results. The Youden index was used to calculate the cutoff value of sIgE.

Results: Cutoff values of sIgE for *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, cat, and dog were 0.69, 1.16, 0.13, and 0.45 kU/L, respectively. The cutoff value of sIgE changed according to age for *D. pteronyssinus* and *D. farinae* but not for cat and dog allergens. When categorizing according to age group, the cutoff values of sIgE for *D. pteronyssinus* and *D. farinae* had a tendency to decrease with age. There was no significant difference in cutoff value according to gender.

Conclusion: The cutoff value for sIgE differed for each antigen and changed with age. Physicians should select the proper cutoff value for sIgE for appropriate criteria according to antigen and patient age rather than using a uniform cutoff value.

(Am J Rhinol Allergy 32, 23–26, 2018; doi: 10.2500/ajra.2018.32.4483)

Allergic rhinitis is defined as symptoms of sneezing, nasal itching, nasal obstruction, and watery rhinorrhea caused by immunoglobulin E (IgE) mediated inflammation against inhaled allergens. The diagnosis of allergic rhinitis is clinically based on concordance between a history of symptoms that correspond with exposure to the sensitizing allergen and diagnostic tests that indicate serum specific IgE (sIgE) values in serum or positive skin-prick test (SPT) results.¹ Allergen provocation tests are the most reliable tests but are limited in clinical practice due to a risk of adverse reactions.² House-dust mites (HDM) are the most common inhalant allergens in Korea.³ However, the clinical correlation between exposure to a specific allergen and the development of nasal symptoms is rarely conclusive. For this reason, a test for the allergen sIgE value is usually used to determine the diagnosis of allergic rhinitis in daily practice. Although both SPT and serum sIgE tests have similar diagnostic properties, SPT is generally considered more accurate.⁴ A previous study reported that SPT is more correlated with the nasal allergen provocation test than with blood testing for a diagnosis of inhalant allergy.⁵

Historically, *in vitro* allergen test results have been dichotomously interpreted as positive or negative at a threshold of 0.35 kU/L of sIgE.

This level is primarily based on the technical limitations of first-generation sIgE assays.⁶ Although levels of sIgE for allergens are divided into semiquantitative classes from class 0 (<0.35 IU/mL) to class VI (>100 IU/mL), a threshold of 0.35 kU/L of sIgE is commonly used without regard to allergen type or patient age group. Although there have been many comparative studies between SPT and the ImmunoCAP system (Thermo Fisher Scientific, Inc., Waltham, MA), to our knowledge, there have been no studies about the optimal cutoff value of sIgE based on the SPT as the clinical criterion standard. In this study, we hypothesized the following: (1) compared with the criterion standard of SPT, the cutoff value of sIgE differs among different inhalant allergens, and (2) this cutoff value changes according to age group. The aim of this study was to determine the cutoff value of sIgE in HDM and animal dander compared with SPT as the criterion standard.

METHODS

Study Subjects

Patients who visited our otorhinolaryngology-head and neck surgery department and presented with one or more rhinitis symptoms (nasal obstruction, nasal itching sense, sneezing, watery rhinorrhea) had both the SPT and the ImmunoCAP test. We excluded patients who did not have both tests or who underwent SPT and ImmunoCAP test on different days. A total of 16,209 patients were enrolled in this study between March 2008 and May 2014. This study protocol was approved by the institutional review board of Samsung Medical Center (SMC 2015-07-023), and the informed consent was waived. S.D. Hong and G. Ryu contributed equally to this work.

SPT and ImmunoCAP Test

Before performing the SPT, we screened patients for anaphylaxis and discontinued medications that interfere with test results, such as

From the ¹Department of Otorhinolaryngology—Head and Neck Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea, and ²Department of Otorhinolaryngology, Keimyung University College of Medicine, Daegu, South Korea

No external funding sources reported

The authors have no conflicts of interest to declare pertaining to this article

Address correspondence to Hun-Jong Dhong, M.D., Department of Otorhinolaryngology—Head and Neck Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul, South Korea 06351

E-mail address: hjdhong@skku.edu

Published online October 25, 2017

Copyright © 2018, OceanSide Publications, Inc., U.S.A.

Table 1 Optimal cutoff values of allergen-specific IgE levels calculated by the Youden index

Allergen	No.	IgE Cutoff, IU/mL	Sensitivity, %	Specificity, %	PPV, %	NPV, %	Misclassified, %
<i>D. pteronyssinus</i>	10,103	0.69	92.1	94.0	90.4	95.0	6.8
<i>D. farinae</i>	10,103	1.16	91.2	91.6	87.3	94.3	8.6
Cat	6517	0.13	92.2	95.4	68.1	99.1	4.9
Dog	7495	0.45	89.2	93.2	34.9	99.5	7.0

IgE = Immunoglobulin E; PPV = positive predictive value; NPV = negative predictive value; *D. pteronyssinus* = *Dermatophagoides pteronyssinus*; *D. farinae* = *Dermatophagoides farinae*.

Table 2 Sensitivity, specificity, and the Youden index according to traditional thresholds

Allergen	IgE cutoff, IU/mL	Sensitivity, %	Specificity, %	Youden Index
<i>D. pteronyssinus</i>	0.1	98.7	72.4	0.71
	0.35	96.5	87.5	0.84
	0.7	91.2	94.9	0.86
	3.5	74.3	99.4	0.74
<i>D. farinae</i>	0.1	99.3	66.0	0.65
	0.35	97.9	80.4	0.78
	0.7	94.7	87.5	0.82
	3.5	81.6	97.0	0.79
Cat	0.1	92.8	94.0	0.87
	0.35	81.7	98.0	0.80
	0.7	69.4	98.9	0.68
	3.5	30.1	99.7	0.30
Dog	0.1	95.6	79.9	0.76
	0.35	90.5	91.6	0.82
	0.7	81.7	95.2	0.77
	3.5	46.4	98.8	0.45

IgE = Immunoglobulin E; *D. pteronyssinus* = *Dermatophagoides pteronyssinus*; *D. farinae* = *Dermatophagoides farinae*.

Bold data is the maximum value of Youden's index. Youden's index is a single statistic (sensitivity + specificity - 1).

antihistamines, antidepressants (amitriptyline, doxepin), antacid, and steroid ointment. SPTs were performed by following manufacturer's guidelines for *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, cat, and dog allergens. Allergen extracts (Allergy Therapeutics, Ltd., Bencard, England), along with the appropriate negative (0.9% saline solution) and positive (1 mg/mL histamine) controls, were applied on the upper back by using the prick technique. SPTs were evaluated 15 minutes after application and interpreted as the presence of sensitization when the wheal diameter was identical or larger than the size of histamine control wheal. A positive SPT result was defined as a wheal of >3 mm or an allergen-to-histamine ratio of ≥ 1 . At the same time that the SPTs were performed, a blood sample was collected to quantify the sIgE levels by using the ImmunoCAP system.

Statistical Analysis

All statistical analyses were performed by using SAS 9.4 (SAS Institute, Cary, NC). Receiver operating characteristic curves were created to evaluate the predictive ability of *D. pteronyssinus*, *D. farinae*, cat, and dog sIgE levels in relationship to the criterion standard of the SPT results. The curve was constructed by using each unique value of the predictor variable as a possible cutoff point by calculating the corresponding sensitivity and specificity based on that cutoff point and then by plotting sensitivity versus 1 - specificity. By using receiver operating characteristic curve analysis, the optimal cutoff point was selected as the value that maximized the sum of sensitivity plus specificity, which is equivalent to using the Youden index.⁷ Sensitivity and specificity were demonstrated for the selected cutoff point compared with traditional threshold values of 0.1, 0.35, 0.7, and 3.5. The Cochran-Armitage trend test was used to test positive rate trends among the age groups, and the Fisher exact test was used to test for gender difference. Absolute values of sIgE according to age

group were analyzed by using analysis of variance with the *post hoc* Tukey test.

RESULTS

A total of 16,209 patients with allergic rhinitis symptoms were enrolled. The mean age was 31.8 years (range, 2–89 years), and male patients were predominant (male patients, 9374; female patients, 6835). The number of patients in each age group was as follows: ≤ 19 years, 5428; 20–29 years, 2865; 30–39 years, 2339; 40–49 years, 1931; 50–59 years, 2174; and ≥ 60 years, 1472. In summary, 10,103 patients were evaluated by using both the SPT and the ImmunoCAP test for *D. pteronyssinus* and *D. farinae*, 6517 patients were evaluated for cat sensitization, and 7495 patients were evaluated for dog sensitization. The results of the optimal cutoff value of sIgE selected by using the Youden index with the SPT as a criterion standard test are summarized in Table 1. The cutoff values of sIgE for *D. pteronyssinus*, *D. farinae*, cat, and dog allergens were 0.69, 1.16, 0.13, and 0.45 kU/L, respectively. There was no significant difference in cutoff value according to gender ($p > 0.05$, Fisher exact test).

The sensitivity and specificity for each selected cutoff point to the traditional threshold values were 0.1, 0.35, 0.7, and 3.5 (Table 2). At a cutoff point of 0.7 kU/L (class 2), the Youden index was maximal among the traditional threshold values for *D. pteronyssinus* and *D. farinae*. Conversely, the Youden index was maximum at 0.1 for cat and at 0.35 for dog allergens. Absolute values of the ImmunoCAP test showed a decreasing tendency for *D. pteronyssinus* and *D. farinae* with increased age (Fig. 1 A). Absolute sIgE values were significantly different among the age groups except years 40s, 50s, and over 60 ($p < 0.001$ by using the analysis of variance test with the *post hoc* Tukey test). However, sIgE values for cat and dog allergens were not significantly changed with age, and the values were highest in the age of

Figure 1. Absolute values of serum-specific immunoglobulin E (IgE). (A) Absolute values of *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* had a tendency to decrease as age increased. (B) The patients with positive skin-prick test results had higher serum-specific IgE levels than the general population, and positive rates decreased with age.

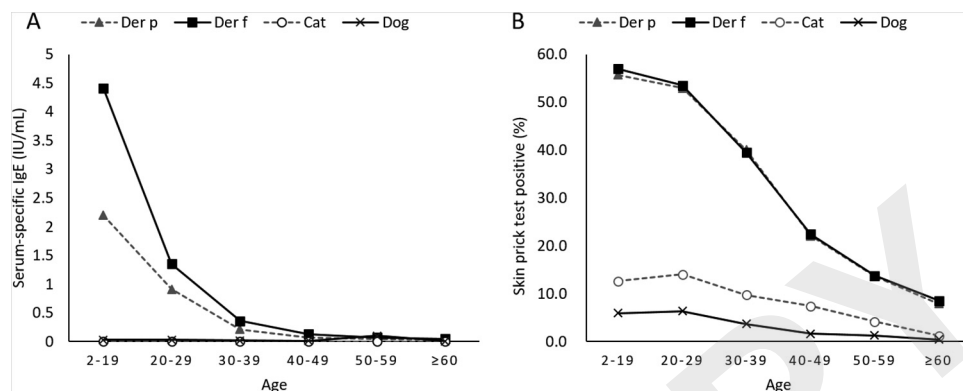


Table 3 Optimal cutoff values of serum-specific IgE according to age group

Allergen	Age, y	IgE cutoff, IU/mL	Sensitivity, %	Specificity, %	Youden Index
<i>D. pteronyssinus</i>	2–19	1.02	93.3	96.1	0.89
	20–29	0.72	92.5	94.2	0.87
	30–39	0.67	88.8	93.3	0.82
	40–49	0.44	92.9	90.0	0.83
	50–59	0.31	96.4	87.7	0.84
	≥60	0.24	97.0	86.5	0.84
<i>D. farinae</i>	2–19	1.38	94.0	95.3	0.89
	20–29	0.93	92.7	94.1	0.87
	30–39	1.36	86.4	92.8	0.79
	40–49	0.78	91.1	86.0	0.77
	50–59	0.63	96.0	84.3	0.80
	≥60	0.84	90.3	86.9	0.77
Cat	2–19	0.20	95.1	96.3	0.91
	20–29	0.15	88.8	93.9	0.83
	30–39	0.16	90.0	96.8	0.86
	40–49	0.10	88.1	95.8	0.84
	50–59	0.17	100.0	98.6	0.99
	≥60	0.13	100.0	97.8	0.98
Dog	2–19	0.45	91.9	91.0	0.83
	20–29	0.38	87.4	88.8	0.73
	30–39	0.62	93.2	95.3	0.89
	40–49	0.25	93.8	92.0	0.86
	50–59	0.14	92.9	90.0	0.82
	≥60	1.72	100.0	99.7	1.00

IgE = Immunoglobulin E; *D. pteronyssinus* = *Dermatophagoides pteronyssinus*; *D. farinae* = *Dermatophagoides farinae*.

20 to 29. The positive rate of SPT results also revealed similar characteristics to sIgE values. Positive rates decreased with age for *D. pteronyssinus* and *D. farinae*. However, those of cat and dog decreased after a peak in the age of 20 to 29 (Fig. 1 B). When categorizing the age groups, cutoff values for *D. pteronyssinus* and *D. farinae* decreased with age ($p < 0.05$, Cochran-Armitage trend test). However, optimal cutoff values did not consistently decrease with age in cat and dog (Table 3).

DISCUSSION

The present study found that the optimal cutoff values of sIgE for ImmunoCAP testing differed with the type of allergen and age group. The cutoff value for dog was approximately class I (0.45 IU/mL), whereas that for cat was lower than class I (0.13 IU/mL), and the cutoff value for HDMs was approximately class II (for *D. pteronyssinus*, 0.69; for *D. farinae*, 1.16 IU/mL). The sensitivity and specificity of immunoassays were previously reported as 60–95% and 30–95%, respectively.⁴ A possible reason for this wide range is the difference in cutoff values according to allergen or age group. Gleeson *et al.*⁸

demonstrated that ImmunoCAP sensitivity by using a cutoff value of 0.35 kU/L was 87% for HDM and 67% for cat. Specificity varied less among the different inhalant allergens (90–99%). In the present study, the maximum Youden index was verified only in dog, with the traditional threshold of sIgE at 0.35 IU/mL. The threshold with the maximum Youden index was >0.35 IU/mL in cat and higher in HDM. A recent study that compared ImmunoCAP and SPT results for 53 inhalant allergens showed diverse sensitivity and specificity according to allergen. Sensitivity and specificity for *D. pteronyssinus* was 69.4 and 90.7, for *D. farinae* was 75.7 and 91.6, for cat was 65.4 and 89.0, and for dog was 70.3 and 85.8, respectively. In that study, the single sIgE cutoff value was 0.35 IU/mL.⁹ Although 65 to 91% accuracy demonstrates good concordance, sensitivity and specificity increased up to 90% for most allergens by using the new optimal cutoff values in the present study.

There could be some disagreement about our results because optimal cutoff values were deduced by using SPT as the criterion standard. The nasal provocation test would be a more suitable method for determining cutoff values; however, even these tests have limitations

and are not practical in clinical settings.^{10,11} In a previous study, an allergy to HDM was confirmed by using the nasal provocation test in 70% patients with a positive SPT result.¹² Definite nasal symptom development after specific allergen exposure would be a better criterion standard than SPT, but there also are some drawbacks. Clinical correlation between exposure to a specific allergen and the development of nasal symptoms is very difficult to confirm. In addition, clinical symptoms of allergic rhinitis can change according to concurrent inflammation, infection, physical stress, psychological stress, exposure to irritants, and hormonal changes.² Nevertheless, our cutoff value of sIgE for cat allergen (0.13 IU/mL) was similar to the cutoff value of sIgE (0.12 IU/mL) of a previous study that analyzed symptom development after allergen exposure history.⁶ Therefore, SPT is the second-best alternative as the criterion standard for allergen sensitization in patients with rhinitis.

We showed that the cutoff value for sIgE differed according to age for *D. pteronyssinus* and *D. farinae* but not for cat and dog allergens. Even in the SPT positive result group, the absolute values of sIgE for *D. pteronyssinus* and *D. farinae* decreased with age. The difference of cutoff value of sIgE between HDMs and animals could derive from divergence of positive rates and exposure histories. The sensitization rate of animal dander is lower than that of HDM, and no data were available regarding real-life pet exposure histories, which was a limitation of the present study. Generally, allergy sensitization rates decrease with aging. In a Korean study, the frequency of sensitization to *D. pteronyssinus*, *D. farinae*, cat, and dog allergens when using SPT peaked in the age group 20–29 years and was lowest in the age group >60 years.³ In the present study, the peak incidence of sensitization to *D. pteronyssinus* and *D. farinae* occurred in the age group 2–19 years and was at a minimum in the age group >60 years. The absolute values of *D. pteronyssinus* and *D. farinae* sIgE also peaked in the age group 2–19 years and were lowest in the age group >60 years.

Total and specific serum IgE levels have been shown to decrease with age in patients with allergic diseases.¹³ In this study, the median absolute value of *D. pteronyssinus* and *D. farinae* sIgEs decreased with age. However, the optimal cutoff value calculated by the Youden index did not uniformly decrease with age. Allergen sensitivity confirmed by SPT usually decreased with age (Fig. 1 B). This lower sensitivity was explained by the altered quality of skin and subcutaneous tissue. However, the decreasing absolute number of sIgE values might be a more potent reason for lower sensitization in elderly patients (Fig. 1 A). A decreasing sIgE level for *D. pteronyssinus* and *D. farinae* with age must be considered when interpreting SPT and ImmunoCAP tests. Many investigators indicate that SPT and serum sIgE testing cannot be used interchangeably.^{9,14–16} However, in some clinical conditions, such as extensive dermatitis, dermatographism, or anaphylaxis, ImmunoCAP test must be used as an alternative to SPT. In such a situation, the sensitivity and specificity of ImmunoCAP tests can be up to 90% if clinicians use optimal cutoff values according to allergen type. Furthermore, clinicians must consider the tendency for a decreased sIgE titer with age when interpreting the results.

Positive SPT and ImmunoCAP results do not mean that a patient has an allergy to that allergen but only represent sensitization to an allergen. Because every enrolled patient had more than one allergic rhinitis symptom, positive SPT or ImmunoCAP test results were assumed to indicate the diagnosis of allergic rhinitis. Optimal cutoff values and sIgE consistently decreased for *D. pteronyssinus*, but the optimal cutoff value for *D. farinae* had a second peak in the age of 30 to 39. Optimal cutoff values differed by age group, and the values in Table 2 could be broadly applied to screen for allergic sensitization.

We recommend that optimal cutoff values should be chosen by considering the importance of higher sensitivity or specificity.

CONCLUSION

The optimal cutoff value for sIgE differed for each antigen and changed according to age. Physicians should select a proper cutoff value by using appropriate criteria according to the antigen and patient's age rather than by using a uniform cutoff value.

ACKNOWLEDGMENTS

We thank the medical technician staff of the Allergy Laboratory and the staff of Biostatistics and Clinical Epidemiology Center, Samsung Medical Center.

REFERENCES

1. Bousquet J, Khaltaev N, Cruz AA, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy*. 2008; 63(suppl. 86):8–160.
2. Siles RI, Hsieh FH. Allergy blood testing: A practical guide for clinicians. *Cleve Clin J Med*. 2011; 78:585–592.
3. Lee JE, Ahn JC, Han DH, et al. Variability of offending allergens of allergic rhinitis according to age: Optimization of skin prick test allergens. *Allergy Asthma Immunol Res*. 2014; 6:47–54.
4. Bernstein IL, Li JT, Bernstein DI, et al. Allergy diagnostic testing: An updated practice parameter. *Ann Allergy Asthma Immunol*. 2008; 100(suppl. 3):S1–148.
5. Bousquet J, Lebel B, Dhivert H, Bataille Y, Martinot B, Mi FB. Nasal challenge with pollen grains, skin-prick tests and specific IgE in patients with grass pollen allergy. *Clin Allergy*. 1987; 17:529–536.
6. Linden CC, Misiak RT, Wegienka G, et al. Analysis of allergen specific IgE cut points to cat and dog in the Childhood Allergy Study. *Ann Allergy Asthma Immunol*. 2011; 106:153–8.e152.
7. Youden WJ. Index for rating diagnostic tests. *Cancer*. 1950; 3:32–35.
8. Gleeson M, Cripps AW, Hensley MJ, Włodarczyk JH, Henry RL, Clancy RL. A clinical evaluation in children of the Pharmacia ImmunoCAP system for inhalant allergens. *Clin Exp Allergy*. 1996; 26:697–702.
9. Calabria CW, Dietrich J, Hagan L. Comparison of serum-specific IgE (ImmunoCAP) and skin-prick test results for 53 inhalant allergens in patients with chronic rhinitis. *Allergy Asthma Proc*. 2009; 30:386–396.
10. Indrajana T, Spieksma FT, Voorhorst R. Comparative study of the intracutaneous, scratch and prick tests in allergy. *Ann Allergy*. 1971; 29:639–650.
11. Oppenheimer J, Marshall G. What does a positive intradermal skin test result really mean? *Ann Allergy Asthma Immunol*. 2009; 102: 267–268.
12. Haxel BR, Huppertz T, Boessert P, Bast F, Fruth K. Correlation of skin test results and specific immunoglobulin E blood levels with nasal provocation testing for house-dust mite allergies. *Am J Rhinol Allergy*. 2016; 30:60–64.
13. Mediaty A, Neuber K. Total and specific serum IgE decreases with age in patients with allergic rhinitis, asthma and insect allergy but not in patients with atopic dermatitis. *Immun Ageing*. 2005; 2:9.
14. Nam YH, Lee SK. Comparison between skin prick test and serum immunoglobulin E by CAP system to inhalant allergens. *Ann Allergy Asthma Immunol*. 2017; 118:608–613.
15. Jiang XD, Li GY, Dong Z, Zhu DD. Correlation analysis of two serum-specific immunoglobulin E test systems and skin-prick test in allergic rhinitis patients from northeast China. *Am J Rhinol Allergy*. 2011; 25:116–119.
16. Cho JH, Suh JD, Kim JK, Hong SC, Park IH, Lee HM. Correlation between skin-prick testing, individual specific IgE tests, and a multiallergen IgE assay for allergy detection in patients with chronic rhinitis. *Am J Rhinol Allergy*. 2014; 28:388–391. □

Copyright of American Journal of Rhinology & Allergy is the property of OceanSide Publications Inc. and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.