

Specific IgE measurement using AdvanSure® system: Comparison of detection performance with ImmunoCAP® system in Korean allergy patients

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ABSTRACT

Background: AdvanSure enzyme immunoassay (EIA) system is a recently developed multiple allergen screen test with specific immunoglobulin E (sIgE) detection assay, while ImmunoCAP fluorescent EIA (FEIA) has been widely used for sIgE detection. There has been no inter-assay comparison data for these two systems. We determined the detection performance of AdvanSure system compared to that of ImmunoCAP.

Methods: We performed an inter-method comparison using sera from 199 Korean allergy patients, including asthma (39.7%), allergic rhinitis (54.8%), atopic dermatitis (36.2%) and food allergies (21.6%). We compared the sIgE detection performance for nine major inhalant and four food allergens.

Results: 950 paired assay results were analyzed. Most allergen sIgE results showed above 0.5 intraclass correlation coefficient except *Blattella germanica*, alternaria and mugwort allergen. Inter-method comparison results showed multiple differences in a few allergens. The inter-method concordance was moderate to substantial for most allergens ($\kappa = 0.528\text{--}0.778$, $p < 0.001$), except for cat dander.

Conclusion: AdvanSure system showed a good detection performance compared with ImmunoCAP in correlation and agreement in Korean allergy patients. However, in terms of differences in the methodologies used by these two systems, careful clinical correlation is needed for interpretation of AdvanSure EIA results.

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1. Introduction

Immunoglobulin E (IgE) is a key mediator of allergic diseases such as asthma, allergic rhinitis and atopic dermatitis [1–3]. Therefore, documentation of allergen-specific immunoglobulin E (sIgE) is crucial for the diagnosis of these diseases [4]. Traditionally, *in vivo* skin test has been widely used to detect allergen sIgE; however, this is not a quantitative test and is difficult to be standardized, which makes it challenging to compare results between patients. The use of antihistamines is also an important limitation of the skin test [5].

In vitro laboratory techniques have been developed and widely used. The radioallergosorbent test (RAST) was the first commercially developed test [6], after which enzyme immunoassay (EIA), or fluorescent enzyme immunoassay (FEIA), was developed by several manufacturers. These assays are high speed, have a high binding

capacity, are free from radioisotopes and standardized to the concentration of IgE in kU/l [7,8].

Since the evolution and development of FEIA, the ImmunoCAP system has been widely accepted as a quasi-standard of sIgE measurement because of its reliability, reproducibility and good accordance with skin test results. However, the system has several clinical limitations [7]. In short, each individual ImmunoCAP test can only detect sIgE against a single allergen, making it quite expensive to use in a clinical setting.

To compensate for the limitations of the single allergen sIgE detection method, several multi-allergen sIgE assays were developed [9–11]. These methods consumed smaller amounts of sera, reduced assay time and be capable chief assay price. Almost all of the new assays are able to simultaneously detect more than 30 allergen sIgEs. The recently introduced AdvanSure system can simultaneously detect 42 allergen sIgEs using only 100 μ L of patient serum [11]. This test is based on the EIA technique with solid-phase allergen absorption and immobilization on nitrocellulose membrane. It has some working-level advantages compared to the ImmunoCAP FEIA in terms of user convenience and processing speed. We evaluated the sIgE detection performance of AdvanSure EIA system versus that of ImmunoCAP FEIA

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system in 199 Korean patients with known allergies for nine dominant inhalant and four food allergens.

2. Material and methods

2.1. Patients

From January to March 2010, allergic patients from infant to the elderly who visited Allergy and Asthma Clinic at Severance Hospital, Yonsei University Health System for the diagnosis and treatment of their allergic diseases were enrolled in this study according to their medical history and clinical diagnosis (asthma, allergic rhinitis, atopic dermatitis and food allergy). All patients underwent allergen sIgE ImmunoCAP tests for their suspected trigger allergens. Informed consent for additional sera sampling for AdvanSure test was obtained from all patients and/or their guardians. The Institutional Review Board of Yonsei University approved this study (IRB no. 1-2011-0038).

The inclusion criteria were as follows: ages from 1 to 75 y; allergic patients clinically diagnosed having IgE-related allergic diseases to inhalant and/or food allergens; no chronic comorbidities including malignancy, autoimmune disease, presenting chronic infection or other immunologic disorder.

2.2. Serum preparation and allergen selection

From every patient, 5 mL of whole blood was collected in a vacuum tube (Vacuette®; Greiner Bio-One GmbH, Kremsmünster, Austria) for serum separation. After centrifugation at 3000 rpm for 5 min, the serum was aliquoted into several round-bottom tubes (5 mL BD Falcon™; BD Bioscience Discovery Labware, Bedford, MA, USA) and frozen at -80°C for long-term (up to 1 to 2 weeks) storage until sIgE measurement.

Thirteen dominant allergens were selected for inter-assay comparison between AdvanSure EIA and ImmunoCAP FEIA tests. Nine inhalant allergens (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Blattella germanica*, cat dander, dog dander, alternaria, birch, timothy and mugwort) and four food allergens (egg white, milk, peanut and shrimp) were included. We selected these allergens according to the clinical importance and prevalence in Korea [12–14].

2.3. In vitro allergen sIgE measurements

Serum aliquots were sent to the laboratory without any patient identification. We performed allergen sIgE detection using two different systems simultaneously (AdvanSure Allergy Screen®; LG Life Science, Seoul, Korea and ImmunoCAP® 250; Phadia, Uppsala, Sweden). Both the AdvanSure® EIA system and ImmunoCAP® FEIA system were operated following the manufacture's instruction. The detection range of AdvanSure EIA was at 0.35 to 100 kU/l and that of ImmunoCAP FEIA was at 0.1 to 100 kU/l. However the sIgE classification scales were the same (class 0: under 0.35 kU/l, class 1: 0.35–0.7 kU/l, class 2: 0.7–3.5 kU/l, class 3: 3.5–17.5 kU/l, class 4: 17.5–50 kU/l, class 5: 50–100 kU/l, class 6: over 100 kU/l).

2.4. Statistical analysis

We analyzed the correlation of sIgE concentration (intraclass correlation analysis). To compare 2 methods for the equality, we used Passing–Bablok regression analysis [15]. Association of class (gamma analysis) and agreement of detection results (Cohen's kappa analysis) was also analyzed. We assessed and categorized kappa value as almost perfect (0.8–1.0), substantial (0.6–0.8), moderate (0.4–0.6), fair (0.2–0.4) and poor (below 0.2) [16]. We calculated three different agreement percentages (positive, negative and total agreement percentage). The positive and negative agreement percentages were

Table 1

Demographic characteristics of the studied patients.

	No. of patients (%)	Male: female	Age, y median [1Q, 3Q] (range)
Total	199 (100.0)	1:0.83	13 [5, 32] (2–74)
Asthma	79 (39.7)	1:1.03	14 [7, 33] (3–74)
Allergic rhinitis	109 (54.8)	1:0.85	25 [11, 40] (3–74)
Atopic dermatitis	72 (36.2)	1:0.57	4 [2, 14] (2–61)
Food allergy	43 (21.6)	1:0.59	4 [3, 7] (2–61)

calculated with the proportions of agreement for the average of their positive and negative responses. The total agreement percentage was calculated following the same methodology used in a previous study: (total number of results – number of discrepancies) $\times$ 100/total number of results [17]. A $p < 0.05$ was considered statistically significant. For the statistical analysis, we used SPSS 12.0 (SPSS Inc., Chicago, IL) and MedCalc 11.0 (MedCalc Software, Belgium) statistical software.

3. Results

3.1. Characteristics of enrolled patients and collected paired result sets

A total of 199 patients [median age 13 years (range 2–74 year) 109 males and 90 females] agreed to participate in this study. Their demographic characteristics according to the disease are shown in Table 1. The 950 matched result sets were obtained and analyzed. The final numbers of matched result sets for each allergen are presented in Table 2.

3.2. Intermethod comparison of sIgE concentrations

Overall, a total of 950 matched tests showed 0.633 in intraclass correlation coefficient (ICC) within 95% confidential interval. Correlation patterns and ICCs of each allergen sIgE are listed in Figs. 1 and 2, and Table 3. Almost all of the allergen sIgE concentrations showed ICCs above 0.5 except *B. germanica*, alternaria and mugwort sIgEs.

As Passing–Bablok regression analysis showed, overall AdvanSure EIA sIgE measurement was similar to ImmunoCAP FEIA result (intercept -0.072 [95% -0.098 , -0.060], slope 1.028 [95% 1.001 , 1.087]). Some allergen sIgE results showed multiple difference (slope 0.550 for *B. germanica*, 4.951 for alternaria, 0.569 for mugwort and 1.998 for peanut) (Table 3).

3.3. Association analysis by class

After the application of class boundaries, the results of the two assays were stratified into classes 0 to 6. Results of the gamma analysis indicated that almost all of the tested allergen sIgEs had a strong association between the 2 assays (Table 3).

Table 2

Tested allergens and number of matched set results.

Allergens (matched set results, n)	
Aeroallergens	Food allergens
<i>Dermatophagoides pteronyssinus</i> (100)	Egg white (103)
<i>Dermatophagoides farinae</i> (149)	Milk (100)
<i>Blattella germanica</i> (57)	Peanut (53)
Cat dander (65)	Shrimp (38)
Dog dander (66)	
Alternaria (53)	
Birch pollen (41)	
Timothy pollen (58)	
Mugwort pollen (67)	

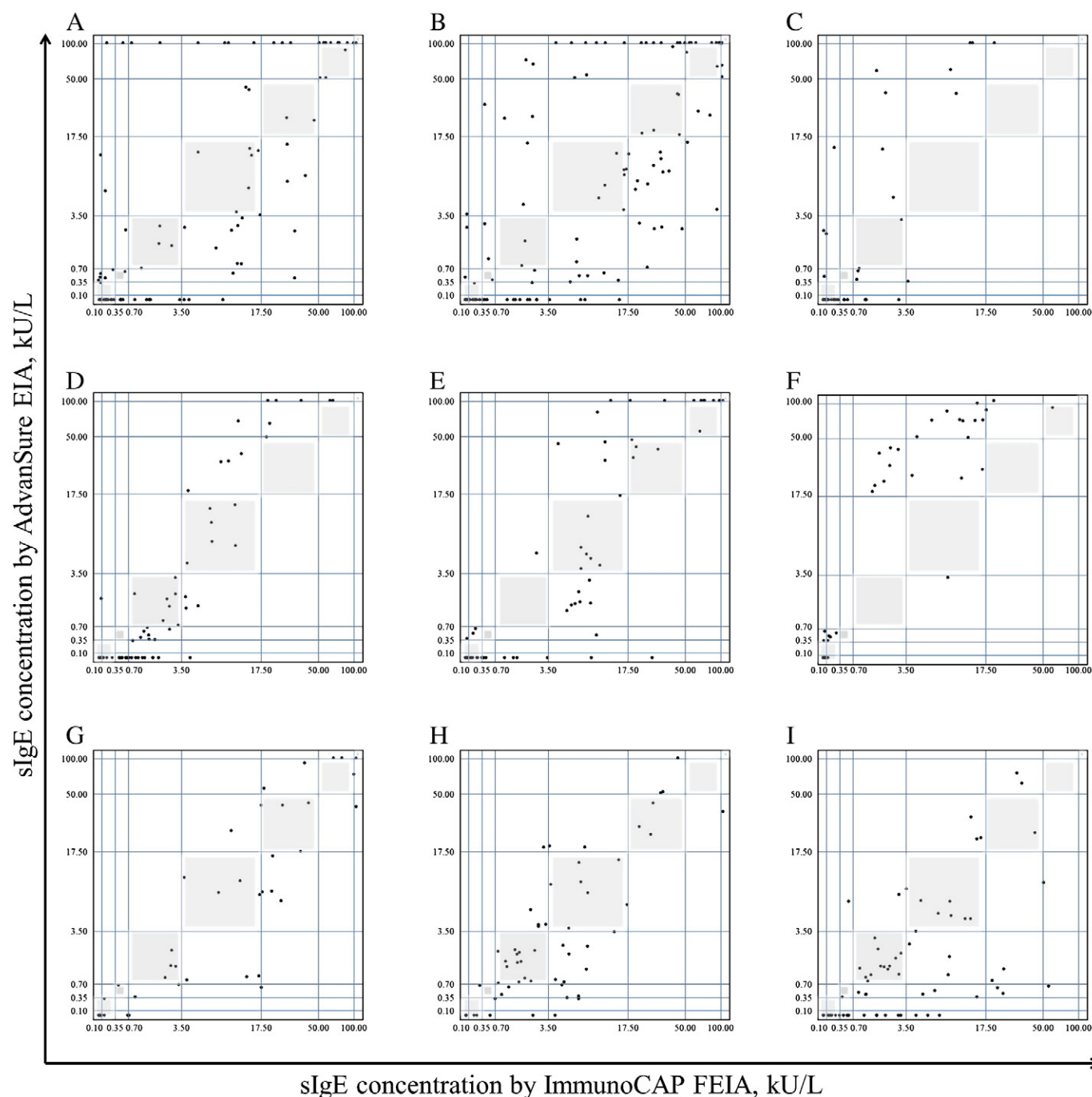


Fig. 1. Scattered plots of inhalant allergen sIgE concentrations measured by the ImmunoCAP FEIA system (x-axis) and the AdvanSure EIA system (y-axis). Each line in the plot represents class cut-off of ImmunoCAP and AdvanSure (class 0: <0.35, class 1: 0.35–0.7, class 2: 0.7–3.5, class 3: 3.5–17.5, class 4: 17.5–50, class 5: 50–100, class 6: >100 kU/l). Shaded boxes are concordant area in concentration class. Each plot represents an inhalant allergen – A) *Dermatophagoides pteronyssinus*, B) *Dermatophagoides farinae*, C) *Blattella germanica*, D) cat dander, E) dog dander, F) alternaria, G) birch, H) timothy and I) mugwort.

3.4. Agreement analysis

As per the manufacturer's suggestion, we adapted 0.35 kU/l as the cutoff value for the positive presence of sIgE in each assay. Table 4 shows positive, negative and total agreement percentage and kappa value between the two methods for each allergen sIgE tested. In almost all of the allergen sIgEs, we observed 76.0% to 93.1% for total agreement (55.0–88.9% for positive and 73.7–95.4% for negative agreement). In the kappa analysis, almost all of the allergen sIgE results showed substantial (8 allergens), or moderate agreement (4 allergens). Cat dander sIgE showed fair agreement ($\kappa=0.393$) (Table 4).

4. Discussion

The AdvanSure EIA system was recently introduced to the world market, including Korea. Thus far, only a few studies are available comparing this new system with already established, well-known systems, including the ImmunoCAP FEIA system [11]. In this study, we performed an inter-assay comparison between AdvanSure EIA and ImmunoCAP FEIA.

In the clinical practice, many multiple allergen sIgE screening assays provided their results as categorical data (classes 0 to 6 for example) instead of exact concentration of sIgE level to the customer. In our study, the AdvanSure EIA showed good correlation and

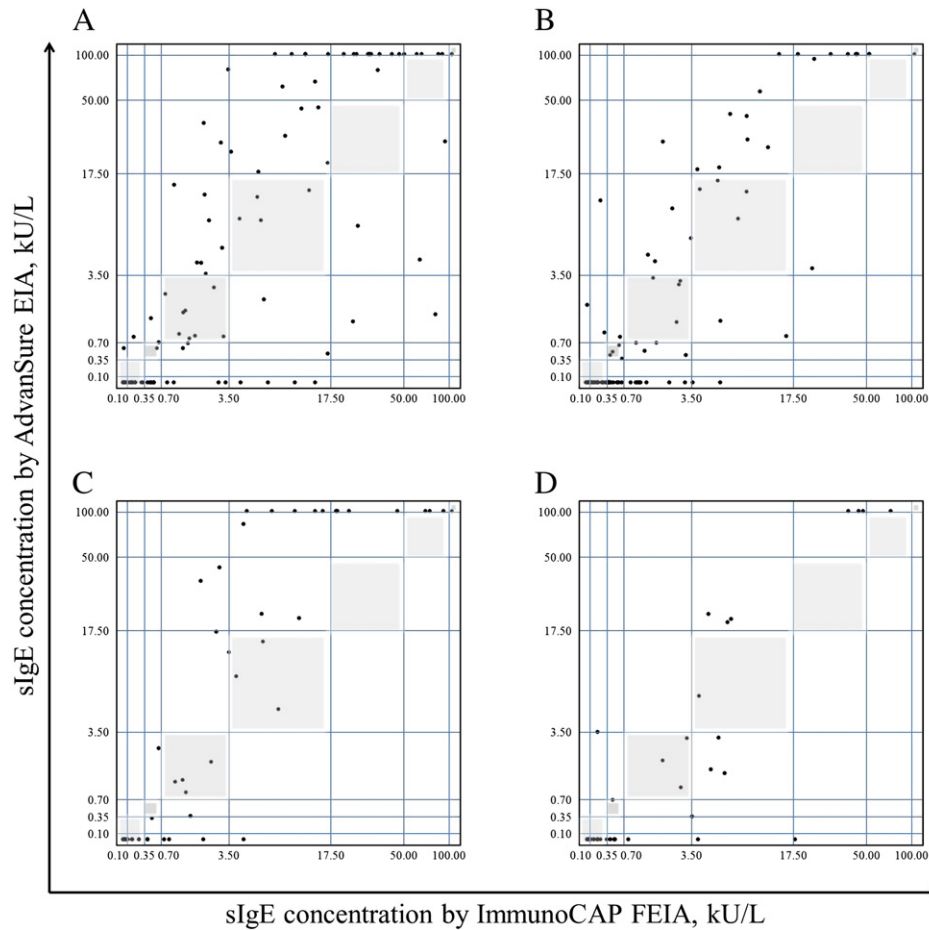


Fig. 2. Scattered plots of food allergen sIgE concentrations measured by the ImmunoCAP FEIA system (x-axis) and the AdvanSure EIA system (y-axis). Each line in the plot represents class cut-off of ImmunoCAP and AdvanSure (class 0: <0.35, class 1: 0.35–0.7, class 2: 0.7–3.5, class 3: 3.5–17.5, class 4: 17.5–50, class 5: 50–100, class 6: > 100 kU/l). Shaded boxes are concordant area in concentration class. Each plot represents a food allergen – A) egg white, B) milk, C) peanut and D) shrimp.

association with ImmunoCAP FEIA. Thus we suggested that AdvanSure EIA assay may be used for sIgE quantification as well as qualification. However, we found multiple differences in some allergens using Passing–Bablok regression. Consequently, AdvanSure EIA may have possibilities to overestimate sIgE for alternaria and peanut allergen compared to ImmunoCAP FEIA and underestimate for *B. germanica* and mugwort.

Both AdvanSure and ImmunoCAP systems use the same assay principle of an indirect immunoassay method employing an allergen-coated solid phase, anti-human IgE conjugate and a substrate tracer to develop a signal. However, the two systems have some differences, including the solid phase for coupling allergens (CNBr-activated cellulose in the ImmunoCAP vs. nitrocellulose in the AdvanSure), the conjugated enzyme (galactosidase vs. alkaline phosphatase), the enzyme substrate

Table 3

Correlation, equality measurement and association analysis between AdvanSure and ImmunoCAP systems.

Allergen	Intermethod comparison			Association of class	
	^a ICC [95% CI]	^b PB intercept [95% CI]	^b PB slope [95% CI]	Gamma	p-Value
Total test	0.633 [0.626, 0.697]	−0.072 [−0.098, −0.060]	1.028 [1.001, 1.087]	0.828	<0.001
<i>D. pteronyssinus</i>	0.590 [0.446, 0.705]	−0.128 [−0.194, −0.026]	1.021 [0.851, 1.123]	0.764	<0.001
<i>D. farinae</i>	0.733 [0.649, 0.799]	−0.040 [−0.301, −0.007]	0.998 [0.723, 1.003]	0.818	<0.001
<i>B. germanica</i>	0.270 [0.012, 0.494]	−0.017 [−0.086, 0.000]	0.550 [0.000, 1.691]	0.869	<0.001
Cat dander	0.625 [0.451, 0.753]	−0.729 [−1.143, −0.220]	1.330 [0.786, 1.633]	0.940	<0.001
Dog dander	0.798 [0.691, 0.872]	−0.117 [−0.335, −0.027]	1.067 [0.890, 1.395]	0.901	<0.001
Alternaria	0.393 [0.145, 0.602]	−0.099 [−0.195, −0.041]	4.951 [4.122, 6.491]	0.980	<0.001
Birch	0.821 [0.689, 0.900]	−0.094 [−0.816, −0.010]	0.851 [0.503, 1.118]	0.883	<0.001
Timothy	0.699 [0.540, 0.810]	−0.357 [−0.974, −0.009]	1.288 [0.923, 1.611]	0.725	<0.001
Mugwort	0.491 [0.286, 0.653]	−0.063 [−0.259, 0.161]	0.569 [0.251, 0.763]	0.609	<0.001
Egg white	0.563 [0.416, 0.682]	−0.215 [−0.447, −0.051]	1.789 [1.263, 2.352]	0.831	<0.001
Milk	0.642 [0.511, 0.744]	−0.151 [−0.341, −0.064]	1.416 [0.981, 1.984]	0.866	<0.001
Peanut	0.551 [0.331, 0.713]	−0.060 [−0.153, −0.012]	1.998 [1.168, 3.812]	0.941	<0.001
Shrimp	0.770 [0.600, 0.874]	−0.069 [−0.244, −0.010]	0.986 [0.259, 1.686]	0.840	<0.001

^a Intraclass coefficient.

^b Passing–Barbolk analysis.

Table 4
Agreement analysis between AdvanSure and ImmunoCAP systems.

Allergen	Agreement %			Kappa analysis	
	Positive %	Negative %	Total % (agree/total)	κ	p-Value
Total test	87.2	76.3	83.4 (792/950)	0.638	<0.001
<i>D. pteronyssinus</i>	72.2	84.4	80.0 (80/100)	0.566	<0.001
<i>D. farinae</i>	75.6	90.7	86.6 (129/149)	0.666	<0.001
<i>B. germanica</i>	86.8	73.7	82.5 (47/57)	0.606	<0.001
Cat dander	55.0	80.0	72.3 (47/65)	0.393	<0.001
Dog dander	71.1	85.1	80.3 (53/66)	0.567	<0.001
Alternaria	88.9	88.5	88.7 (47/53)	0.776	<0.001
Birch	82.4	95.4	92.7 (38/41)	0.778	<0.001
Timothy	75.0	96.0	93.1 (54/58)	0.711	<0.001
Mugwort	62.5	88.2	82.1 (55/67)	0.528	<0.001
Egg white	76.2	89.5	85.4 (88/103)	0.662	<0.001
Milk	73.9	77.8	76.0 (76/100)	0.532	<0.001
Peanut	85.0	90.9	88.7 (47/53)	0.762	<0.001
Shrimp	81.1	82.1	81.6 (31/38)	0.638	<0.001

(fluorescent substrate vs. visible substrate) and the signal amplification method (a biotin–streptavidin system in the AdvanSure) [8,11].

Furthermore, different allergen sources and exposure of the IgE epitope in the solid phase should be considered with the other technical problems related to the assays. ImmunoCAP FEIA and AdvanSure EIA used the same crude allergens for their assay. Although the same species of plants or mites were used, there may have been inter-assay differences due to the minor differences in allergens because of the cultivating conditions in various geographic locations, feeding materials, genetic polymorphisms, the allergen extractions and manufacturing processes, the type of solid phases and the final development systems [18]. The major sources of allergens for allergy diagnostics are produced by extracting raw biological materials, which manufacturers may obtain from different suppliers. Variations in extraction methods can have a strong influence on the performance of an *in vitro* assay.

For the IgE epitope, the ImmunoCAP system uses a nitrocellulose block with numerous holes which enable the IgE epitope to bind allergens to the solid phase with a 3-dimensional formation; however, this conjugation process requires a specific conjugate, such as biotin [19]. This method allows every IgE binding epitope to be exposed to free space. On the other hand, the AdvanSure system uses a direct absorption technique in which the crude allergen extract is absorbed by a 2-dimensional nitrocellulose membrane without modification. There is no best practice for binding allergens to the solid phase, but we should consider that the allergen modifications during these processes may affect the final outcome [20].

In the agreement analysis, alternaria, birch, peanut and timothy pollen sIgE showed an excellent agreement percentage, as well as substantial agreement in cross-table analysis. This means that the ability of the AdvanSure EIA to detect these sIgEs is similar as that of the ImmunoCAP FEIA. However, as evidenced by cat dander sIgEs showed fair agreement, the ImmunoCAP FEIA is better for detecting this allergen than the AdvanSure EIA.

Although the AdvanSure EIA assay showed some discordance, it has several clinical advantages, such as the ability to detect sIgEs against multiple allergens at once on the continuous standard scale (kU/l), according to the WHO International Reference Preparation 75/502 for Human IgE [7]. Several other multiple allergen detecting assays have been developed by major manufacturers. RIDA Allergy Screen (R-biopharm, Germany) and MAST CLA (Hitachi, Japan) are brands used in the allergy and clinical immunology field for diagnosis of atopy. The advantages of these multiple allergen sIgE detecting assays include rapidity, fewer samples and the provision of more clinical information [21]. Oh et al. compared the AdvanSure EIA with RIDA Allergy Screen by analyzing 180 matched tests. The overall agreement rate of sIgE was 86.7% (kappa 0.293). They also compared two other systems with the ImmunoCAP FEIA in discordant samples;

AdvanSure EIA showed a higher concordance rate than RIDA Allergy Screen (70.9% vs. 29.1%) [11].

In our study, the AdvanSure EIA showed good correlation and accordance with ImmunoCAP FEIA. In this system, multiple allergens are coated in one solid phase onto separate areas. Because all allergens are influenced by one anti-IgE antibody conjugate, the potency of one allergen may be influenced by the activities of other allergens. Therefore, the optimization of each allergen concentration should be precisely controlled during the production process.

All assay methods have their disadvantages due to technical limitations or other variables. For the quality control of sIgE detection assays, a standardized purified allergen is a very important factor for the calibration of the assay, as well as continuous quality control and improvement. In order to ensure the standardization of allergen supplements, under the United States Food and Drug Administration, the Center for Biologics Evaluation and Research is responsible for the control of allergen products and related biologics and validate and standardize 19 dominant allergens [22]. The European Union organized the CREATE project to establish international allergen standardization [23]. Furthermore, international quality control of standardized allergens is needed for the improvement of sIgE assays and the reduction of inter-assay discordance [24].

In conclusion, AdvanSure EIA system showed a good detection performance compared with that of the ImmunoCAP FEIA system in almost all allergen sIgEs, but careful clinical interpretation is needed for some allergens. Moreover, when considering the genetic influence on allergic diseases, other ethnicities could show different IgE binding affinities for the same allergens [25]. Thus, careful clinical application of our data to other ethnic populations is needed.

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