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ORIGINAL ARTICLE



Comparison of allergen-specific IgE levels between Immulite 2000 and ImmunoCAP systems against six inhalant allergens and ten food allergens

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ABSTRACT

In vitro allergen-specific immunoglobulin E (sIgE) measurement has been used as an important diagnostic tool for allergic diseases. Currently, quantitative sIgE levels are detected mainly by using ImmunoCAP and Immulite 2000 assay system. These two systems have the same calibration scale at 0–100 kUA/L, but they differ in used allergens, detection methods and automation systems. We compared 1600 paired sIgE results for 204 allergic patients, including 100 paired sIgE assay results for each of 16 allergens (*Alternaria alternata*, birch-alder mix, cat dander, *D. farinae*, *D. pteronyssinus*, dog dander, buckwheat, crab, egg white, mackerel, milk, peach, peanut, shrimp, soybean and wheat flour). Inter-method comparison was performed for qualitative data with a cutoff of 0.35 kUA/L and a detection limit of 0.1 kUA/L, semi-quantitative class results and quantitative data. In qualitative comparisons, the overall concordance rate ranged from 81.0% to 99.0% (k : 0.599–0.949) with the cutoff value of 0.35 kUA/L. It also ranged from 80.0% to 99.0% (k : 0.521–0.951) with the detection limit of 0.1 kUA/L. The class results from these two assays showed good agreements for all allergens. For quantitative sIgE results, these two assays showed moderate positive correlations for Dog dander (r = 0.683) and Mackerel (r = 0.573) but high to very high correlations for the other 14 allergens (r = 0.734–0.972). Immulite 2000 and ImmunoCAP assays demonstrated good concordance and correlation for 16 common allergens, but international standards against each specific allergen for calibration and harmonization of sIgE tests are still needed.

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Introduction

The prevalence of allergic diseases has increased in the last few decades [1]. Diagnosis of allergic diseases requires a compatible clinical history of allergic symptoms after allergen exposure and *in vitro* laboratory tests to detect allergen-specific immunoglobulin E (sIgE) against target allergens [2–4]. Identifying specific allergens for allergic patients is important for allergen-specific management and immunotherapy. National Institute of Allergy and Infectious Disease (NIAID) guidelines recommend that healthcare professionals should check clinical history and perform a physical examination and laboratory tests to identify sIgE [5]. The inclusion criteria for initiating allergen immunotherapy include elevated serum-sIgE levels in addition to clinical symptoms. Although the presence of sIgE is not specific for allergic symptom development, sIgE or the ratio of sIgE to total IgE can be used as an important risk factor or a marker to predict the clinical outcome after allergen immunotherapy [6].

In vitro sIgE measurement in serum has been improved. It is used as an important diagnostic tool for allergic diseases. Wide et al. [7] introduced a radioallergosorbent test (RAST) to detect sIgE in 1967. Since then, a great number of techniques have been developed and advanced to

immunoassays for quantitative sIgE detection using autoanalyzers [8–11]. Commercially available autoanalyzers have improved precision and sensitivity with monoclonal antibodies, good characterized allergens, shortened assay time and enzyme labels instead of radioactive labels [10,12,13]. Besides, there have been improvements in allergen species, composition of allergens and detection methods. Currently, quantitative sIgE levels are detected mainly by using the ImmunoCAP system (Thermo Fisher Scientific, Uppsala, Sweden) and Immulite 2000 assay system (Siemens Healthcare Diagnostics, NY). ImmunoCAP system has been regarded as a classic method for quantitative sIgE detection due to its widespread use in many clinical studies in comparison with a skin-prick test [14,15]. Immulite 2000 assay was developed later as a two-step chemiluminescent enzyme immunoassay with good interlaboratory and intermethod agreements [16,17]. This system detects sIgE levels in a fluid phase using monoclonal antibodies and a continuous standardized scale calibrated against WHO International Reference Preparation 75/502 for IgE. Although these two systems differ in terms of allergens used and detection methods, they have the same calibration scale at 0–100 kUA/L. Both systems offer a wide range of allergens in the

diagnostic platform, thereby making it easier to test similar allergens on both platforms. However, several previous comparative studies have shown inconsistent findings, and the differences in quantified levels were due to the allergens studied [2,9,13,15,18–20]. In addition, previous studies included a limited number of allergens, and their results varied depending on the study population. Understanding the characteristics of different measuring systems and their differences in measured levels depending on the allergens is crucial to interpret the results appropriately and diagnose allergic disorders. Thus, comparative studies with a large sample size including many commonly requested allergens are still needed.

Therefore, the objective of this study was to compare qualitative, semi-quantitative (class) and quantitative sIgE data for 16 common allergens obtained with Immulite 2000 and ImmunoCAP systems. Since current consensus guidelines recommend the positivity of sIgE with a lower detection limit of the quantitative assay [21,22], we analyzed concordance rates between the two assays with a cutoff of 0.35 kUA/L and the detection limit of 0.1 kUA/L in this study. In addition, we considered a larger number of food allergens and enrolled a larger number of patients with clinical food allergy compared with previous studies.

Materials and methods

Patients and serum samples

We enrolled 204 Korean patients diagnosed with a clinical allergic reaction to inhalant or food allergen who visited Seoul St. Mary's Hospital. Left-over sera routinely requested for sIgE screening test by semiquantitative AdvanSure allergy screen test (LG Chem, Seoul, Korea) were used in this study. Each serum specimen from the patient was separated into 10 aliquots. We randomly selected sera (100 sera for each allergen) with a wide spectrum of sIgE results by AdvanSure allergy screen test for 16 allergens. Finally, a total of 1600 serum aliquots was obtained. All serum aliquots were preserved at -20°C until sIgE measurements by two assays. This study was approved by the Institutional Review Board (KC15SISI0253).

Allergen-specific IgE measurements

Measurements of sIgE levels for 16 allergens were performed using Immulite 2000 and ImmunoCAP 250 according to manufacturers' instructions. Both assays have the same detection limit (0.1 kUA/L) and measurement range (0.1–100 kUA/L). Positive result for qualitative sIgE was defined as concentration ≥ 0.35 kUA/L or above the detection limit ≥ 0.1 kUA/L. Sixteen allergens (6 common inhalant allergens and 10 major food allergens) were tested using 100 serum samples per allergen: *Alternaria alternata* (M6), birch-alder mix (T3), cat dander (E1), *D. farinae* (D2), *D. pteronyssinus* (D1), dog dander (E5), buckwheat (F11), crab (F23), egg white (F1), mackerel (F50), milk (F2), peach (F95), peanut (F13), shrimp (F24), soybean (F14) and wheat

flour (F4). We selected these allergens according to their prevalence [23,24].

Statistical analysis

A total of 1600 paired results for 16 allergen specificities were analyzed for inter-method comparison. First, concordance rates and Cohen's kappa coefficients for the qualitative results between the two assays were determined. Kappa values were shown with 95% confidence interval (CI) and interpreted as very good (0.81–1.00), good (0.61–0.80), moderate (0.41–0.60), fair (0.21–0.40) or poor (<0.20). Second, we evaluated the agreement (%) for the class results from the two assays by calculating the intraclass correlation coefficient (ICC) for each allergen [25]. The sIgE values were categorized as class 0 (<0.35 kUA/L), class 1 (0.35–0.70 kUA/L), class 2 (0.70–3.50 kUA/L), class 3 (3.50–17.5 kUA/L), class 4 (17.5–50.0 kUA/L for ImmunoCAP, 17.5–52.5 for Immulite 2000), class 5 (50–100 kUA/L for ImmunoCAP, 52.5–100 kUA/L for Immulite 2000) and class 6 (≥ 100 kUA/L). The level of agreement using ICC was expressed as very good (ICC >0.90), good (0.71–0.90), moderate (0.51–0.70), mediocre (0.31–0.50) or poor (ICC <0.31). Third, Spearman's correlation analysis was performed for the quantitative results and correlation coefficient (r_s) values were interpreted as very high (0.90–1.00), high (0.7–0.9), moderate (0.50–0.70), low (0.30–0.50) or negligible (<0.30). Scatter plots with regression equation of logarithmic quantitative results were then obtained. The significant level was defined at p value <0.05 . MedCalc version 14.12.0 (MedCalc software, Mariakerke, Belgium) was used for all statistical analyses.

Results

Characteristics of enrolled patients

Demographic features of the patients are shown in Table 1. The most common diseases of these allergic patients were

Table 1. Demographic features of the study population.

Demographic features	Number (%)
Patients	204
Sex	
Men	89 (43.6)
Women	115 (56.4)
Age	
Years (mean $\pm$ SD)	32.1 $\pm$ 4.0
Years (range)	1–96
Diseases	
Asthma	25 (12.3)
Allergic dermatitis	40 (19.6)
Allergic rhinitis	36 (17.6)
Urticaria and angioedema	43 (21.1)
Food allergy	19 (9.3)
Anaphylaxis	2 (1.0)
Others	39 (19.1)
Tested allergens	16
Inhalant	6
Food	10
Tested samples	1600
Inhalant	600
Food	1000

skin allergy and respiratory allergic diseases, including urticaria (21.1%), allergic dermatitis (19.6%), allergic rhinitis (17.6%) and asthma (12.3%). Nineteen patients with confirmed food allergy were included. A total of 1600 paired results was analyzed, including 600 results for 6 inhalant allergens and 1000 results for 10 food allergens. For the inhalant allergens, the average positivity rate above the detection limit (0.1 kUA/L) by ImmunoCAP was 40.6%, ranging from 11.0% (*Alternaria*) to 71.0% (*D. farinae*). For food allergens, the average positivity rate by ImmunoCAP was 21.3%, ranging from 4.0% (Mackerel) to 40.0% (Peanut).

Concordance between Immulite 2000 and ImmunoCAP assays for qualitative sIgE detection

Results of positive-, negative- and total concordance rate (%) and weighted kappa values (κ) between the two systems are shown in Table 2. With a cutoff value of 0.35 kUA/L, the overall concordance in a total of 1600 paired tests was 81.5% ($\kappa=0.817$). For 16 allergens tested, concordance rates ranged from 81.0% (*D. pteronyssinus*) to 99.0% (*Alternaria*). Cohen's kappa analysis showed good to very good agreements for 14 allergens ($\kappa=0.640$ – 0.949) and moderate agreements for *D. pteronyssinus* (D1) and dog dander (E5) ($\kappa=0.599$ and $\kappa=0.572$, respectively). Detection of sIgE above 0.1 kUA/L also demonstrated concordance rates of 80.0% to 99.0% with good to very good agreements for all tested allergens except for *D. pteronyssinus* (D1), dog dander (E5) and mackerel (F50).

Among discrepant results, sIgEs for *D. farinae*, *D. pteronyssinus* and dog dander allergens were more frequently detected in Immulite 2000 assay, whereas those for wheat flour, shrimp and mackerel allergens were more frequently detected in ImmunoCAP assay.

Agreement between Immulite 2000 and ImmunoCAP for class results of sIgE

The sIgE results were categorized into classes 0 to 6, according to the standard classification system. Good to very good

agreements between the two systems were obtained for all 16 allergens based on ICC values (0.778–0.992) (Table 3).

Correlation analysis between Immulite 2000 and ImmunoCAP for quantitative sIgE values

We analyzed the degree of association between the quantitative results of sIgE measured by Immulite 2000 and ImmunoCAP. Spearman's correlation analysis showed that the correlation coefficient (r_s) values ranged from 0.573 to 0.972 ($p<.05$) (Table 4). Logarithmic scale of scatterplots and equations of Immulite 2000 versus ImmunoCAP are depicted in Figure 1. Strong positive correlations were observed more prominently among eleven allergens. One inhalant [Dog dander (E5)] and four food allergens [Crab (F23), Mackerel (F50), Shrimp (F24), Wheat flour (F4)] showed relatively less identical results between the two assays ($r<0.9$).

Discussion

ImmunoCAP and Immulite 2000 are two major assays for quantitative sIgE measurement. They differ methodologically. However, they use similar units of values according to the same standard of total IgE (WHO IgE Standard 75/502). Ideally, allergen-specific IgE measuring systems should be standardized with high precision, sensitivity, specificity, accuracy and good quality control [6]. In the present study, we evaluated 1600 paired sIgE results for 16 common allergens obtained by these two assays. Our data on the concordance analysis of qualitative sIgE (cutoff ≥ 0.35 kUA/L) showed good to very good agreements for all allergens, with a concordance of more than 90.0% except allergen *D. pteronyssinus* (D1) and dog dander (E5). This observation is consistent with the previous study based on the CAP survey in 2010 [8]. In contrast, Lee et al. [15] have shown variable agreements ranging from 56.3% (for shrimp) to 100% (for birch) in qualitative comparison of 14 allergens with the cutoff of 0.35 kUA/L. The discrepancy between the assays might be caused by differences in methodology, allergens used and study population [15,26].

Table 2. Concordance between Immulite 2000 and ImmunoCAP for qualitative sIgE detection with different cutoffs ≥ 0.35 kUA/L and ≥ 0.1 kUA/L.

Allergen	Allergen code	No. of tests	Concordance (%) (cutoff ≥ 0.35 kUA/L)			Weighted kappa k (95% CI)	Concordance (%) (cutoff ≥ 0.1 kUA/L)			Weighted kappa k (95% CI)
			Negative %	Positive %	Total %		Negative %	Positive %	Total %	
<i>Alternaria</i>	M6	100	100.0	90.0	99.0	0.942 (0.829–1.000)	100.0	90.9	99.0	0.948 (0.843–1.000)
Birch–Alder mix	T3	100	100.0	92.9	98.0	0.949 (0.880–1.000)	98.6	96.6	98.0	0.951 (0.885–1.000)
Cat dander	E1	100	89.9	100.0	92.0	0.788 (0.651–0.926)	84.6	100.0	88.0	0.708 (0.559–0.856)
<i>D. farinae</i>	D2	100	85.7	96.9	93.0	0.843 (0.731–0.955)	51.7	100.0	86.0	0.603 (0.427–0.780)
<i>D. pteronyssinus</i>	D1	100	76.3	83.9	81.0	0.599 (0.437–0.760)	60.0	92.9	83.0	0.566 (0.385–0.747)
Buckwheat	F11	100	100.0	85.7	99.0	0.918 (0.758–1.000)	98.9	77.8	97.0	0.807 (0.595–1.000)
Crab	F23	100	96.4	70.6	92.0	0.703 (0.510–0.896)	97.5	85.0	95.0	0.841 (0.705–0.976)
Dog dander	E5	100	84.9	92.9	86.0	0.572 (0.381–0.763)	75.6	95.5	80.0	0.550 (0.389–0.710)
Egg white	F1	100	93.8	100.0	95.0	0.857 (0.736–0.978)	89.5	95.8	91.0	0.776 (0.638–0.913)
Mackerel	F50	100	99.0	75.0	98.0	0.740 (0.393–1.000)	95.8	75.0	95.0	0.521 (0.156–0.886)
Milk	F2	100	94.1	100.0	95.0	0.828 (0.682–0.973)	89.0	92.6	90.0	0.763 (0.625–0.900)
Peach	F95	100	98.8	88.2	97.0	0.891 (0.770–1.000)	97.5	80.0	94.0	0.805 (0.655–0.955)
Peanut	F13	100	100.0	81.8	94.0	0.858 (0.749–0.967)	96.7	92.5	95.0	0.895 (0.806–0.985)
Shrimp	F24	100	100.0	75.0	97.0	0.841 (0.666–1.000)	98.8	60.0	93.0	0.682 (0.464–0.900)
Soybean	F14	100	98.8	84.2	96.0	0.865 (0.735–0.994)	93.5	95.7	94.0	0.840 (0.717–0.963)
Wheat flour	F4	100	98.7	56.5	89.0	0.640 (0.450–0.830)	98.6	66.7	89.0	0.714 (0.559–0.868)

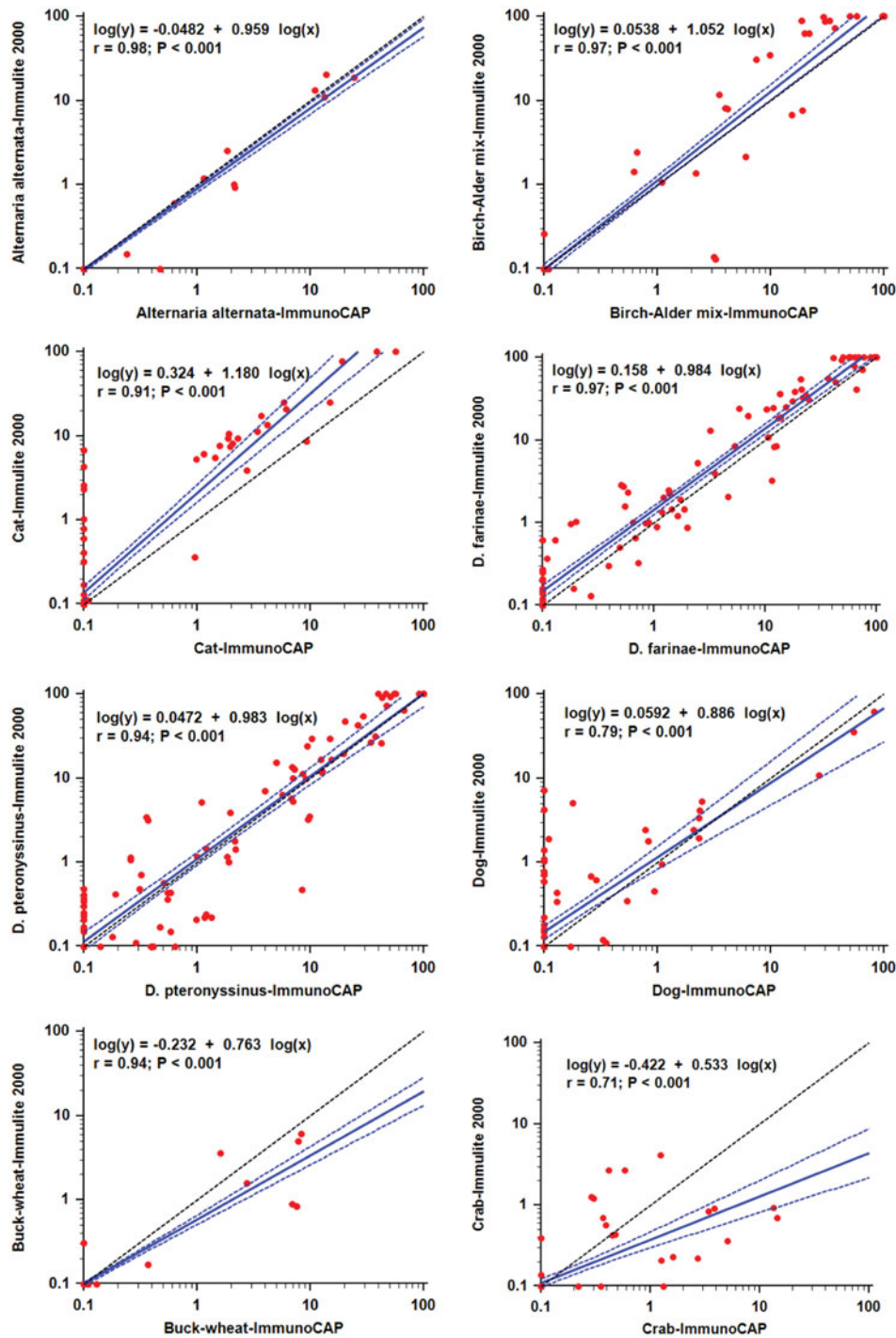


Figure 1. Scatterplots of method comparison between Immulite 2000 and ImmunoCAP for 6 inhalants and 10 food allergens. Dotted lines show 95% confidence intervals.

The sIgE assays simply indicate sensitization to the specific allergens. They do not define certain allergic diseases. Previous consensus guidance recommended that all clinical laboratories should report their IgE antibody results as analytical measurements based on the accepted lower limit of quantitation of the assay [27]. Therefore, we also performed concordance analysis with a detection limit of 0.1 kUA/L, the analytical sensitivity of two assays. We achieved similar concordance rates to those with a cutoff of 0.35 kUA/L. Based on class results, we found good to very good agreements ($ICC > 0.7$) between the two assay systems for all

tested allergens. In comparison with ImmunoCAP assay, Immulite 2000 showed lower positive concordance rates for wheat flour, shrimp and mackerel and lower negative concordance rates for *D. farinae*, *D. pteronyssinus* and dog dander. These results are similar to the previous studies showing low ICC values for shrimp [2,15,28]. In the future, harmonized sIgE assay working ranges should be generated to provide the same quantitative results to clinicians.

Immulite 2000 and ImmunoCAP assays use the same total IgE standard (WHO IgE Reference standard 75/502), the gold standard calibration method [17] for the

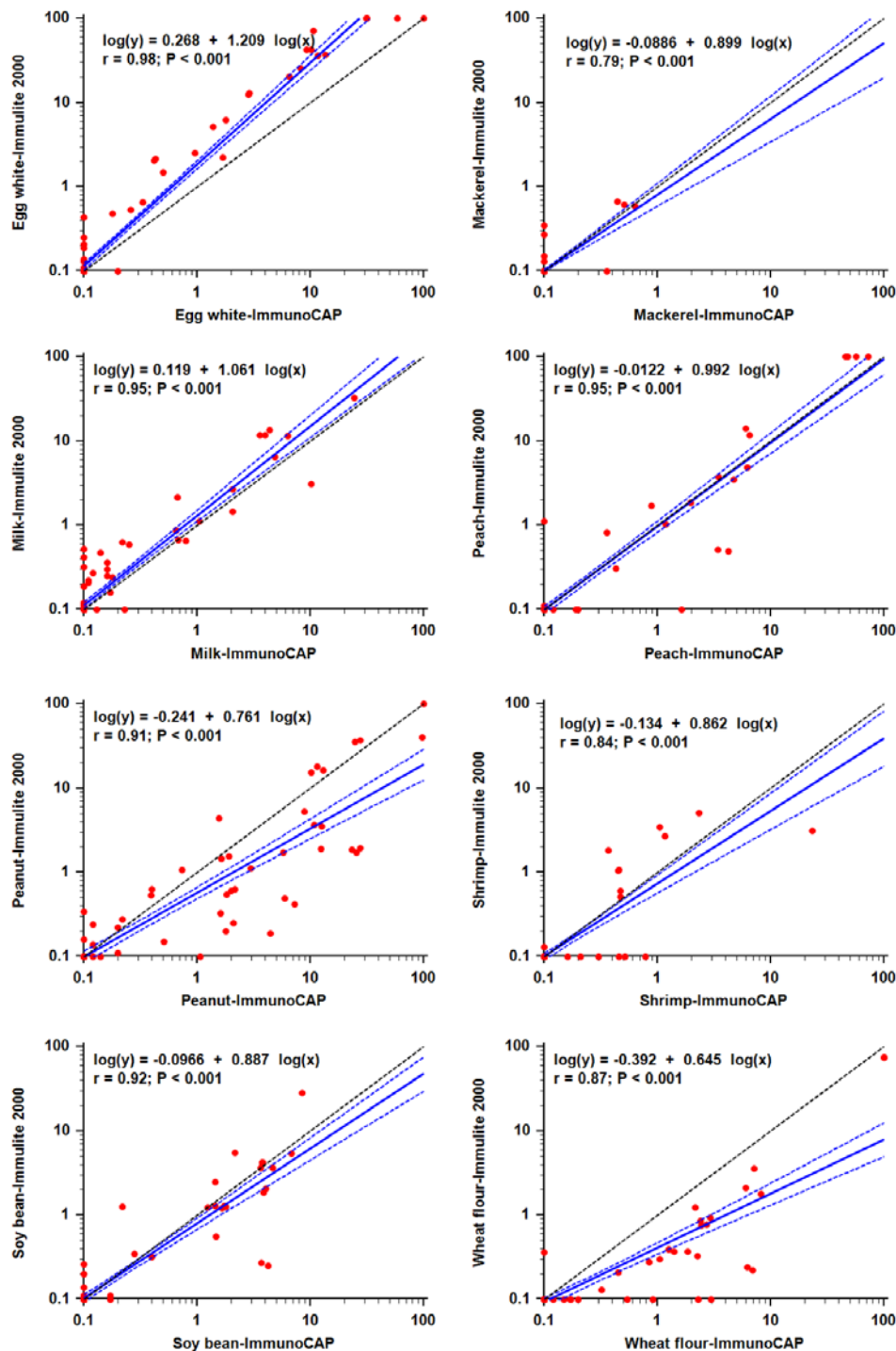


Figure 1. Continued.

quantification of sIgE values. For quantitative sIgE comparison, previous studies have reported variable conclusions [2,11,29]. Wood et al. [29] have reported the differences of sIgE assay systems, showing that sIgE antibodies to birch and *D. pteronyssinus* determined by Immulite were three-fold higher than those obtained by ImmunoCAP. Thus, they concluded that sIgE levels measured by different assay systems were not equivalent. Such results might have an influence on the treatment for allergic patients. In contrast, our study showed good correlations for Birch–Alder mix (T3) and *D. pteronyssinus* ($r_s = 0.972$ and $r_s = 0.897$, respectively).

Most results were scattered around the line of identity as shown in Figure 1. Hamilton et al. [8] reported fair to good correlations between two detection systems for most allergens except for crab and shrimp, which showed poor correlation by scatterplots and correlation analysis. Those observations were different from our results, which showed a fair correlation for shrimp (F24) between the two assays ($r_s = 0.734$). In this comparison study, we included relatively a large number of various food allergens (11 allergens). The sIgE results for egg, milk, peanut and wheat flour allergens showed good correlations between the two methods,

Table 3. Intraclass correlation coefficient (ICC) of sIgE class results of 100 sera for each allergen obtained from Immulite 2000 and ImmunoCAP assays.

Allergen	Allergen code	No. of tests	ICC (95% CI)	
<i>Alternaria alternata</i>	M6	100	0.992	(0.987–0.994)
Birch–Alder mix	T3	100	0.983	(0.975–0.989)
Cat dander	E1	100	0.916	(0.875–0.944)
<i>D. farinae</i>	D2	100	0.968	(0.953–0.979)
<i>D. pteronyssinus</i>	D1	100	0.949	(0.925–0.966)
Dog dander	E5	100	0.833	(0.753–0.888)
Buckwheat	F11	100	0.974	(0.962–0.983)
Crab	F23	100	0.778	(0.671–0.851)
Egg white	F1	100	0.962	(0.943–0.974)
Mackerel	F50	100	0.852	(0.780–0.900)
Milk	F2	100	0.968	(0.952–0.978)
Peach	F95	100	0.955	(0.934–0.970)
Peanut	F13	100	0.912	(0.869–0.941)
Shrimp	F24	100	0.886	(0.830–0.923)
Soybean	F14	100	0.922	(0.884–0.947)
Wheat flour	F4	100	0.872	(0.810–0.914)

Table 4. Correlation between Immulite 2000 and ImmunoCAP for quantitative sIgE values.

Allergen	Allergen code	No. of tests	rs	(95% CI)
<i>Alternaria alternata</i>	M6	100	0.956	(0.935–0.970)
Birch–Alder mix	T3	100	0.972	(0.958–0.981)
Cat dander	E1	100	0.837	(0.767–0.887)
<i>D. farinae</i>	D2	100	0.964	(0.947–0.976)
<i>D. pteronyssinus</i>	D1	100	0.897	(0.850–0.929)
Dog dander	E5	100	0.683	(0.562–0.775)
Buckwheat	F11	100	0.832	(0.760–0.884)
Crab	F23	100	0.858	(0.796–0.902)
Egg white	F1	100	0.881	(0.828–0.919)
Mackerel	F50	100	0.573	(0.425–0.692)
Milk	F2	100	0.847	(0.780–0.894)
Peach	F95	100	0.854	(0.790–0.900)
Peanut	F13	100	0.933	(0.902–0.954)
Shrimp	F24	100	0.734	(0.628–0.813)
Soybean	F14	100	0.897	(0.850–0.930)
Wheat flour	F4	100	0.804	(0.721–0.864)

rs: Spearman's correlation coefficient.

although absolute quantities of sIgE were somewhat different. Such intermethod differences might be due to the heterogeneity of the allergen extracts in these two different assays. Total allergen extracts used as agents of sIgE assay systems have not been standardized. To solve the heterogeneity problem of allergen extracts, immunoassays with allergen components as the reagents should be used [30]. Although sIgE levels are measured extensively for the diagnosis of allergic disorders, there are no international standards for calibration yet. To make quantitative results from one assay applicable to another assay, it needs to be standardized by using international standard materials on each allergen.

This study included relatively a large sample size with a large spectrum of results for common allergens. However, there are some limitations to this study. Our data were obtained from a single laboratory. Thus, we might not notice possible interlaboratory variability. In addition, the number of positive samples on some specific allergens was not enough. Moreover, as we could not associate sIgE results with the clinical symptoms or provocation test results, it might be difficult to assess the accuracy of the sIgE results or distinguish from the cross-reactivity. Further

studies including a larger number of clinically meaningful allergens related with the clinical symptoms are needed to confirm the true positivity of the assay.

In conclusion, Immulite 2000 and ImmunoCAP systems in sIgE measurements demonstrated good concordance rates and agreements for the qualitative results, class results and quantitative results. However, the quantitative results were not interchangeable for some allergens. International standards for common allergens are needed for calibration so that sIgE results from one assay could be comparable with those measured in another assay. Thus, clinicians should be aware of interassay differences and interpret results appropriately.

Disclosure statement

No potential conflict of interest was reported by the authors.

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