

Concordance of skin prick test and serum-specific IgE to locally produced component-resolved diagnostics for cockroach allergy



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ABSTRACT

Background: Diagnosis of *Periplaneta americana* (American cockroach, ACR) allergy is commonly performed based on clinical history and skin prick test (SPT) or specific serum IgE (sIgE) measurement. The concordance of the findings with the SPT and sIgE results has never been investigated.

Objective: To compare the results of SPT with commercial ACR-extract (C-ACE) and sIgE measurement, using commercial kit and in-house enzyme-linked immunosorbent assay (ELISA) to the locally produced ACR extract (L-ACE) and native Per a 1, Per a 5, Per a 7, and Per a 9.

Methods: Sera from 66 individuals clinically diagnosed with chronic allergic rhinitis were included; 46 were positive SPT to C-ACE, and 20 were negative. Specific serum IgE levels were established by using a commercial test kit (ImmunoCap) and an in-house IgE-ELISA

Results: The percentage the C-ACE SPT-positive cases that were positive by the ImmunoCap-sIgE was 32.6%, indicating low concordance of the 2 assays. With the in-house ELISA, Per a 9 gave the highest sensitivity (98.00%), positive predictive value (PPV; 95.74%), and negative predictive value (NPV; 94.74%) of the sIgE quantification. The correlation coefficients (*R*) of the L-ACE-SPT and sIgE to L-ACE, Per a 1, Per a 5, Per a 7, and Per a 9 and ImmunoCap sIgE were 0.133, 0.278, 0.419, 0.280, and 0.432, and 0.256, respectively.

Conclusion: Skin prick test and sIgE measurement using commercial reagents have low concordance. Data of this study showed that sIgE to the native Per a 9 should be considered as an adjunct to the clinical history in diagnosis of ACR sensitization/allergy, particularly when the SPT and the nasal challenge, which is the gold standard method, cannot be performed.

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Introduction

Cockroaches (CR) are ubiquitous insects of public health concern, because they are not only a potential source of pathogens, but also produce potent allergens that are hazardous to human health. An estimated 4,000 extant species of CR exist. Whereas most species dwell in tropical and subtropical forests, approximately 50 species have adapted to life as domiciliary pests within the human environment.¹

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In Thailand, the American cockroach *Periplaneta americana* is the predominant species.² Exposure to cockroach (CR) allergens represents a high risk for IgE sensitization^{3,4} and allergic symptoms, particularly allergic rhinitis and atopic asthma after allergen reexposure.^{5,6} To date, several *P. americana*-derived proteins have been recognized as allergens, including Per a 1,^{7,8} Per a 2 or inactive aspartic protease-like,⁹ Per a 3 or arylphorin hemocyanin,^{10–12} Per a 5 or glutathione S-transferase,^{13,14} Per a 6 or Troponin-C,¹⁵ Per a 7 or tropomyosin,^{16,17} Per a 9 or arginine kinase,¹⁸ Per a 10 or serine protease,¹⁹ Per a 11 or α -amylase,²⁰ Per a 12 or chitinase,²⁰ and troponin T.²¹ Cockroach-allergic cases in Thailand exhibit 100% positive serum IgE reactivity to Per a 1,⁸ Per a 5,¹⁴ and Per a 9,¹⁸ whereas the reactivity to Per a 7 was 57%.¹⁷ Therefore, these 4 proteins are regarded as the major *P. americana* allergens among the Thai population.

Correct allergy diagnosis based on clear case history, physical examination/clinical data, and valid allergy test results enable the physician to provide proper counseling to the patients on allergen

avoidance and therapeutic measures, such as a tailored, allergen-specific immunotherapy. Although the nasal challenge is the gold standard method, the in vivo skin prick test (SPT) for immediate hypersensitivity and the in vitro detection of serum specific IgE (sIgE) (blood test) are currently used to diagnose specific allergic disease and to monitor the allergic status for airborne allergens, including house dust mites, cockroaches, animal dander, molds, and pollens.^{22–26} Skin prick test is used also for allergies to foods (SPT with fresh food performs better than commercially available extracts), insect stings, drugs/antibiotics, and household and industrial chemicals.^{27–30} The in vitro sIgE determination is used when the in vivo skin test cannot be done. Because SPT is not dose dependent (an unknown and unstandardized amount of allergens/proteins is introduced), sIgE can provide valuable information of the degree/level of sensitization and also the longitudinal development.

Only low concordance has been found of diagnosis of several allergies as well as the CR allergy by SPT using total (crude) allergenic extracts and the sIgE assay accomplished using commercially available test kits.³¹ One explanation for this discrepancy includes variability in protein profile, quantity, quality, and potency (kU/L) of allergens in crude extracts that are used in the SPT. In tandem, the variation in sIgE reactivity likely reflects solubility of the antibody and therefore may not reflect natural distribution of the protein as well as cross-reactivity of the IgE responses to the cross-reactive allergens of different sources.²³ With respect to CR allergy, the deployment of standardized CR extracts with reliable potency and content possibly would enhance the accuracy and performance of diagnosis and treatment.²³ A cocktail of 4 recombinant cockroach allergens that consisted of Bla g 1, Bla g 2, Bla g 4, and Bla g 5 would identify 95% of cockroach-allergic patients, and a cocktail of 5 allergens Per a 1, Bla g 2, Bla g 4, Bla g 5, and Bla g 7 or Per a 7 would be expected to diagnose 50% to 64% of cases of cockroach allergy worldwide.²³ Moreover, purified native cockroach allergens are expected to improve diagnosis of CR allergy.²³ However, data are lacking on the correlation of sIgE using component-resolved diagnostics (CRDs) for American cockroach allergy with the skin prick test (a clinically relevant standard based on the “ARIA” guideline). The aim of this study was to determine the concordance levels of SPT to commercial cockroach extract and sIgE measurement by a bespoke (in-house) indirect enzyme-linked immunosorbent assay (ELISA), using locally produced *P americana* crude extract (L-ACE) and native Per a 1, Per a 5, Per a 7, and Per a 9 for component-resolved diagnosis (CRD).

Methods

Subjects and Serum Samples

The study protocol was approved by Siriraj Institutional Review Board (COA no. Si327/2013). Written informed consent was signed by each patient before the start of the study. It was conducted as a prospective, comparative single-center study and included 66 patients with allergic rhinitis (AR) who had visited the Allergy Clinic, Department of Oto-Rhino-Laryngology, Siriraj Hospital, Bangkok, Thailand. Forty-six patients (P1–P46) were positive by skin prick test (SPT) to a commercial *P americana* extract (C-ACE). Twenty AR patients who were negative to the C-ACE SPT (but positive SPT to commercial house dust mite extract instead) served as control patients (CP1–CP20). Blood samples were collected on the same day as the SPT was performed. ImmunoCAP test kits (Phadia 250, Thermo Fisher Scientific, Michigan) were used to measure sIgE levels to American cockroach extract according to the manufacturer's instructions. An sIgE value of 0.35 kU/L or greater was considered positive. The sIgE levels of the serum samples were additionally determined by in-house ELISA against L-ACE, purified native Per a 1, Per a 5, Per a 7, and Per a 9. Table 1 provides demographic data for the study

participants. The participants included 22 female and 24 male patients (P), age range 17 to 58 years, and 20 control patients (CP) (10 male and 10 female; age range, 18–55 years).

Locally Produced American Cockroach Extract (L-ACE) and Major Allergens

The L-ACE was prepared from laboratory-reared adult *P americana* of the cockroach culture as described previously.¹⁸ Briefly, the frozen cockroaches were ground in liquid nitrogen into fine pieces, homogenized by sonication in phosphate-buffered saline (PBS) and centrifuged. The supernatant was sterilized by membrane filtration, and the protein content was quantified (Bradford assay) by using bovine serum albumin as standard.

Native Per a 1 and Per a 9 of *P americana* were isolated from the L-ACE by using specific monoclonal antibody-based affinity resins as described previously.³² Purified mouse monoclonal IgG to Per a 1 and Per a 9³² were used to coat sepharose resins, and the affinity resins were used for capturing out the respective allergens from the L-ACE. Native Per a 5 was isolated from the L-ACE, using GSTrap FF affinity column (GE Healthcare, Uppsala, Sweden).¹⁴ Per a 7 was prepared as described previously.¹⁷ Briefly, the L-ACE powder was incubated in 50 mL of extraction buffer (1 M KCl and 0.5 mM dithiothreitol, pH 7.0) for 16 hours at room temperature and centrifuged. The precipitate was dissolved in 0.5 mM dithiothreitol, pH 7.0, and dialyzed against phosphate-buffered saline. Ammonium sulfate (40%) was added to precipitate the Per a 7.

The purified native Per a 1, Per a 5, Per a 7, and Per a 9 were checked for purity by sodium dodecyl sulfate polyacrylamide gel electrophoresis and protein staining and verified by liquid chromatography tandem mass spectrometry.

Skin Prick Test

The subjects abstained from anti-allergy drugs for at least 7 days were tested by SPT,³³ using commercial *P americana* extract (C-ACE). Histamine (2.5 mg/mL) was used as positive control, whereas buffered saline solution served as a negative control. The same lots of test allergen and control materials were used in all subjects.

Indirect ELISA for Determining sIgE

Wells of microplate (Corning; Corning, New York) were coated separately with 1 µg L-ACE, purified Per a 1, Per a 5, Per a 7, and Per a 9 in 100 µL of carbonate-bicarbonate buffer, pH 9.6. After blocking the empty sites on the well surface, individual serum samples (diluted to 1:2) were added appropriately. Biotin-conjugated mouse anti-human IgE (SouthernBiotech, Birmingham, Alabama), streptavidin-horseradish peroxidase conjugate (SouthernBiotech), and 2,2'-azino-bis (3-ethylbenzthiazoline-6-sulphonic acid; ABTS) substrate (SeraCare Life Sciences, Inc, Milford, Massachusetts) were used for color development. The OD_{405nm} of the content in each well was determined against blank (wells added with PBS instead of serum sample). An OD_{405nm} ≥ 0.05 above background was considered positive.

Statistical Analysis

Statistical analysis was performed using the SPSS program, version 18.0 (SPSS Inc, Chicago, Illinois). Two-by-two tables were used to calculate the percent sensitivities, specificities, positive predictive values (PPVs), negative predictive values (NPVs), and correlation of the sIgE measurements against individual allergens with the SPT. The receiver operating characteristic (ROC) curve was generated to evaluate the diagnostic capacity of the test for specific IgE levels. In this study, sIgE levels to L-ACE, Per a 1, Per a 5, Per a 7, and Per a 9

Table 1
Background Information of the *P. americana* Allergic Patients and Results of SPT to Commercial Allergenic Extracts, sIgE Determination by Using ImmunoCap Test Kit, and in-House Indirect ELISA

Subject	Sex	Age (years)	Result of SPT (mm) ^a	ImmunoCap specific serum IgE to <i>P. americana</i> extract (kU/L)	In-house indirect ELISA OD _{405nm} of specific serum IgE to				
					<i>P. americana</i> extract	Per a 1	Per a 5	Per a 7	Per a 9
P1	F	25	CR(25) Dp(10)	0.45	0.337	0.033	0.207	0.460	0.250
P2	F	33	CR(16) Dp(4)	1.87	0.133	0.239	0.179	0.263	0.315
P3	M	53	CR(9)	1.18	0.160	0.198	0.181	0.157	0.255
P4	M	19	CR(16) Dp(9)	0	0.040	0.089	0.104	0.115	0.135
P5	M	29	CR(20) Dp(16)	0	0.025	0.110	0.102	0.036	0.113
P6	M	22	CR(20) Dp(12)	0	0.089	0.132	0.136	0.013	0.159
P7	M	37	CR(16) Dp(4)	0	0.078	0.113	0.078	0.038	0.143
P8	F	31	CR(9) Dp(4)	0.65	0.035	0.211	0.079	0.155	0.165
P9	M	17	CR(42) Dp(16)	0	0.003	0.086	0.143	0.048	0.131
P10	M	19	CR(30) Dp(20)	2.62	0.196	0.115	0.108	0.116	0.150
P11	M	22	CR(9)	1.86	0.184	0.068	0.191	0.133	0.085
P12	M	33	CR(20) Dp(16)	0	0.103	0.092	0.134	0.117	0.311
P13	F	29	CR(9)	0	0.091	0.036	0.099	0.019	0.082
P14	M	54	CR(25) Dp(20)	0.35	0.106	0.050	0.149	0.176	0.172
P15	F	58	CR(42) Dp(9)	0	0.012	0.013	0.171	0.005	0.065
P16	M	38	CR(56) Dp(16)	0	0.007	0.074	0.128	0.055	0.144
P17	M	53	CR(30) Dp(10)	0.6	0.038	0.154	0.09	0.142	0.176
P18	M	32	CR(9) Dp(4)	0	0.078	0.301	0.274	0.210	0.373
P19	F	24	CR(20) Dp(9)	0	0.049	0.047	0.076	0.036	0.079
P20	F	54	CR(49) Dp(42)	0	0.089	0.077	0.150	0.273	0.196
P21	M	43	CR(9) Dp(4)	0	0.032	0.082	0.095	0.127	0.153
P22	F	23	CR(20) Dp(10)	4.34	0.162	0.157	0.160	0.451	0.079
P23	M	31	CR(35) Dp(12)	0	0.084	0.226	0.200	0.199	0.209
P24	F	22	CR(9)	0	0.021	0.222	0.094	0.058	0.139
P25	F	37	CR(20) Dp(12)	0	0.033	0.243	0.244	0.120	0.286
P26	F	19	CR(9) Dp(4)	0	0.059	0.088	0.091	0.034	0.068
P27	F	27	CR(9)	0	0.102	0.106	0.259	0.024	0.165
P28	F	43	CR(9)	0	0.105	0.290	0.145	0.162	0.394
P29	M	21	CR(9)	0	0.037	0.068	0.137	0.082	0.152
P30	F	51	CR(9)	0	0.086	0.074	0.076	0.002	0.079
P31	F	57	CR(16) Dp(10)	1.06	0.153	0.267	0.225	0.108	0.272
P32	F	53	CR(12) Dp(4)	0	0.072	0.116	0.084	0.012	0.087
P33	F	29	CR(16) Dp(10)	0	0.337	0.140	0.106	0.308	0.180
P34	M	56	CR(30) Dp(20)	2.68	0.409	0.149	0.100	0.454	0.180
P35	F	43	CR(12) Dp(9)	0	0.004	0.146	0.107	0.016	0.126
P36	F	47	CR(10)	0	0.019	0.097	0.054	0.046	0.064
P37	M	21	CR(35) Dp(16)	0	0.069	0.345	0.223	0.111	0.245
P38	M	32	CR(20) Dp(9)	2.59	0.126	0.278	0.149	0.235	0.267
P39	M	34	CR(20) Dp(4)	2.33	0.156	0.128	0.154	0.015	0.169
P40	F	20	CR(16)	0	0	0.199	0.163	0.119	0.274
P41	M	28	CR(9)	0	0	0.115	0.079	0.017	0.141
P42	F	52	CR(9) Dp(4)	0	0.060	0.240	0.178	0.133	0.210
P43	M	21	CR(16) Dp(10)	0.8	0	0.159	0.131	0.075	0.199
P44	M	23	CR(9) Dp(6)	0	0.017	0.267	0.446	0.202	0.358
P45	M	21	CR(30) Dp(16)	1.9	0.163	0.140	0.09	0.082	0.171
P46	F	22	CR(16) Dp(10)	0	0.045	0.194	0.219	0.129	0.172
CP1	M	21	Dp(20)	0	0.078	0.082	0.017	0.113	0.084
CP2	M	25	Dp(16)	0	0.022	0.053	0.023	0.071	0.023
CP3	F	35	Dp(25)	0	0.099	0.016	0.024	0.128	0.054
CP4	M	24	Dp(30)	0	0.054	0.058	0.020	0.032	0.014
CP5	M	32	Dp(9)	0	0.077	0.032	0.030	0.050	0.011
CP6	F	50	Dp(4)	0	0.068	0.026	0.017	0.014	0.013
CP7	F	31	Dp(16)	0	0.083	0.063	0.065	0.037	0.022
CP8	M	40	Dp(20)	0	0.11	0.108	0.132	0.111	0.056
CP9	M	55	Dp(9)	0	0.05	0.012	0.019	0.028	0.037
CP10	F	33	Dp(56)	0	0.066	0.010	0.016	0.033	0.011
CP11	F	24	Dp(63)	0	0.093	0.099	0.024	0.121	0.013
CP12	F	18	Dp(9)	0	0.04	0.023	0.004	0.085	0.006
CP13	M	38	Dp(42)	0	0.078	0.019	0.012	0.096	0.123
CP14	M	37	Dp(30)	0	0.063	0.056	0.049	0.059	0.022
CP15	M	40	Dp(20)	0	0.093	0.041	0.081	0.156	0.048
CP16	M	43	Dp(70)	0	0.078	0.028	0.014	0.012	0.004
CP17	F	19	Dp(9)	0	0.074	0.014	0.046	0.068	0.032
CP18	F	41	Dp(20)	0	0.064	0.039	0.061	0.021	0.016
CP19	F	24	Dp(16)	0	0.083	0.015	0.101	0.123	0.025
CP20	F	39	Dp(4)	0	0.04	0.032	0.024	0.027	0.028

Abbreviations: AR, Allergic rhinitis; CP, control patients who had allergic rhinitis and positive SPT to house dust mite extract; CR, *P. americana* extract; Dp, *Dermatophagoides pteronyssinus* extract; ELISA, enzyme-linked immunosorbent assay; F, female; kU/L, Kilo-allergy units/liter; M, male; P, Patient with allergic rhinitis; SPT, skin prick test.

and ImmunoCap IgE were compared with values of wheal size of patients by the C-ACE SPT (clinically relevant method for cockroach allergy diagnosis). The areas under the curve and standard errors under the nonparametric assumption were calculated using the SPSS program to quantify the accuracy of the test. *P* values < .05 were considered statistically significant.

Results

Fifteen patients (32.6%) were positive for sIgE as determined by the ImmunoCap sIgE measurement, whereas none of the control patients was positive. The results of the indirect ELISA to measure sIgE of the patients and control patients to the L-ACE and the purified native Per a 1, Per a 5, Per a 7, and Per a 9 are shown in Table 1 and Figure 1. Performance of the sIgE ELISAs to L-ACE, Per a 1, Per a 5, Per a 7, and Per a 9 in comparison with the SPT results using C-ACE are given in Table 2.

The ROC curves for sIgE levels to L-ACE, Per a 1, Per a 5, Per a 7, Per a 9, and ImmunoCap IgE are illustrated in Figure 2. The areas under the ROC curves for the ImmunoCap IgE and sIgE to L-ACE, Per a 1, Per a 5, Per a 7, and Per a 9 are shown in Table 2. The ROC curves of individual major allergens (locally produced CRDs) were significantly different from that of the crude extract (L-ACE) (*P* < .05) (Fig 2). The ROC curves of Per a 1, Per a 5, and Per a 9 were similar but were all different from Per a 7 and ImmunoCap IgE (*P* < .05).

Spearman's rank correlation coefficients (*R*) of the SPT to L-ACE and the sIgE to L-ACE, Per a 1, Per a 5, Per a 7, and Per a 9 and ImmunoCap IgE were 0.133, 0.278, 0.419, 0.280, and 0.432.

The correlation coefficients of Per a 5 and Per a 9 to the C-ACE SPT were not different statistically (0.419 vs 0.432; *P* > .05) but were different from Per a 1.

Discussion

The concordance of the SPT using C-ACE and the ImmunoCap sIgE measurement in this study was low, which is similar to some other IgE-mediated allergies, such as pollen.²⁶ The cockroach extract contains both allergenic and nonallergenic components in variable proportions; some of the components are of diagnostic significance (clinically relevant), whereas many others are less so or not useful for diagnosis. The crude extract may contain cross-reactive components that react to serum IgE of the patients that had been incited by allergens of other sources. A new approach for increasing accuracy and clinical relevancy of sIgE measurement is desirable, particularly where the clinical case history is uncertain, patients cannot be abstained from antihistaminergic drugs before skin testing, or for infants.

Component-resolved (molecular) diagnosis using either purified native or recombinant allergens to quantify sIgE levels to individual allergens has gained increased acceptance and utility in the clinic and has been shown as a valuable tool in diagnosis of allergies such as those provoked by pollens, food, or house dust mite.^{26,34–37} By comparing the areas under the ROC curves for the sIgE of L-ACE and the purified Per a 1, Per a 5, Per a 7, and Per a 9, individual CRDs were seen to have performed better than the crude extract and also better than the ImmunoCap IgE. Among the CRDs, the Per a 1, Per a 5, and Per a 9 performed better than the Per a 7. The Per a 7 was previously found to bind IgE in 57% of ACR-allergic Thais.¹⁷ Although this allergen can be regarded as the American cockroach major allergen, its allergenicity was lower than the Per a 1, Per a 5, and Per a 9, which bound to serum IgE of 100% of the American cockroach-allergic patients that were tested.^{8,14,17} This might account for the inferior performance of the Per a 7 to the other 3 CRDs.

Although the ROC curves of Per a 1, Per a 5, and Per a 9 looked similar, when the performance of the 3 allergens in the diagnostic

Table 2
Performance of sIgE Detection by ImmunoCap IgE and in-House Indirect ELISA in Comparison with Skin Prick Test (SPT) to Commercial Crude Cockroach (C-ACE) Extract among Patients with Allergic Rhinitis

Test	Area under ROC curve $\pm$ standard error	Asymptotic significance	Asymptotic 95% confidence interval (CI) Lower bound Upper bound	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
ImmunoCap IgE	0.663 $\pm$ 0.066	0.036	0.533 0.793	33	100	100	39.22
Indirect ELISA to:							
<i>P. americana</i> extract	0.502 $\pm$ 0.069	0.978	0.367 0.638	26	100	100	37.04
Per a 1	0.914 $\pm$ 0.035	0.000	0.845 0.983	87	85	93.02	73.91
Per a 5	0.953 $\pm$ 0.028	0.000	0.898 1.000	98	85	93.75	94.44
Per a 7	0.643 $\pm$ 0.067	0.066	0.513 0.774	54	70	80.64	40.00
Per a 9	0.982 $\pm$ 0.014	0.000	0.954 1.000	98	90	95.74	94.74

Abbreviations: C-ACE, commercial crude cockroach; CI, confidence interval; ELISA, enzyme-linked immunosorbent assay; IgE, immunoglobulin E; ROC, receiver operating characteristic; SPT, skin prick test.

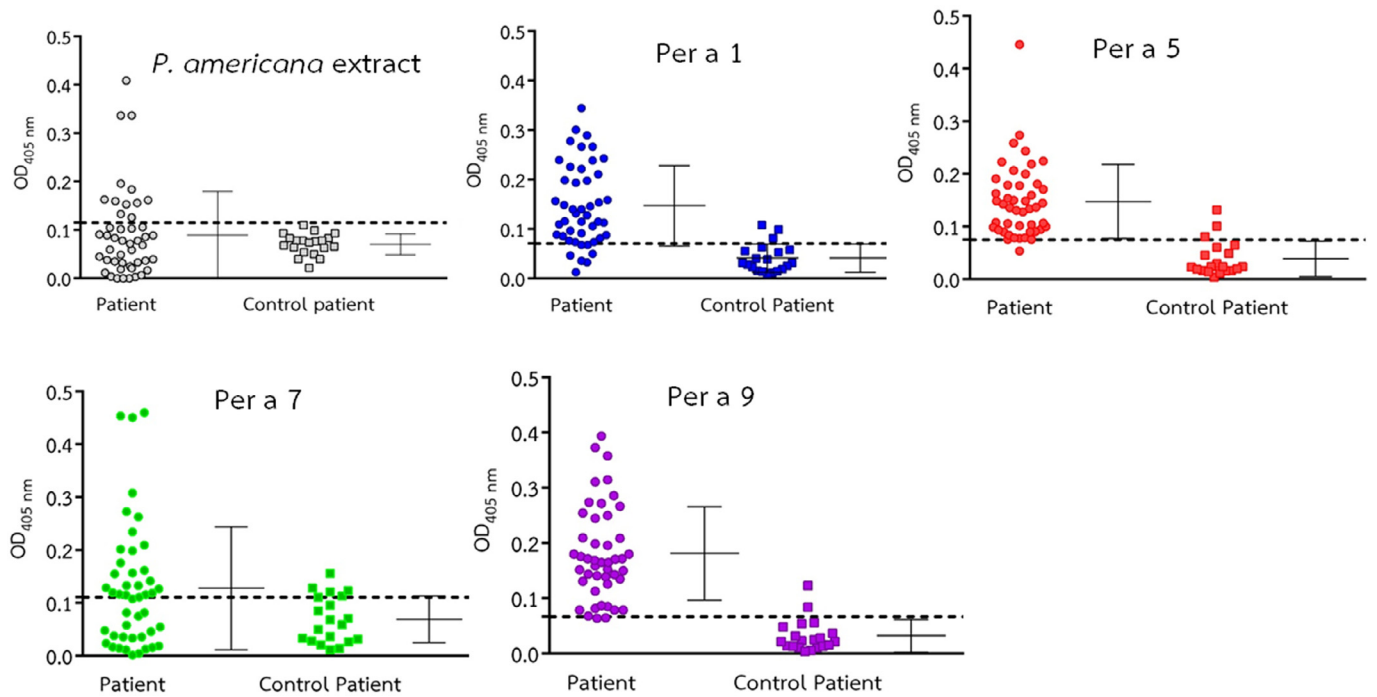


Figure 1. Results of in-house indirect enzyme-linked immunosorbent assay of the sera of 46 patients who were clinically diagnosed with chronic allergic rhinitis and positive SPT to commercial cockroach extract (patients) in comparison with 20 control patients (allergic rhinitis positive SPT to commercial *Dermatophagoides pteronyssinus* extract but negative SPT to commercial cockroach extract) using locally produced American cockroach crude extract (gray circles vs gray squares) and component-resolved diagnostics, ie, purified, native Per a 1 (blue circles vs squares), Per a 5 (red circles vs squares), Per a 7 (green circles vs squares), and Per a 9 (purple circles vs squares). Abbreviation: SPT, skin prick test.

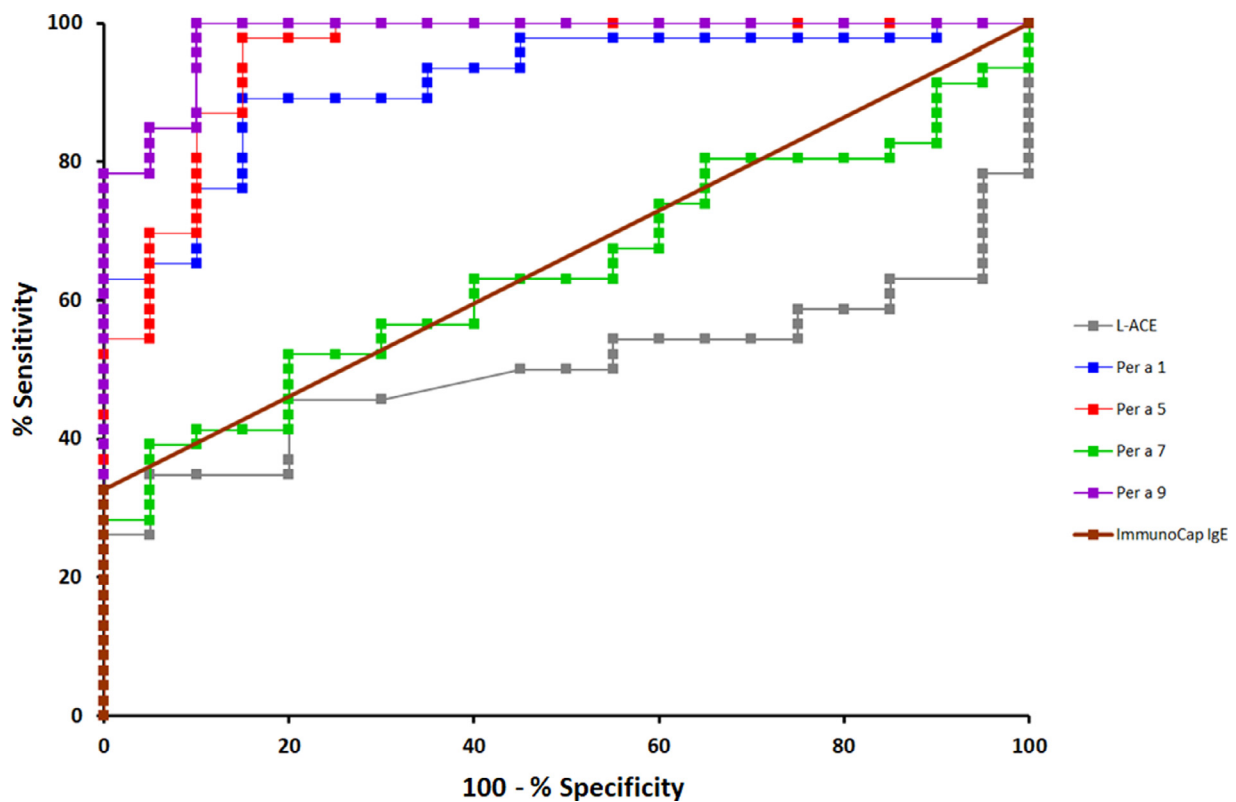


Figure 2. Receiver operating characteristic curves showing percent sensitivity (Y-axis, true-positive rates) plotted against the percent specificity (X-axis, false-positive rates) for sIgE levels to locally produced American cockroach crude extract (gray), Per a 1 (light blue), Per a 5 (red), Per a 7 (green), and Per a 9 (purple) and ImmunoCap IgE (brown).

tests, that is, percent sensitivity, specificity, PPV, and NPV, also was considered, the performance of Per a 9 was superior to Per a 1 and Per a 5.

Definite diagnosis (gold standard method) of cockroach sensitization should be the nasal/bronchial challenge test. Nevertheless, the method is not performed routinely in most allergy clinics in Thailand. The clinical history and the SPT-positive results to commercial cockroach extract were used for the clinical relevancy following the “Allergic Rhinitis and its Impact on Asthma (ARIA) guideline,” which was developed in collaboration with the World Health Organization and global clinical practice. The overall data of this study indicated a high concordance and cogent agreement between SPT against C-ACE and sIgE to Per a 9. Therefore, we recommend that sIgE to purified, native Per a 9 should be considered an alternative to SPT to C-ACE as an adjunct to the clinical history in diagnosis of sensitization/allergy to the American cockroach. To our knowledge, this is the first report on component-resolved diagnosis of American cockroach allergy.

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