

Ara h 2 Is the Best Predictor for Peanut Allergy in Adults

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What is already known about this topic? The diagnostic accuracy of specific IgE to Ara h 2 to diagnose peanut allergy in pediatric populations is high.

What does this article add to our knowledge? Specific IgE to Ara h 2 is the best predictor for peanut allergy in an adult population.

How does this study impact current management guidelines? Specific IgE to Ara h 2 in adults accurately diagnoses peanut allergy but cannot properly exclude peanut allergy or discriminate between mild or severe allergy in individual patients.

BACKGROUND: Specific IgE (sIgE) to Ara h 2 as a clinical predictor for peanut allergy in children has a diagnostic value comparable with a prediction model that contains sex, skin prick test (SPT), sIgE to peanut extract, and total IgE minus sIgE. In adults, the diagnostic value of peanut components has not yet been studied.

OBJECTIVE: To validate a pediatric prediction model in an adult population; to define the diagnostic value of sIgE to peanut components.

METHODS: Validation was performed by discrimination with an area under the receiver operating characteristic curve (AUC) and calibration with the Hosmer-Lemeshow test. The diagnostic value of the peanut components was assessed with the AUC.

RESULTS: Validation of the pediatric model in 94 adults showed poor discrimination (AUC, 0.64) but good calibration ($P = .48$); sIgE to Ara h 2 was the best diagnostic predictor (AUC, 0.76).

By using a cutoff value with a 100% positive predictive value

(≥ 1.75 kU/L), 28% of patients could be diagnosed with 100% accuracy. The highest negative predictive value was 63%. A higher negative predictive value could not be calculated for any other test. Although sIgE to Ara h 2 was significantly correlated with severity, it did not discriminate between mild and severe allergy in individual patients (AUC < 0.65).

CONCLUSION: sIgE to Ara h 2 has the best discriminative ability of all diagnostic tests. It can accurately diagnose peanut allergy in 28% of patients but cannot be used to exclude a peanut allergy in an adult population. © 2013 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2013;1:632-8)

Key words: Adults; Ara h 2; Food challenge; Peanut allergy; Peanut components; Diagnostic prediction model; Severity; Skin prick test; Specific IgE; Validation

Peanut allergy is one of the most common food allergies worldwide, with sometimes severe consequences.^{1,2} In the past decade, the prevalence seems to be increasing.^{3,4} The reference standard to diagnose peanut allergy is the double blind, placebo-controlled food challenge (DBPCFC). This test is time consuming and stressful for the patient, has high costs, and requires high standard hospital facilities.^{2,5,6} Routine tests to diagnose peanut allergy, such as specific IgE (sIgE) and skin prick test (SPT) reactivity to peanut, perform suboptimally with an area under the receiver operating characteristic curve (AUC) ranging from 0.77 to 0.87 for sIgE to peanut extract and 0.79 to 0.93 for SPT.⁷⁻¹⁰ Cutoff values for sIgE to peanut extract and SPT with a 95% positive predictive value (PPV) have been calculated and validated in the past, which could be used to reduce the need for DBPCFCs.^{7,8,11}

One way of further improving diagnostics is to combine several clinical characteristics and diagnostic tests into 1 diagnostic prediction model, as recently published by DunnGalvin et al.¹² It is known that prediction models perform better in the population in which they were built.^{9,13-15} Therefore, we validated the model of DunnGalvin et al.¹² in a tertiary Dutch pediatric population of patients with suspected peanut allergy.⁹ Validation by discrimination was good, but calibration was poor. Discrimination (diagnostic value) was assessed with an AUC, calibration (agreement between predicted and observed frequencies of peanut allergy in the study

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Abbreviations used

AUC- Area under the curve

CI- Confidence interval

DBPCFC- Double-blind, placebo-controlled food challenge

IgE- Immunoglobulin E

LR⁻- Negative likelihood ratio

LR⁺- Positive likelihood ratio

NPV- Negative predictive value

OR- Odds ratio

PPV- Positive predictive value

ROC- Receiver operating characteristic

SD- Standard deviation

sIgE- Specific immunoglobulin E

SPT- Skin prick test

population) with a calibration plot and Hosmer-Lemeshow test. Because of the poor calibration, the model was updated, which resulted in a model that contained 4 predictors from the original model: sex, SPT, sIgE to peanut extract, and total IgE minus sIgE to peanut extract. sIgE to Ara h 2 did not add significantly to this updated model, with an AUC of 0.94. However, sIgE to Ara h 2 as a single predictor in the same study showed an AUC of 0.90. In other recent studies, sIgE to Ara h 2 had an AUC of 0.90-0.99.¹⁶⁻²⁰ However, all these studies focused mainly on children. The diagnostic value of peanut components in an adult population is not known yet. In addition, our updated pediatric diagnostic prediction model should be validated in an adult population.⁹

The objective of the current study was to validate our updated pediatric diagnostic model in an adult population and, if necessary, to build a new diagnostic prediction model. We also analyzed the single and combined diagnostic values of the peanut components and their possible correlation with clinical severity.

METHODS

Patients

All adult patients (n = 136) who underwent a DBPCFC with peanut between 2002 and 2012 at the University Medical Centre Utrecht, The Netherlands, were included. One patient was excluded because of an inconclusive DBPCFC (Figure 1). A DBPCFC was conducted either with a diagnostic purpose if peanut allergy was suspected based on history, regardless of sensitization by SPT or sIgE to peanut extract (diagnostic group, n = 94) or as part of 2 previous studies performed at our center (previous study group, n = 41) (Figure 1).^{21,22} In the diagnostic group, 19 patients had a sIgE level <0.35 kU/L to peanut extract and an SPT <3 mm, and, therefore, were not sensitized to peanut.

The 41 patients in the study group were preselected because sensitization was required for recruitment, which resulted in significant differences between the diagnostic group and the study group with regard to sIgE to peanut extract (median, 2.1 kU/L vs 15.7 kU/L; *P* = .001) and SPT reactivity (median, 5.0 mm vs 9.3 mm; *P* = .001). To avoid selection bias, the 41 patients in the study group were only used to analyze the correlation between sIgE to peanut components and severity, and were excluded for analyses regarding the diagnostics of peanut allergy. As a consequence, 3 patients with a negative challenge from the study group were excluded because they could not be used for any analysis.

Outcome

A DBPCFC was performed in all patients to diagnose or exclude a peanut allergy. The challenge was performed according

to the international consensus protocol with the recipe described by Peeters et al.^{22,23} The challenge was discontinued and considered positive in case of objective symptoms or if a severe, suggestive subjective symptom occurred on at least 3 subsequent doses and lasted for >45 minutes.

Diagnostic predictors

Histories regarding previous reactions to peanut were drawn from patient records. The SPT was performed with peanut extract (ALK-Abello, Nieuwegein, The Netherlands), with histamine dihydrochloride 10 mg/mL and glycerol diluent as positive and negative controls. SPT reactivity was recorded after 15 minutes. Total and sIgE to peanut extract and the peanut components Ara h 1, Ara h 2, Ara h 3, Ara h 8, and Ara h 9 were determined by using the ImmunoCAP method (Thermo Fisher Scientific, Uppsala, Sweden) by using serum collected before the DBPCFC was performed. All measurements were performed by using a uniform batch of reagents. The SPT and sIgE results were analyzed as continuous variables. In 9 patients, a new blood sample had to be taken because no serum from the past was left. The study was approved by the local ethics committee.

Severity

We used 3 different outcome measures for severity: an adapted Mueller score for history or food challenge, and a severity score, based on the combination of the adapted Mueller score for the food challenge and the eliciting dose. The adapted Mueller score was divided into 5 categories as previously described: 0, oral symptoms; 1, cutaneous symptoms; 2, gastrointestinal symptoms; 3, respiratory symptoms; 4, cardiovascular symptoms.^{24,25} The severity score was assessed as follows: the Mueller score at the DBPCFC, which ranged from 0 to 4 plus 1 (to avoid calculating with 0) times the dose score. The dose score ranged from 1 to 10, which corresponded with the 10 peanut doses that ranged from 1 µg to 10 g.^{25,26} This resulted in a severity score that ranged from 1 to 50.

Study design

The study consisted of 3 phases: (1) validation of our updated pediatric diagnostic prediction model (phase 1a) and, if necessary, building a new diagnostic prediction model for adults (phase 1b); (2) assessment of the diagnostic value of sIgE to peanut-specific components (Ara h 1, 2, 3, 8, and 9), both by univariate and multivariate analysis compared with currently used SPT and sIgE; and (3) correlation of severity to the different diagnostic tests.

Data analysis

For phase 1a (validation), data regarding sex, sIgE, SPT, and total IgE minus sIgE was required. Of the 94 patients in the diagnostic group, SPT data were missing in 14 patients (Figure 1). No significant differences were found between these 14 patients and the remaining 80 patients with regard to the other 3 variables used in the prediction model.

For each patient, the probability of having peanut allergy was calculated by the following formula by using the regression coefficients of the updated pediatric prediction model: $\exp(-1.77 + [-1.93 \times \text{sex}] + [0.25 \times \text{SPT in mm}] + [0.15 \times \text{sIgE peanut}] + [-0.002 \times \{\text{total IgE} - \text{sIgE peanut}\}]) / (1 + \exp[-1.77 + [-1.93 \times \text{sex}] + [0.25 \times \text{SPT in mm}] + [0.15 \times \text{sIgE peanut}] + [-0.002 \times \{\text{total IgE} - \text{sIgE peanut}\}])$.⁹ Discrimination and calibration of the model were analyzed as earlier described.^{9,27} In short, discrimination was assessed with an AUC, which is a measure of how well a diagnostic test can

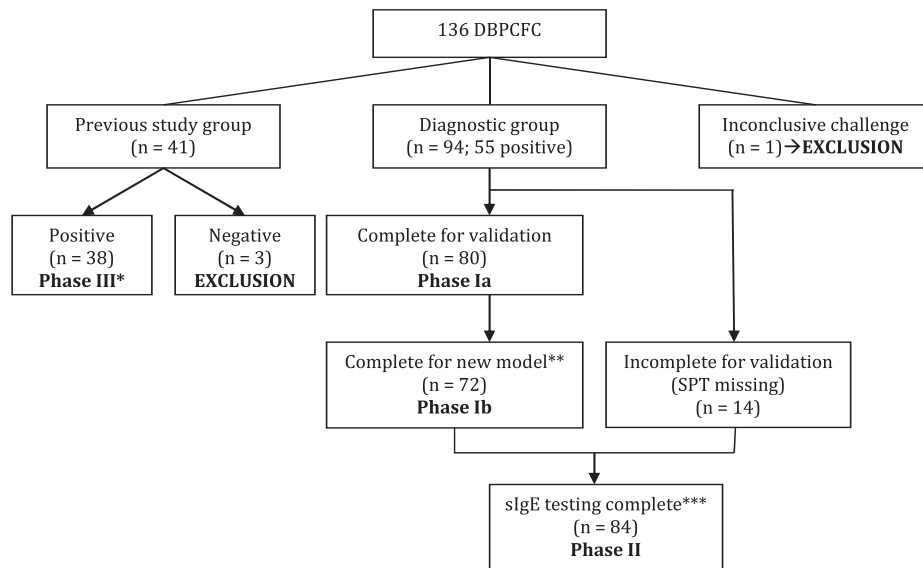


FIGURE 1. Patients used for different analyses. *Together with positive challenges from diagnostic group used for phase 3 analysis regarding correlation with severity. **Both SPT data and sIgE to most peanut components available, in 8 patients sIgE to Ara h 2 could not be assessed. ***In 1 patient sIgE to Ara h 8 and in 1 patient sIgE to Ara h 9 could not be assessed.

distinguish between 2 diagnostic groups (in this case, patients with allergy and tolerant subjects). A value of 0.5 indicates “no discrimination,” and a value of 1 indicates “perfect discrimination.” Calibration was assessed with a calibration plot, which compares observed versus predicted outcomes, and the Hosmer-Lemeshow test, in which a P value $< .05$ indicates poor calibration.²⁸ Different cutoff points were used to calculate sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV), and positive likelihood ratio (LR^+) and negative likelihood ratio (LR^-).²⁹ In case of poor validation (phase 1b), a new multivariate logistic regression analysis would be performed by a stepwise forward method with the probability of entering a variable .05 and removing a variable .10. Discrimination and calibration of this possible new model would be assessed as described before.

In phase 2, we assessed the diagnostic value of sIgE to Ara h 1, 2, 3, 8, and 9 by the AUC and compared it with the most often used history, SPT, and sIgE to peanut extract. In addition, a multivariate logistic regression analysis was performed as described before with sIgE to the peanut components as candidate predictors. In 10 patients of the diagnostic group, data on sIgE to at least one of these peanut components was missing (Figure 1). However, we found no significant differences between these 10 patients, and the remaining patients of the diagnostic group with regard to sex, age, atopic features, sIgE to peanut extract, or SPT. In phase 3, the different diagnostic tests were related to severity. The Spearman rho correlation was used for these analyses. All analyses were performed with SPSS version 20.0 (SPSS Inc, Chicago, Ill). The calibration plot was made by using Microsoft Office Excel 2003 (Microsoft Corp, Redmond, Wash).

RESULTS

Patients

Patient characteristics of the diagnostic group are listed in Table I. The mean (SD) age was 30 ± 12.5 years, with 37.2% being men. Significant differences between the group with peanut allergy and the peanut-tolerant group were found for age

(26.5 vs 35 years), SPT wheal (8 vs 3.3 mm), sIgE to peanut extract (3.5 vs 0.49 kU/L), and sIgE to Ara h 2 (1 vs 0.06 kU/L) when analyzing the 95% CIs of the odds ratios (Table I). The patient characteristics of the patients with peanut allergy in the previous study group ($n = 38$), who were only used for the severity analyses, can be found in Table E1 (in this article's Online Repository at www.jaci-inpractice.org).

Phase 1: Validation of the pediatric diagnostic prediction model in the adult population was poor

The probability of peanut allergy for every patient was calculated by using the formula as described in the Methods section. Validation by means of discrimination showed an AUC of 0.64. The best combination of PPV and NPV was found when using a cutoff value of a probability of ≥ 0.7 , with a PPV of 100% and an NPV of 48%. Corresponding sensitivity and specificity were 35% and 100%, respectively, with a LR^+ of infinity and LR^- of 0.65. The calibration plot, which compares predicted probabilities of peanut allergy with observed patients with peanut allergy in our study population, showed data points around the reference line, which indicates good calibration (Figure 2). This also was shown by the Hosmer-Lemeshow test, with a P value of .48.

Because of the poor validation by discrimination, we built a new model specific for an adult population. We chose a maximum of 4 candidate predictors based on literature and our univariate analyses to minimize the risk of overfitting: sIgE to peanut extract and Ara h 2, SPT reactivity, and age. In addition to the 14 patients with missing SPT data, sIgE to Ara h 2 could not be assessed in 8 patients because of a lack of serum, which left 72 patients of the diagnostic group ($n = 94$) to build a new model (Figure 1). No significant differences were found between the 8 patients with missing Ara h 2 data and the remaining 72 patients with regard to the other 3 candidate predictors: SPT, sIgE to peanut, and age. When entering the 4 candidate predictors in a multivariate logistic regression model, only SPT was included in the final model with an AUC of 0.72. The best

TABLE I. Patient characteristics of the diagnostic group*

	Total diagnostic (N = 94)	Peanut allergic (N = 55)	Peanut tolerant (N = 39)	Odds ratio (95% CI)
Men	35 (37)	21 (38)	14 (36)	1.1 (0.47-2.58)
Age (y)	30 ± 12.5	26.5 ± 9.5	35 ± 16	0.95 (0.91-0.98)
SPT wheal (mm)	5 (0-9.8)	8 (2.8-15)	3.3 (0-6.0)	1.2 (1.1-1.3)
sIgE peanut extract (kUa/L)	2.1 (0.35-11)	3.5 (0.66-18)	0.49 (0.35-3.8)	1.1 (1.0-1.1)
Total IgE-sIgE peanut extract (kUa/L)	316 (72-782)	381 (87-1013)	262 (51-488)	1.0 (1.0-1.0)
sIgE Ara h 1 (kUa/L)	0.02 (0.00-0.43)	0.05 (0.00-5.1)	0.01 (0.00-0.04)	1.7 (0.91-3.0)
sIgE Ara h 2 (kUa/L)	0.20 (0.04-2.9)	1.0 (0.06-8.1)	0.06 (0.03-0.13)	3.3 (1.2-9.0)
sIgE Ara h 3 (kUa/L)	0.02 (0.01-0.11)	0.03 (0.01-0.64)	0.01 (0.01-0.03)	8.57 (0.34-215)
sIgE Ara h 8 (kUa/L)	2.0 (0.04-9.0)	2.0 (0.1-8.8)	0.72 (0.03-9.9)	1.0 (0.98-1.0)
sIgE Ara h 9 (kUa/L)	0.02 (0.00-0.07)	0.02 (0.00-0.08)	0.01 (0.00-0.06)	0.74 (0.46-1.2)
Allergic rhinitis	68 (72)	43 (78)	25 (64)	2.0 (0.80-5.0)
Atopic dermatitis	54 (57)	35 (64)	19 (49)	1.8 (0.80-4.2)
Allergic asthma	50 (53)	32 (58)	18 (46)	1.6 (0.71-3.7)
History, Mueller score†				
0	38 (40)	26 (47)	12 (31)	Reference category
1	6 (7)	2 (4)	4 (10)	0.23 (0.04-1.4)
2	19 (20)	14 (26)	5 (13)	1.2 (0.35-4.1)
3	14 (13)	6 (11)	8 (21)	0.29 (0.08-1.1)
4	6 (7)	6 (11)	0 (0)	2.8 (0.30-26)

*Data represent medians (interquartile ranges), means ± SDs, or no. (%).

†History was not clear in 11 patients (12%), 3 in the peanut allergic group (6%), and 9 in peanut tolerant group (23%).

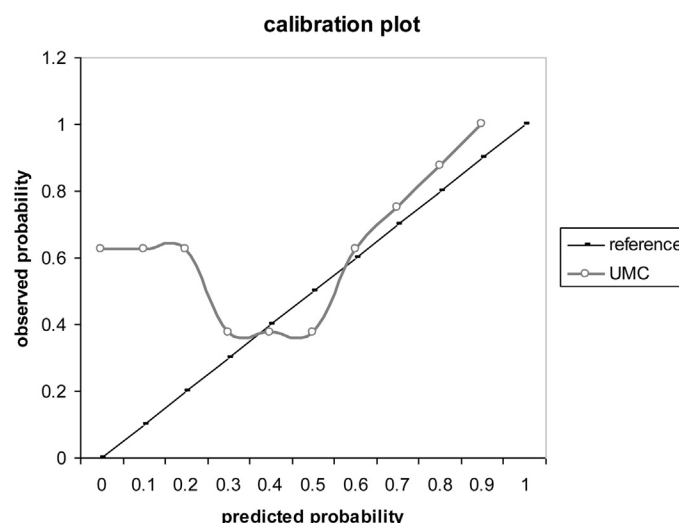


FIGURE 2. Calibration plot of the pediatric prediction model in our adult population.

combination of PPV and NPV was found when using a cutoff value of ≥ 15 mm with a PPV of 100% and a NPV of 49% (Table II). Corresponding sensitivity and specificity were 26% and 100%, respectively, with LR^+ of infinity and LR^- of 0.74. By using this cutoff value with a 100% PPV, peanut allergy could be predicted in 12.5% of patients with 100% certainty.

Phase 2: sIgE to Ara h 2 has the best diagnostic value of all peanut components

Ara h 2 had the best discriminative ability of all peanut components (AUC, 0.76) (Figure 3). This value also was higher compared with the currently used history, SPT, and sIgE to peanut extract (AUC, 0.67, 0.72, and 0.70, respectively) (Figure 3). The

difference with SPT and sIgE to peanut extract, however, was not significantly different (P values of .15 and .09, respectively).

Specific IgE to Ara h 2 was the only predictor that remained in the model when performing a multivariate analysis with sIgE to Ara h 1, 2, 3, and peanut extract as candidate predictors. Because the highest AUC with both univariate and multivariate analysis was found for sIgE to Ara h 2, we used several cutoff points to calculate PPV, NPV, sensitivity, specificity, LR^+ , and LR^- (Table III). The best combination of PPV and NPV was found by using a cutoff point of ≥ 1.0 kU/L (93% PPV and 54% NPV) with corresponding sensitivity, specificity, LR^+ , and LR^- of 57%, 94%, 9.5, and 0.46, respectively. A 100% PPV was found when using a cutoff value of ≥ 1.75 kU/L (Table III). Twenty-eight

TABLE II. Diagnostic value of the predictor SPT in mm for different cutoff points

Cutoff point (mm)	PPV (%)	NPV (%)	Sensitivity (%)	Specificity (%)	LR ⁺	LR ⁻
≥3	66	52	66	52	1.38	0.65
≥5	76	59	66	70	2.22	0.49
≥8	88	56	51	86	3.64	0.57
≥10	91	49	34	84	2.13	0.79
≥15	100	49	26	100	Infinity	0.74

percent of all the patients had a higher value than this cutoff and, therefore, could be predicted as being peanut allergic with 100% certainty. A 95% PPV was calculated at a cutoff value of ≥ 1.32 kU/L. The highest NPV was 63% when using a cutoff value for Ara h 2 of ≥ 0.1 kU/L, which was comparable with the SPT when a cutoff value of ≥ 5 mm was used (59%). It was not possible to calculate a higher NPV with any of the other diagnostic tests.

Phase 3: Ara h 2 was correlated to clinical severity as assessed in 3 different ways

In phase 3, all 93 patients with a positive food challenge to peanut (55 from the diagnostic group and 38 from the study group) were used to analyze the relationship between the diagnostic tests and clinical severity as assessed in 3 different ways (Figure 1). The sIgE to Ara h 2 was the only diagnostic test that significantly correlated with clinical severity with all 3 methods of scoring severity: Mueller based on history, Mueller based on food challenge and severity score (*P* values of .007, <.001, and .030, respectively; Spearman rho) (Table IV). However, also for sIgE to peanut extract, Ara h 1, and Ara h 3, there was a trend of higher sIgE values with a more severe reaction. In contrast, there was a significantly negative correlation between sIgE to Ara h 8 or Ara h 9 and clinical severity, but only when the adapted Mueller score based on history was used (*P* values .004 for Ara h 8 and .04 for Ara h 9, respectively). All correlations are shown in Table IV. SPT reactivity was not correlated with clinical severity.

Based on these results, we calculated the discriminative ability of sIgE to Ara h 2 between mild and severe allergy based on both history and food challenge (with Mueller 0, 1, and 2 being mild, and Mueller 3 and 4 being severe). This resulted in an AUC value of only 0.58 and 0.65, respectively, which indicates poor discrimination between mild and severe allergy. When a severe allergy was defined as a Mueller score >0 , these AUC values were 0.65 and 0.79, respectively.

DISCUSSION

In this study, we validated a pediatric prediction model for peanut allergy in an adult population suspected of peanut allergy. Because of poor validation, we analyzed a possible new model with 4 candidate predictors, which left only SPT as a predictor. The diagnostic value of sIgE to Ara h 2, however, was an even better predictor and also appeared to be correlated to clinical severity.

Validation of a prediction model is essential before it can be applied to a different patient group, in this case, an adult population.¹³⁻¹⁵ Validation by discrimination showed a striking difference between the 2 populations with an AUC of 0.64 in adults versus 0.94 in children, in which the original model was updated.⁹ This is best explained by population differences. Therefore, our pediatric model could not be generalized to this adult population. In general, prediction models tend to perform better in the original

data set on which the model was built than in the data set of another study population that is used for validation.¹³

A general rule when building a prediction model states that, for every candidate predictor, at least 10 patients with the smallest outcome are required.³⁰ To minimize the risk of overfitting, we only entered 4 candidate predictors in a multivariate logistic regression analysis: SPT, sIgE to Ara h 2 and peanut extract, and age. Our choice of the 4 predictors was based on the literature and univariate analyses of our data. We found age to be negatively correlated with severity based on history, which meant that older subjects reported milder symptoms. This could probably explain the significantly higher age in the tolerant subjects because only mild symptoms ultimately led to a smaller chance of meeting the criteria for a positive food challenge. When analyzing the 4 candidate predictors, it was interesting that only SPT was left as a predictor in the model, because the diagnostic value of sIgE to Ara h 2 as a single predictor was higher (0.76 vs 0.72). This can be explained by the type of logistic regression analysis we used.³¹ We performed the stepwise forward method in which the model is built from the most significant variable between the peanut allergic group and the peanut tolerant group, which was the SPT. Thereafter, variables that have a significant additional value in the model are included one by one. This is in contrast with the backward elimination method by starting with all candidate predictors and with every step eliminating the least contributing. Use of backward regression in our data set would result in Ara h 2 being the only predictor. The stepwise forward method was chosen to compare our results with our pediatric study, which was a validation study of the prediction model published by DunnGalvin et al,¹² in which the same method was used. This choice was supported by the fact that there is no consensus about the best method of selecting variables for a prediction model.

The diagnostic value of the SPT (AUC, 0.72), in general, was lower than that found in other studies in which the AUC ranged from 0.79 to 0.93.⁷⁻¹⁰ The cutoff value of 8 mm with a 95% PPV, as previously described by Sporik et al,¹¹ led to an 88% PPV in our population. The differences could be caused by the fact that all aforementioned studies were performed in children with sometimes different inclusion criteria. In some of these studies, many patients were included based on sensitization only, regardless of history.

The sIgE to Ara h 2 as a single predictor had the best diagnostic value of all studied diagnostic tests (AUC, 0.76), although not significantly different compared with SPT or sIgE to peanut extract. The major advantage of Ara h 2, however, is that it can be standardized. The AUC of sIgE to Ara h 2 was lower than the AUC found in recent diagnostic studies in children (AUC ranging from 0.90-0.99).^{9,16-20} In addition, the cutoff value for a 100% PPV was much lower compared with our former study in children (>1.74 kU/L vs >5.17 kU/L) but applicable to a similar number of patients (28 % vs 26%).⁹ This means that, both in children and adults, peanut allergy can be well predicted with Ara h 2. Predicting tolerance, however, seems difficult in adults, reflected by a lower AUC and very low NPV values. We think that this difference could be explained by the fact that many patients with allergy recognized the Bet v 1 related Ara h 8 (62%, vs 36% in our pediatric database). This is probably because birch pollen allergy usually becomes clinically significant at an older age. Twenty-one patients in the adult population did not recognize Ara h 2 but did have a positive food challenge (22%). These patients mainly recognized Ara h 8 (61% monosensitized) and to a lesser extent the other peanut components. Most of these patients (84%) experienced only mild symptoms after

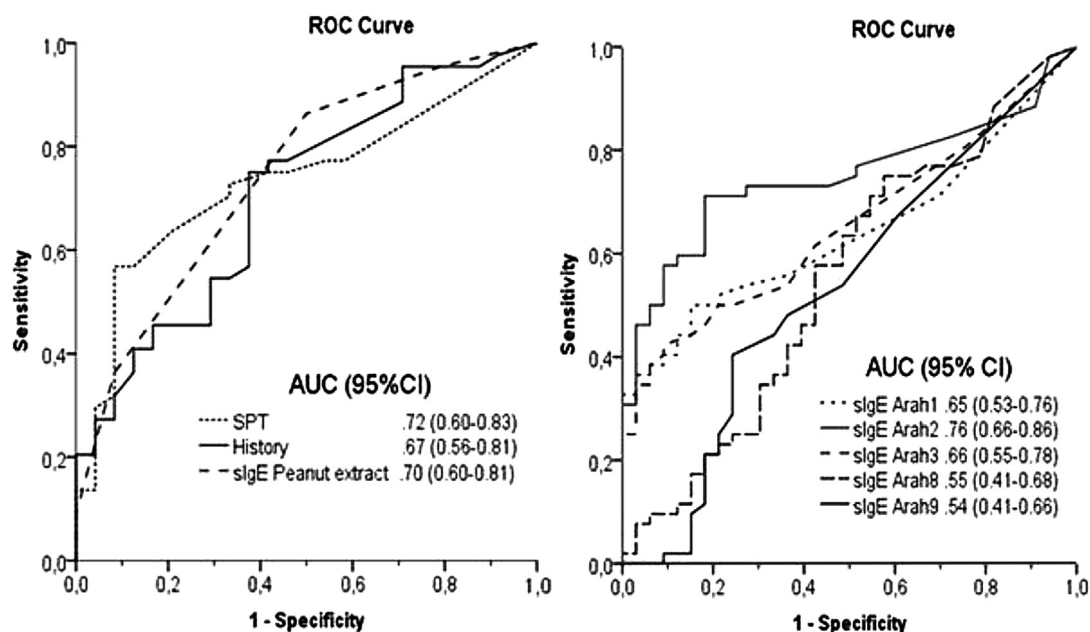


FIGURE 3. ROC curves of slgE to Ara h 1, 2, 3, 8, and 9 compared with the currently used history, SPT reactivity, and slgE to peanut extract. *ROC*, Receiver operating characteristic.

TABLE III. Diagnostic value of the predictor slgE to Ara h 2 for different cutoff values

Cutoff point (kU/L)	PPV (%)	NPV (%)	Sensitivity (%)	Specificity (%)	LR ⁺	LR ⁻
≥0.1	81	63	74	73	2.74	0.36
≥0.2	84	63	70	82	3.89	0.37
≥0.35	86	57	60	85	4.00	0.47
≥0.5	88	56	57	89	5.18	0.48
≥1.0	93	54	57	94	9.50	0.46
≥1.32	95	54	49	97	16.33	1.90
≥1.75	100	53	45	100	Infinity	1.81

the ingestion of peanut. However, Ara h 8 does not discriminate well between peanut allergy and peanut tolerance because, in the tolerant group, a large proportion of patients reacted to Ara h 8 as well (AUC, 0.55), which corresponds with other populations.^{9,16-20} In addition, the different diagnostic value between children and adults could be caused by different selection criteria. Many subjects in pediatric studies are included based on sensitization only, whereas, in our study, all adult patients had a suggestive history, regardless of sensitization.

We used 3 different methods of measuring severity because, in the literature, there is no consensus about the best method and Hourihane et al²⁶ previously described only a weak correlation between severity based on history and food challenge. Ara h 2 showed a correlation with severity when using all methods. Interestingly, Ara h 8 and Ara h 9 showed a negative correlation with severity, but this was only significant when using the severity classification based on history. In general, a similar trend was seen among the 3 different scoring methods for all diagnostic tests. Previous studies that analyzed the relationship between slgE to peanut allergens and severity had contradictory results. Peeters et al,²² in general, found a larger SPT reactivity to Ara h 1,

TABLE IV. Correlation between all diagnostic tests and severity as scored in 3 different ways

	Mueller based on history	Mueller based on food challenge	Severity score*
Ara h 1			
Correlation coefficient†	0.19	0.34	0.19
P value	.07	<.001	.08
Ara h 2			
Correlation coefficient†	0.28	0.416	0.23
P value	.01	<.001	.03
Ara h 3			
Correlation coefficient†	0.21	0.25	0.10
P value	.04	.02	.37
Ara h 8			
Correlation coefficient†	-0.29	-0.09	-0.02
P value	<.001	.43	.85
Ara h 9			
Correlation coefficient†	-0.22	-0.02	-0.04
P value	.04	.89	.68
slgE to peanut extract			
Correlation coefficient†	0.22	0.22	0.15
P value	.03	.04	.15
SPT			
Correlation coefficient†	0.13	0.17	0.09
P value	.23	.12	.43

*Combination of Mueller score based on food challenge and eliciting dose (see also the Methods section).

†Spearman's rho.

2, 3, and 6 in the case of a more-severe reaction in an adult population. A similar study in a pediatric population, however, showed no correlation between clinical severity and SPT reactivity or slgE to Ara h 1, 2, and 3.³² This finding is in agreement with our

previously published study in children,⁹ in which no significant correlation was found between clinical severity based on food challenge and sIgE to Ara h 1, 2, 3, and 8. Moverare et al³³ recently suggested that a positive sIgE value to the major peanut allergens Ara h 1, Ara h 2, and Ara h 3 is associated with severe reactions, but they did not take into account the exact sIgE values. The differences can possibly be explained by the fact that the study of Peeters et al²² and our study were conducted in adult patients only. We would like to point out that, although a correlation was seen on a population level, sIgE to Ara h 2 could not be used to predict the severity of peanut allergy in an individual patient in our study.

A possible limitation of our study was that not every subject with a suspected peanut allergy who visited our outpatient department underwent a food challenge, which could have influenced the prevalence of peanut allergy in our study population and, therefore, the exact PPV and NPV values. However, 59% of the patients were peanut allergic, which was comparable with other studies performed in children in tertiary centers (prevalence of 47%-56%).^{9,12} We also presented likelihood ratios, which are a diagnostic measure that is independent of the prevalence. With likelihood ratios, the difference between pre- and posttest probability can be assessed.²⁹ Another possible limitation to our study is that we had some missing data. However, no significant differences were found between the groups with or without missing values. The strength of this study was that we used a diagnostic design, comparable with clinical practice. In addition, we included a large cohort of adults, which, to our knowledge, has not been previously studied. All the patients in our study underwent a DBPCFC to diagnose or exclude a peanut allergy.

In conclusion, we showed that Ara h 2 has the best diagnostic value to diagnose peanut allergy in adults. Ara h 2, however, was not able to exclude a peanut allergy and could not discriminate between mild and severe allergy in individual patients, which indicates that patients with negative or low sIgE levels to Ara h 2 can still be peanut allergic and even have a severe peanut allergy. Future prospective studies should validate the cutoff values in other adult populations.

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TABLE E1. Patient characteristics study group (N = 38)*

Men	13 (34)
Age (y)	26 ± 8
SPT wheal (mm) (n = 37)	10 (7.8-14)
sIgE peanut extract (kUa/L)	17 (4.1-54)
Total IgE-sIgE peanut extract	430 (166-2434)
sIgE Ara h 1 (kUa/L)	0.35 (0.28-13)
sIgE Ara 2 (kUa/L)	2.4 (0.44-15)
sIgE Ara h 3 (kUa/L)	0.35 (0.28-4.1)
sIgE Ara h 8 (kUa/L)	3.8 (0.35-12)
sIgE Ara h 9 (kUa/L)	0.04 (0.01-0.20)
Atopic dermatitis	32 (84)
Allergic rhinitis	33 (87)
Allergic asthma	31 (82)
History	
Ingestion unknown	1 (3)
Mueller	
0	16 (42)
1	6 (16)
2	11 (29)
3	2 (5)
4	2 (5)

*Data represent medians (interquartile ranges), means ± SDs, or no. (%).