The diagnostic value of specific IgE to Ara h 2 to predict peanut allergy in children is comparable to a validated and updated diagnostic prediction model

Rob J. B. Klemans, MD,[a]* Dianne Otte, MD,[a]* Mirjam Knol, PhD,[b,c] Edward F. Knol, PhD,[a] Yolanda Meijer, MD,[d,e] Frits H. J. Gmelig-Meyling, PhD,[f] Carla A. F. M. Bruijnzeel-Koomen, MD, PhD,[a] André C. Knulst, MD, PhD,[a] and Suzanne G. M. A. Pasmans, MD, PhD[a,e] *Utrecht and Bilthoven, The Netherlands*

Background: A diagnostic prediction model for peanut allergy in children was recently published, using 6 predictors: sex, age, history, skin prick test, peanut specific immunoglobulin E (sIgE), and total IgE minus peanut sIgE.
Objectives: To validate this model and update it by adding allergic rhinitis, atopic dermatitis, and sIgE to peanut components Ara h 1, 2, 3, and 8 as candidate predictors. To develop a new model based only on sIgE to peanut components.
Methods: Validation was performed by testing discrimination (diagnostic value) with an area under the receiver operating characteristic curve and calibration (agreement between predicted and observed frequencies of peanut allergy) with the Hosmer-Lemeshow test and a calibration plot. The performance of the (updated) models was similarly analyzed.
Results: Validation of the model in 100 patients showed good discrimination (88%) but poor calibration ($P < .001$). In the updating process, age, history, and additional candidate predictors did not significantly increase discrimination, being 94%, and leaving only 4 predictors of the original model: sex, skin prick test, peanut sIgE, and total IgE minus sIgE. When building a model with sIgE to peanut components, Ara h 2 was the only predictor, with a discriminative ability of 90%. Cutoff values with 100% positive and negative predictive values could be calculated for both the updated model and sIgE to Ara h 2. In this way, the outcome of the food challenge could be predicted with 100% accuracy in 59% (updated model) and 50% (Ara h 2) of the patients.
Conclusions: Discrimination of the validated model was good; however, calibration was poor. The discriminative ability of Ara h 2 was almost comparable to that of the updated model, containing 4 predictors. With both models, the need for peanut challenges could be reduced by at least 50%. (J Allergy Clin Immunol 2013;131:157-63.)

Key words: *Diagnostics, peanut allergy, food challenge, prediction model, validation, Ara h 2*

Peanut allergy can be life threatening, and its prevalence seems to be increasing.[1-3] It has an important influence on daily life for both children and their parents, especially because of the strict elimination diet that is generally prescribed.[4-6]

The gold standard to diagnose a peanut allergy is a double-blind, placebo-controlled food challenge (DBPCFC).[7] This is a costly and, especially for young children, burdensome test demanding specialized medical facilities. It can also result in severe reactions.[8] However, other diagnostic test methods, such as specific IgE (sIgE) to peanut and skin prick test (SPT) reactivity to peanut, perform suboptimally. Studies that investigated the diagnostic value of these methods showed an area under the receiver operating characteristic curve (AUC) of 0.79 to 0.86 for SPT and 0.77 to 0.87 for sIgE to peanut, respectively.[9-11]

DunnGalvin et al[12] found that one way of improving the diagnostic accuracy without using food challenges was to combine several diagnostic tests and patient characteristics into one prediction model. Their prediction model, including sex, age, history, SPT, sIgE to peanut, and total IgE minus specific IgE to peanut as predictors, was developed by using data from 94 patients. They all underwent an oral food challenge, both open and double blind, of which 53% were positive. When validated in the same center in 30 patients, the model showed an AUC of 0.97 to predict peanut allergy. As they already indicated, validation, preferably in a similar population in another pediatric center, is an important step to verify whether such a prediction model can be implemented in a broader setting.[13-16] It is known that prediction models tend to perform better on data on which the model was built compared with the performance of the model on new data derived from another population.[16]

Another way to improve the diagnostics of peanut allergy is the determination of sIgE to peanut-specific components. Previous studies showed that sensitization particularly to Ara h 2 was useful to distinguish peanut-allergic subjects from peanut-tolerant subjects.[17-22] The AUC of sIgE to Ara h 2 in 2 of these studies ranged from 0.95 to 0.99.[19,21,22]

Given the strong need for improved diagnostics of peanut allergy without making use of food challenges, the aim of this study was to validate the promising prediction model as published by Dunn-Galvin et al[12] The validation was performed in a pediatric population from a tertiary clinic, in which all patients suspected of having a peanut allergy underwent a food challenge. Furthermore, we evaluated whether additional candidate predictors such as atopic dermatitis, allergic rhinitis, and sIgE to the peanut-specific

From [a]the Department of (Paediatric) Dermatology and Allergology, [b]the Julius Center for Health Sciences and Primary Care, [d]the Department of Paediatric Pulmonology, and [f]the Department of Immunology, University Medical Center Utrecht; [c]the Centre for Infectious Disease Control, National Institute for Public Health and the Environment, Bilthoven; and [e]the Center for Paediatric Allergology, Wilhelmina Children's Hospital, University Medical Center Utrecht.

*These authors contributed equally to this work.

This study was partially funded by an unrestricted grant from Thermo Fisher Scientific, Sweden and The Netherlands.

Disclosure of potential conflict of interest: A. Knulst has received research support from Thermo Fisher Scientific, Netherlands/Sweden. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication March 26, 2012; revised July 17, 2012; accepted for publication August 9, 2012.

Available online September 29, 2012.

Corresponding author: Rob J. B. Klemans, MD, Department of Dermatology and Allergology, University Medical Center Utrecht (G02.124), PO Box 85.500, 3508 GA Utrecht, The Netherlands. E-mail: r.j.b.klemans-3@umcutrecht.nl.

0091-6749/$36.00

http://dx.doi.org/10.1016/j.jaci.2012.08.010

Abbreviations used
AUC: Area under the curve
DBPCFC: Double-blind, placebo-controlled food challenge
NPV: Negative predictive value
PPV: Positive predictive value
sIgE: Specific immunoglobulin E
SPT: Skin prick test

components Ara h 1, 2, 3, and 8 could increase the diagnostic accuracy. In addition, another prediction model was built in which only sIgE to the peanut-specific components and peanut extract were analyzed as candidate predictors. The diagnostic value of this model was compared with the diagnostic value of the validated model of DunnGalvin et al.[12]

METHODS

Patients

All patients (n = 261) with a suspected peanut allergy who visited the Centre of Pediatric Allergy in the Wilhelmina Children Hospital in Utrecht, The Netherlands, between 2008 and 2010 were considered for inclusion in this study if they had no missing data. Required data comprised sex, age, SPT, history, presence of allergic rhinitis and eczema, and the outcome of the food challenge; 200 patients had complete records in this regard. Suspicion was based either on a positive history irrespective of SPT or sIgE result or sensitization (positive sIgE or SPT to peanut extract) in case of unknown ingestion. The severity of the reaction was reported by the patients themselves or by their parents/caregivers. A suspected history was defined as an allergic reaction within 2 hours after the ingestion of peanut or a food product containing peanut. Because additional laboratory tests were needed, we randomly selected 100 of the 200 eligible patients for all analyses. No significant differences were found between the 3 groups (100 included, 100 excluded, 61 missing values) with regard to sex, age, sIgE to peanut extract, prior ingestion of peanut, presence of eczema, presence of allergic rhinitis, and outcome of food challenge. sIgE to Ara h 1, 2, 3, and 8 and total IgE were measured only in the 100 patients who were included in this study.

Outcome

All patients underwent a food challenge to confirm or exclude peanut allergy. The challenges were performed according to the international consensus protocol,[23] using the recipe described by Flinterman et al.[24] Oral allergy symptoms, nausea, abdominal discomfort, and throat tightness were considered subjective. Rhinoconjunctivitis, angioedema, generalized urticaria, emesis, diarrhea, hoarseness, stridor, wheezing, or significant drop in FEV_1 or blood pressure were referred to as objective symptoms. The challenge was discontinued and considered positive in case of objective symptoms, if suggestive subjective symptoms occurred at 3 subsequent doses, or if a severe, suggestive subjective symptom lasted for more than 45 minutes. None of the patients had an inconclusive food challenge. No late allergic reactions were reported the next day during a telephone call.

Predictors

To validate the model of DunnGalvin et al,[12] the same predictors were used as described in their study: sex, history, SPT, sIgE to peanut extract, total IgE minus sIgE to peanut extract, and age. Symptoms in history were similarly divided into 4 categories: 1, skin or oral or gastrointestinal or upper respiratory tract symptoms only; 2, upper respiratory tract and gastrointestinal or 2 systems; 3, lower respiratory tract or 3 systems; 4, cardiovascular or 4 systems.[12]

An SPT was performed with peanut extract with a single-headed lancet (ALK-Abelló, Nieuwegein, The Netherlands). For the positive and negative controls, histamine dihydrochloride 10 mg/mL and glycerol diluent were used, respectively.

Allergic rhinitis, as diagnosed by a physician, atopic dermatitis, according to the criteria of Williams et al,[25] and sIgE to the most important peanut allergens (Ara h 1, 2, 3, and 8) were analyzed as additional predictors. sIgE to the aforementioned allergen components and peanut extract was determined by using the ImmunoCAP method (Phadia, Uppsala, Sweden) according to the manufacturer's instruction. The SPT and sIgE results were analyzed as continuous variables. All serum samples were collected during routine clinical practice. The local ethics committee approved the study.

Data analysis

This study consisted of 3 phases: (1) validation (discrimination and calibration) of the model published by DunnGalvin et al,[12] (2) analyzing whether the model could be updated with additional predictors, and (3) calculating the diagnostic value of a model by using only peanut-specific allergens (peanut extract and Ara h 1, 2, 3, and 8).

In phase 1, the existing model published by DunnGalvin et al[12] was validated. Therefore, we calculated for each patient the probability of having peanut allergy by using the regression coefficients as described by DunnGalvin et al with the following formula: probability of having peanut allergy = exp [−11.63 + (4.60 × gender) + (3.32 × history group 1) + (4.61 × history group 2) + (7.86 × history group 3) + (11.08 × history group 4) + (2.85 × SPT) + (0.50 × sIgE to peanut extract) + (−0.002 × total IgE − sIgE to peanut extract) + (−0.37 × age)]/{1 + exp[−11.63 + (4.60 × gender) + (3.32 × history group 1) + (4.61 × history group 2) + (7.86 × history group 3) + (11.08 × history group 4) + (2.85 × SPT) + (0.50 × sIgE to peanut extract) + (−0.002 × total IgE − sIgE to peanut extract) + (−0.37 * age)]}.[12] The performance of the model was described by means of discrimination and calibration. Discrimination shows the degree of distinction between positive and negative outcomes of a model and was studied with a receiver operating characteristic curve. The AUC was calculated with this curve, with a value of 0.5 indicating "no discrimination" and a value of 1 indicating "perfect discrimination." Calibration refers to the agreement between predicted probabilities and observed frequencies of peanut allergy as assessed by a food challenge. This was tested with a calibration plot where a slope of 1, together with a Hosmer-Lemeshow test with a *P* value of .05 or more, indicates good calibration.

In phase 2, the additional predictors allergic rhinitis, atopic dermatitis, and sIgE to Ara h 1, 2, 3, and 8 were analyzed as to their ability to enhance the diagnostic value of the model. Therefore, a new multivariate logistic regression analysis was performed entering all candidate variables (from the original model as well as possible additional predictors) simultaneously. This analysis was performed in the same way as described by DunnGalvin et al[12] (ie, stepwise forward with the probability of entering a variable .05 and removing a variable .06). The categorical predictor history was graded into 4 categories as described above with no symptoms/ingestion unknown as the reference. In addition, the diagnostic value was analyzed without entering the subjective predictor history and the labor-intensive SPT as possible predictors in a multivariate logistic regression analysis.

In phase 3, only sIgE to peanut allergens was used to develop a prediction model to examine the diagnostic value of these frequently investigated allergens. We again used multivariate logistic regression and a receiver operating characteristic curve, as earlier described.

All analyses were performed with SPSS (version 16.0; SPSS, Inc, Chicago, Ill). The calibration plot was made by using Microsoft Office Excel 2003.

RESULTS

Patient characteristics

Table I shows the patient characteristics for both the peanut-allergic (n = 47) and the peanut-tolerant (n = 53) group. The predictors as used in the prediction model of DunnGalvin et al[12] are listed above the dotted line. The median age of the total group was 6.0 years, and 65% were males. A DBPCFC was performed in 81 patients. In 19 patients, the food challenge was open because of