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Original article

Development of a prediction model of severe reaction in boiled egg challenges

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AUC, Area under the curve; OFC, Oral food challenge; OIT, Oral immunotherapy; NPV, Negative predictive value; PPV, Positive predictive value; ROC, Receiver operating characteristic; sIgE, Specific IgE

ABSTRACT

Background: We have proposed a new scoring system (Anaphylaxis SCoring Aichi: ASCA) for a quantitative evaluation of the anaphylactic reaction that is observed in an oral food challenge (OFC). Furthermore, the TS/Pro (Total Score of ASCA/cumulative protein dose) can be a marker to represent the overall severity of a food allergy. We aimed to develop a prediction model for a severe allergic reaction that is provoked in a boiled egg white challenge.
Methods: We used two separate datasets to develop and validate the prediction model, respectively. The development dataset included 198 OFCs, that tested positive. The validation dataset prospectively included 140 consecutive OFCs, irrespective of the result.
A 'severe reaction' was defined as a TS/Pro higher than 31 (the median score of the development dataset). A multivariate logistic regression analysis was performed to identify the factors associated with a severe reaction and develop the prediction model.
Results: The following four factors were independently associated with a severe reaction: ovomucoid specific IgE class (OM-sIgE: 0–6), aged 5 years or over, a complete avoidance of egg, and a total IgE < 1000 IU/mL. Based on these factors, we made a simple scoring prediction model. The model showed good discrimination in a receiver operating characteristic analysis; area under the curve (AUC) = 0.84 in development dataset, AUC = 0.85 in validation dataset. The prediction model significantly improved the AUC in both datasets compared to OM-sIgE alone.
Conclusions: This simple scoring prediction model was useful for avoiding risky OFC.

Introduction

Oral food challenges (OFC) have been performed for the definitive diagnosis of a food allergy and more frequently, for the discernment of tolerance to the allergen.[1] In addition to these conventional purposes, OFCs are performed to determine the threshold dose of food allergens for individuals beginning oral immunotherapy (OIT) or to determine the threshold of minimal avoidance. More severe reactions tend to be provoked in these OFC settings.

Sampson's grade stratification[2] is commonly used for an assessment of the severity of allergic reaction provoked in an OFC, and the Japanese Guideline for Food Allergy 2014 adopted it with minor modifications.[3] This classification mostly aims to evaluate the severity of a reaction to decide the indications for therapy including intramuscular epinephrine injection. For that purpose, severity is judged based on the highest grade of symptoms, even if multi-organ reactions are provoked.

On the other hand, an evaluation of multi-organ symptoms can be an important severity marker in some purposes because the number of symptomatic organs involved in an allergic reaction affects the outcome of achieving tolerance afterward.[4,5] For this purpose, we have developed an original scoring system named Anaphylaxis Scoring Aichi (ASCA) for a quantitative evaluation of multi-organ reactions provoked in OFCs.[6] ASCA lists and sorts allergic symptoms according to five organ systems (respiratory, skin-mucosal, gastrointestinal, psycho-neurological, and cardiovascular). In the gastrointestinal symptoms, the degree of abdominal pain was expressed as face scale (Supplementary Fig. 1). Each symptom was given an organ system score of 0–60 points in

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accordance to the severity. The gradient of the points was set for the purpose that the sum of plural mild points does not exceed one severe organ system point. The organ system score of 40 points almost corresponds to grade 4 of Sampson's grade[2] (Table 1).

The total score (TS) was defined as the sum of 5 organ system scores (maximum 240 points) based on the highest organ system score observed throughout a course of OFC. We have already validated the TS to be correlated to Sampson's grade[6] (Fig. 1).

Several studies have tried to predict the result of OFCs and their severity of outcome. Although a probability curve of specific Immunoglobulin E (sIgE) provides useful information for predicting a positive challenge[7] and a severe reaction,[8] another report suggested a limitation in its predictive accuracy.[9] Component-resolved diagnostics for wheat (ω-5 gliadin)[10] and peanut (Ara h 2)[11] provided a promising prediction for the positive result of an OFC, but failed to predict the threshold dose and the severity of symptoms. Clinical backgrounds should also be considered to predict the outcome of an OFC including the severity of the provoked reactions.[4,12,13]

A recent article suggested that a complex model incorporating both test results and a clinical history had a better predictive ability compared to simply relying on the sIgE and skin prick test (SPT) either alone or in combination with one another.[4] For the purpose of identifying a severe allergic reaction, a complex model is thought to be a better predictor.[12]

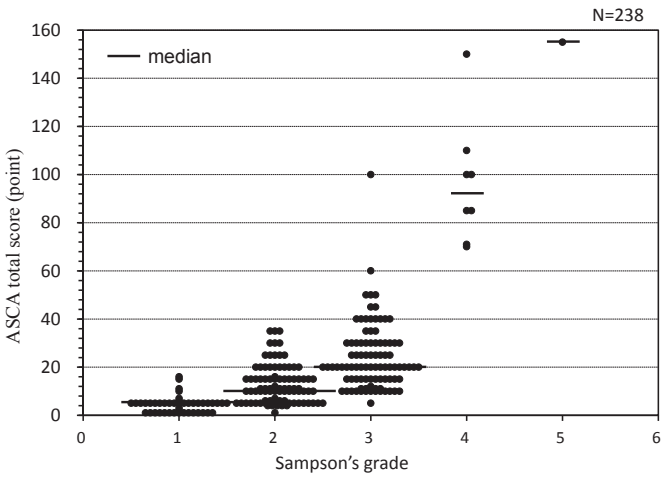

Fig. 1. The correlation between total score of ASCA and Sampson's anaphylaxis grading. ASCA, Anaphylaxis scoring Aichi. Adapted from Ref. 6 with modification.

The aim of this study was to identify the clinical factors contributing to a severe reaction provoked in an OFC and use them to develop a prediction model.

Table 1
Anaphylaxis scoring Aichi (ASCA).

Score organ	0	① 1 point	① 5 points	② 10 points	② 20 points	③ 40 points	④ 60 points
Respiratory (*subjective*)	None	Itchy nose	Laryngeal discomfort	Nasal congestion Suffocating breath	Speech disturbance Difficulty in breathing	Loss of voice	
(*objective*)		Sneeze	Mild transient coughing Runny nose	Intermittent coughing Mild wheezing	Frequent coughing Apparent wheezing Hoarseness	Continuous coughing Strong wheezing Intentional breathing Inspiratory stridor Retraction	Weak breath sounds Strong retraction Cyanosis $SpO_2 \leq 90\%$
Skin/Mucosal (*subjective*)	None	Itch (around mouth) Mild discomfort, Burning sensation	Itch (local and mild)	Itch (whole body)	unbearable itch		
(*objective*)		*<Peri-oral>* Hives, Erythema, Swelling, Vesicle	*<Local>* Eye edema, Bloodshot Hives, Erythema, Swelling, Angioedema	*<Multiple>* Hives, Erythema, Swelling Angioedema	*<Spreading, Generalized>* Hives, Erythema, Swelling Angioedema		
Gastrointestinal (*subjective*)	None	Oral or pharyngeal itch, Hot taste, Sore throat	Mild nausea, Abdominal pain (FS1)	Mild nausea, Abdominal pain (FS2)	Strong abdominal pain (FS3)	Unbearable abdominal pain (FS4)	
(*objective*)			Increased bowel sounds	Diarrhea, Vomiting	Recurrent vomiting	Dehydration by vomiting	
Psycho-neurological	None	Refusal to eat Mild excitement	Loss of activity Irritation	Sleep, Tendency to lay down Mild excitement	Sleep (not usual) Agitating, Crying	Tend to fall unconscious Uncontrolled panic	Unconsciousness
Cardiovascular	None					Pale, Tachycardia Cold extremities, Cold sweat	Bradycardia
(*Blood pressure*)						Mild decrease of blood pressure <1 y: <70 mmHg 1–10 y: <70+ (2 x age) mmHg 11–17 y: <90	Low Blood Pressure <1 y: <50 mmHg 1–10 y: <60 mmHg ≥11 y: <70 mmHg

Allergic symptoms are categorized into 5 organ systems, and each organ symptom score (0–60 points) is given based on the severity of the symptoms. Total score (TS) is defined as a sum of the highest organ symptom score observed throughout the course of allergic symptom (maximum 240 points).
FS, Face scale to express the degree of abdominal pain (Supplementary Fig. 1).