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Title: Development of a prediction model for severe wheat allergy

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Running title

Prediction of severe wheat allergy

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Abbreviations:

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

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The authors have no conflict of interest relevant to manuscript.

To the editor:

The purpose of oral food challenges (OFCs) has gradually transformed from a definitive diagnosis of a food allergy to determining the threshold dose of food allergens at the beginning of oral immunotherapy (OIT) or the amount of minimal intake, which has recently come to be considered a better method of managing IgE-mediated food allergy [1][2]. However, OFCs in patients with severe food allergies, defined as low-threshold and severe reactions, carry a risk of triggering anaphylaxis. To predict such severe reactions before OIT, we previously reported prediction models consisting of multiple factors for hen's egg [3] and cow's milk [4] allergy.

Wheat is the third-most common causative antigen among IgE-mediated food allergies in Japan [5]. An OFC to wheat was identified as an independent risk factor for anaphylaxis requiring epinephrine administration to low-dose antigen [6]. Therefore, predicting severe cases before a wheat OFC is a more important issue than with other antigens.

Component-resolved diagnostics for wheat (ω -5 gliadin; ω 5G) have proven promising for predicting a positive result on an OFC but failed to predict the threshold dose or severity of symptoms [7]. Although a recent article showed an association between the ω 5G-specific IgE titer (sIgE) and severe allergic reactions provoked in a wheat OFC [8], that report did not take into account the amount of allergen eliciting the allergic reaction. The aim of this study was to identify the clinical factors contributing to severe cases and to develop a prediction model.

Open OFCs using udon noodle (wheat protein, 26 mg/g) were performed in accordance with the Japanese Guideline for Food Allergy 2014 [5]. Briefly, we selected 4 to 6 consecutive doses from 0.2, 0.5, 1, 2, 5, 10 and 20 g of udon noodle depending on the age and estimated severity of the patient. The severity of provoked symptoms was determined based on the Total Score (TS) of Anaphylaxis Scoring Aichi (ASCA) [3]. We also used “TS/Pro” for the simultaneous expression of severity and threshold dose of antigen. “Pro” represents the cumulative protein dose of the allergen that provoked the symptoms, and the TS/Pro was obtained by simply dividing the TS by Pro.

The developmental dataset was obtained from OFCs to udon noodle conducted from April 2012 to December 2014. During this period, 360 OFCs to udon noodle were conducted, and 234 (65.0%) were positive. Forty-three cases were excluded because of the lack of appropriate laboratory data (total IgE, sIgE to wheat and ω 5G) collected within 180 days from the OFC, resulting in 191 cases analyzed. To validate this model in an independent clinical setting, 123 consecutive OFCs to udon noodle (84 positive and 39 negative, validation dataset) were analyzed from January 2015 to March 2016 in a prospective manner.

The following factors were analyzed as candidates for contribution to the challenge result: age, sex, history of anaphylaxis to wheat, history of atopic dermatitis or bronchial asthma and total IgE, wheat (WH)-sIgE and ω 5G-sIgE (ThermoFisher Scientific, Uppsala, Sweden). The diagnosis of anaphylaxis was made based on the Anaphylaxis Guidelines [9].

We divided patients in the development dataset into two groups (severe and non-severe cases) by TS/Pro=50 on the basis of our clinical practice. At this point or lower, patients could start ingestion of at least 2 g of udon noodle at home safely and feasibly [10].

For a univariate analysis, the Mann-Whitney U test was used to compare the sequential data, and a chi-squared analysis was used to compare the binary variables. All factors with statistical significance in the univariate analysis were used for a stepwise multiple regression analysis to identify the independent predictors of a severe reaction. To calculate WH-sIgE, which has a logarithmic scale nature, the sIgE class (0-6; Table S1) was applied. For age and total IgE, the cut-off points (total IgE =1000 IU/mL, age=5 years old) were set roughly in the upper quartile of the individual variables.

Based on the results, we constructed a logistic regression model using the independent factors with a probability value $P < 0.05$. We next created a simple scoring model by assigning the point scores of each variable. The discriminatory ability of the model was assessed using the area under the receiver operating characteristic (ROC) curve. The goodness of fit of the model was tested with the Hosmer-Lemeshow test, with $P < 0.05$ indicating a lack of deviation between the model and observed event rate.

This study was approved by the institutional review board of Aichi Children's Health and Medical Center. All analyses were performed with the STATA (version 12.1 for Mac; STATA Inc, College

Station, TX, USA) software program. For all analyses, a 2-sided probability value below 0.05 was considered to indicate statistical significance.

The characteristics of the development dataset are shown in Table 1. The median age of the dataset was 3.0 years, and 68.1% were males. The median TS was 10 points, and the median cumulative dose of udon noodle was 8 g, resulting in a median TS/Pro of 87. Severe cases (TS/Pro>50) constituted 61% of the development dataset.

A univariate analysis identified five variables (WH-sIgE, ω 5G-sIgE, history anaphylaxis, age, total IgE) with a significant difference between the severe and non-severe groups (Table 1). WH-sIgE and ω 5G-sIgE showed a strong correlation (Spearman's $R=0.61$), and they both showed a statistically significant correlation with the TS/Pro (Spearman's $R=0.56$ and 0.46 , respectively, both p -values < 0.001 , Fig. S1). Therefore, we selected WH-sIgE, but not ω 5G-sIgE, as a candidate factor for the multivariable analysis to avoid multicovariance. However, considering the clinical importance of ω 5G-sIgE, “ ω 5G-sIgE-positive” was incorporated into the multiple logistic regression analysis as a candidate factor.

A stepwise multiple regression analysis revealed “WH-sIgE class”, “history of anaphylaxis”, “total IgE < 1000 IU/mL” and “ ω 5G-sIgE-positive (>0.34 kU_A/L)” to be independent factors associated with severe cases (Table 2), enabling us to construct a logistic regression model and a simple scoring model by approximating the logistic coefficients (β). The prediction score consisted of the base point of WH-sIgE (1 point / class), one point each for “total IgE $<1,000$ IU/mL” and “ ω 5G-sIgE-positive”, and 2 points for “history of anaphylaxis”, resulting in a maximum of 10 points.

The prediction score showed a significant correlation with the TS/Pro (Fig. 1). The median score of the development dataset was 6 (ranging from 0 to 10). The area under the ROC curve was 0.84 (95% confidence interval [CI], 0.79 to 0.90) for the simple scoring model, which was almost identical to that obtained from the logistic regression model (0.85; 95% CI, 0.79 to 0.90). The Hosmer-Lemeshow statistic was not significant (probability values of 0.70 and 0.55 for the logistic model and the simple scoring model, respectively). The simple scoring model was significantly superior in its discriminatory ability for predicting severity (AUC=0.84) to the prediction obtained using the WH-sIgE class alone (AUC=0.79) ($p < 0.001$, Fig. S2, left).

In the validation dataset, among 31 OFCs with a prediction score ≥ 8 , responses to 29 OFCs (93.5%) were classified as severe cases (TS/Pro > 50). In contrast, responses to 21 of 24 OFCs (87.5%) with a prediction score ≤ 4 were non-severe cases. The sensitivity and specificity of each cut-off are shown in Table S2. In this dataset, the area under the ROC curve was 0.82 for the simple scoring model, which was superior in its discriminatory ability to the WH-sIgE class alone ($p=0.004$, Fig. S2, right), and the Hosmer-Lemeshow statistic was not significant ($P=0.55$).

In the present study, as in our previous reports for hen's egg [3] and cow's milk [4] allergies, we successfully developed a simple prediction model for a severe allergic case to wheat OFCs.

Similar to the previous analysis [3][4], the specific IgE titer has the strongest impact on the severity.

Given that WH-sIgE showed a stronger correlation to TS/Pro than $\omega 5G$ -sIgE (Fig. S1), we selected WH-sIgE as a predictive factor. This may suggest that although $\omega 5G$ is known as a representative wheat component in the gluten fraction, there are many other gliadins, glutenins and water-soluble proteins that cause an allergic reaction in sensitized patients. Instead of including the $\omega 5G$ -sIgE value as the

direct variable in the model, “ω5G-sIgE-positive” was used in the model since it was defined as an independent factor associated with severe cases (Table 2).

In the multivariate model, a low total IgE value (< 1000 IU/mL) was identified as a risk factor for a severe allergic reaction, which was inversely affected in the univariate analysis. This result was thought to be caused by interaction between total IgE and wheat sIgE. Similar results were observed in our prediction models of egg [3] and milk [4] allergy, which were thought to be due to competition between sIgEs to the target antigen and those with other specificities on the surface of mast cells.

In cases of a mild result in an OFC, we instruct patients to ingest 2 g or more of udon noodle at home [10]; this instruction is given at roughly $TS/Pro < 50$. For example, when a localized urticaria and intermittent cough are provoked ($TS=15$) after ingesting 8.7 g of udon noodle (protein 0.23 g, $TS/Pro=65$), we instruct the patient to continue complete avoidance. However, when the same symptoms are provoked after ingesting 18.5 g udon noodle (protein 0.48 g, $TS/Pro=31$), the patient is allowed to ingest 2 g of udon noodle.

Based on the findings in the present study, we do not recommend performing an OFC for patients with a prediction score ≥ 8 . In contrast, if the prediction score is ≤ 4 , an OFC may be performed safely, or ingestion of a small amount of allergen may be allowed without an OFC.

One limitation of this study is that we did not assess celiac disease as a comorbidity of subjects because this disease was reported to be very rare in Japanese population [11]. Therefore our result should not be applied to the patients with celiac disease.

In conclusion, our prediction model showed a good discrimination of severe allergic reactions based on the TS/Pro. It may therefore be clinically useful for many pediatric allergists to avoid performing an OFC for high-risk patients while also encouraging them to carry out an OFC for low-risk patients.

Acknowledgements

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Figure Legends

Fig. S1. Correlation between specific IgE and the TS/Pro. Wheat-specific IgE correlated with the TS/Pro (right, $R_s=0.56$, $P<0.001$) better than $\omega 5$ gliadin-specific IgE (left, $R_s=0.46$, $P<0.001$). TS/Pro: Total Score of ASCA / cumulative protein dose

Figure 1. Correlation between the prediction score and the TS/Pro. The box plots of TS/Pro in each prediction score are shown. A line is drawn at TS/Pro=50. The prediction score was significantly correlated with the TS/Pro ($R_s=0.67$, $P<0.001$). TS/Pro: Total Score of ASCA / cumulative protein dose

Fig. S2. An ROC analysis of the prediction score and specific IgE class. In the development dataset (left), the prediction score (diamond, dash line, AUC=0.84) showed better discrimination ability ($p < 0.001$) for severe cases than the wheat-specific IgE class (circle, solid line, AUC=0.75). The result was reproduced in the validation dataset (right); AUC=0.82 and 0.75, respectively ($p=0.004$). ROC: receiver operating characteristic, AUC: area under the curve.

	Development dataset				Validation dataset			
	total	severe	non-severe	p-value	total	severe	non-severe	p-value
Number	191	116	75		124	71	52	
Age	3.0 (1.8-5.2)	4.0 (2.4 - 5.6)	3.0 (1.5 - 4.2)	< 0.001	3.6 (1.6-6.2)	4.7 (2.9-6.5)	2.1 (1.4-4.9)	< 0.001
Male	130 (68.1%)	77 (66.4%)	53 (70.7%)	0.55	89 (72.4%)	52 (73.2%)	37 (71.2%)	0.80
Atopic dermatitis	155 (81.2%)	92 (79.3%)	63 (84.0%)	0.42	98 (79.7%)	56 (78.9%)	42 (80.8%)	0.80
Bronchial asthma	54 (28.3%)	36 (31.0%)	18 (24.0%)	0.29	25 (20.3%)	17 (23.9%)	8 (15.4%)	0.24
History of anaphylaxis	53 (27.8%)	49 (42.2%)	4 (5.3%)	< 0.001	36 (29.3%)	31 (43.7%)	5 (9.6%)	< 0.001
Total IgE	482 (172-1009)	598 (222 - 1017)	300 (125 - 1009)	0.044	523 (242-1219)	720 (340-1299)	454 (181-914)	0.056
Wheat sIgE	21.6 (8.21 - 68.35)	50.8 (15.7 - 91.5)	9.6 (4.6 - 21.0)	< 0.001	35.70 (8.92-88.45)	62.40 (30.60-100.00)	14.00 (4.46-34.8)	< 0.001
ω-5 gliadin sIgE	1.78 (0.52 - 4.57)	2.8 (1.0 - 7.8)	1.15 (0.34 - 2.21)	< 0.001	2.24 (0.52-7.78)	5.04 (1.35-12.50)	0.52 (0.34-1.85)	< 0.001
Total ASCA score	10 (5 - 20)	15 (10 - 25)	5 (5 - 10)	< 0.001	10 (0-20)	15 (10-20)	0 (0-2)	< 0.001
Total dose	8 (3.5 - 18)	3.7 (1.7 - 5.0)	18.5 (8.7 - 21.9)	< 0.001	3.7 (1.7-8.7)	1.7 (1.0-3.7)	8.7 (8.4-18.5)	< 0.001
TS/Pro	87 (23 - 223)	156 (104 - 410)	21 (10 - 27)	< 0.001	68 (0-373)	282 (123-577)	0 (0-7)	< 0.001

Table 1. Background characteristics of the development and validation dataset.

Values are presented as median (first and third quartiles) or number (proportion). Each p-value is calculated using the Mann Whitney U test (sequential variables) or chi-squared test (binary variables).

ASCA: Anaphylaxis Scoring Aichi, TS/Pro: total score of ASCA / cumulative protein dose of the allergen

Table 2. Results of the stepwise forward logistic regression analysis of the development dataset and the score points given in a simple scoring system.

	β	SE	OR (adjusted)	P-value	Score point
Wheat sIgE (class)	1.0	0.22	2.8	< 0.001	1/ class
ω 5G sIgE > 0.34	1.2	0.50	3.3	0.017	1
Total IgE < 1000	1.8	0.56	6.3	0.001	1
anaphylaxis	2.5	0.62	12.6	< 0.001	2

Log (p/1 – p) = –6.1 + 1.0 × Class + 1.2 × [ω5G positive] + 1.8 × [tIgE < 1000] + 2.5 × [history of anaphylaxis]
Simple scoring model: 1 × Class + 1 × [ω5G positive] + 1 × [tIgE < 1000] + 2 × [history of anaphylaxis]

Fig. 1

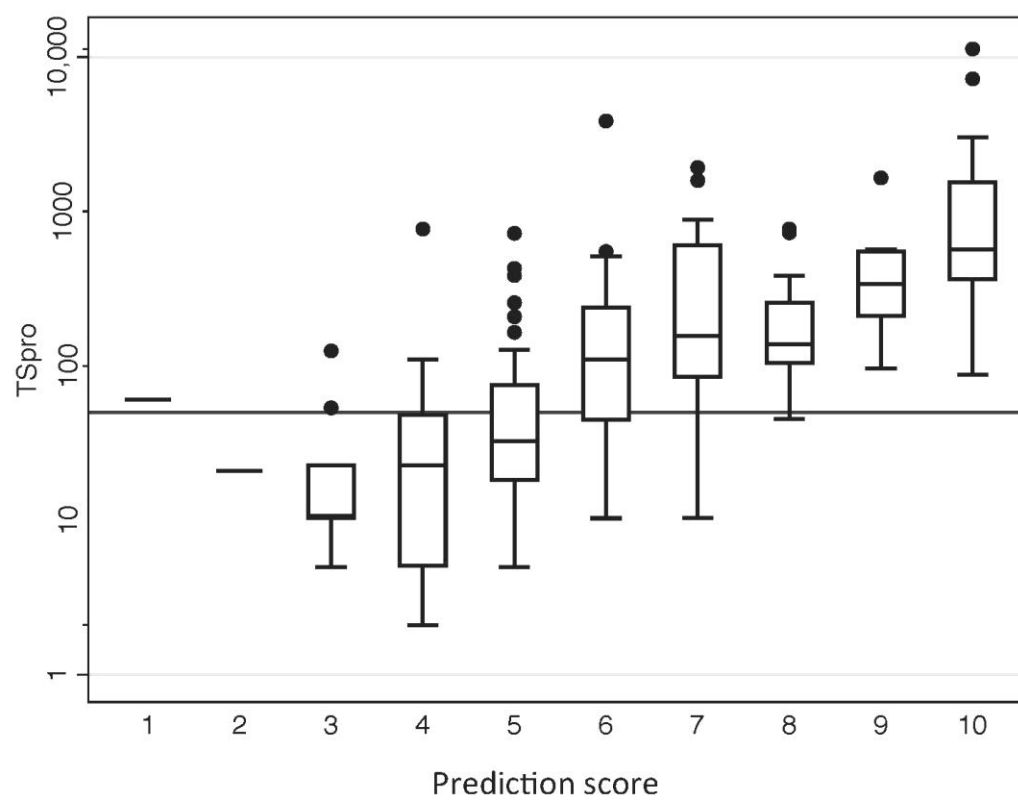
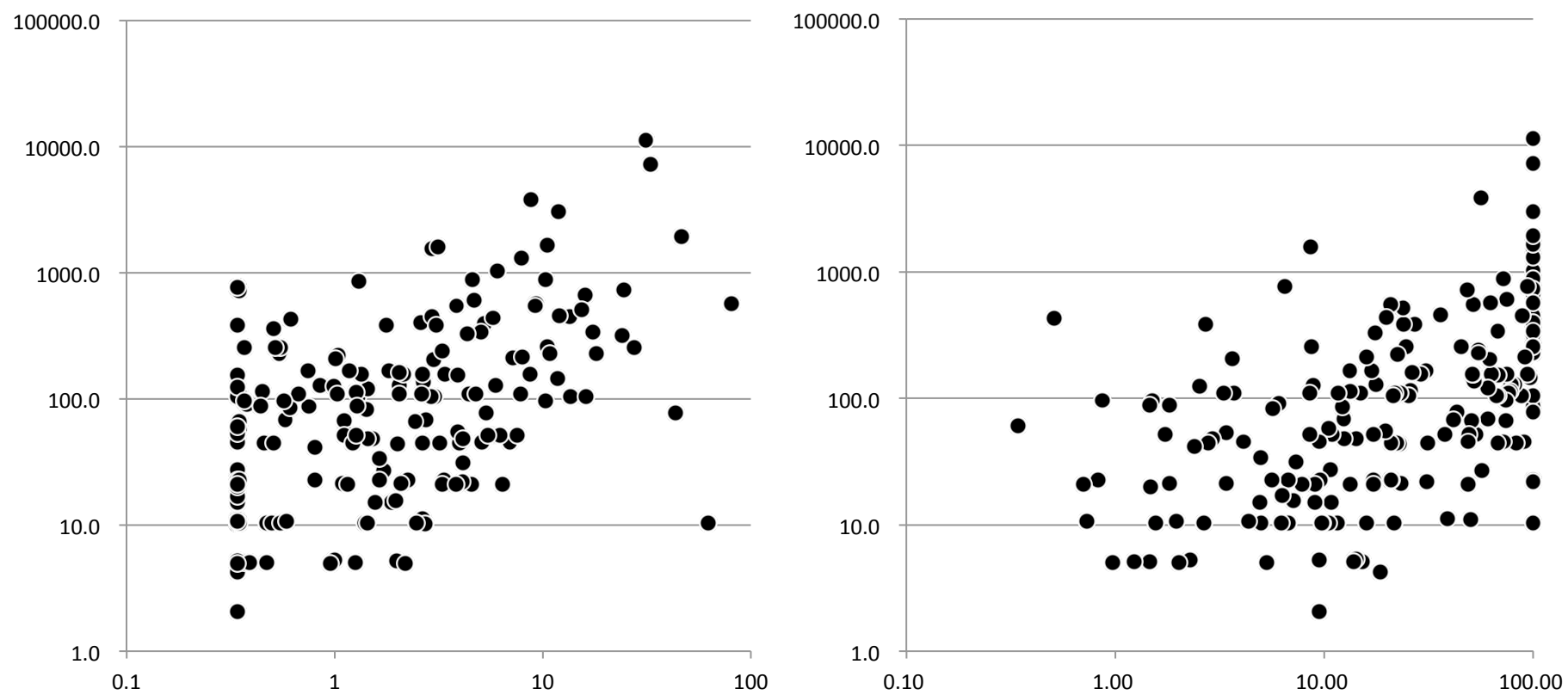


Table S1. Specific IgE class

Specific IgE class	Specific IgE (kU _A / L)
0	< 0.34
1	0.35 - 0.69
2	0.70 - 3.49
3	3.50 - 17.49
4	17.50 - 49.99
5	50.00 - 99.99
6	100 <

Fig. S1



Score	Sensitivity	Specificity	PPV	NPV
8-10	40.9%	96.2%	93.6%	54.4%
0-4	95.8%	40.4%	68.7%	87.5%

Table S2. Power of the simple scoring system to predict severe allergic reactions in the validation dataset.

PPV: positive predictive value, NPV: negative predictive value

Fig. S2

