Allergy Asthma Immunol Res. 2024 Mar;16(2):179-190
https://doi.org/10.4168/aair.2024.16.2.179
pISSN 2092-7355·eISSN 2092-7363

Allergy, Asthma & Immunology Research AAIR

Original Article

Check for updates

# Predicting the Outcome of Pediatric Oral Food Challenges for Determining Tolerance Development

**Hamin Kim**,[1] **Kyunguk Jeong**,[2] **Mireu Park**,[3] **Yun Young Roh**,[1] **Jae Hwa Jung**,[1] **Soo Yeon Kim**,[1] **Jong Deok Kim**,[1] **Min Jung Kim**,[4] **Yoon Hee Kim**,[3] **Myung Hyun Sohn**,[1] **Sooyoung Lee**,[2] **Kyung Won Kim**[1*]

[1]Department of Pediatrics, Severance Hospital, Institute of Allergy, Institute for Innovation in Digital Healthcare, Yonsei University College of Medicine, Seoul, Korea
[2]Department of Pediatrics, Ajou University School of Medicine, Suwon, Korea
[3]Department of Pediatrics, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea
[4]Department of Pediatrics, Yongin Severance Hospital, Yonsei University College of Medicine, Yongin, Korea

OPEN ACCESS

**Received:** Jul 23, 2023
**Revised:** Dec 5, 2023
**Accepted:** Jan 9, 2024
**Published online:** Mar 13, 2024

**Correspondence to**
**Kyung Won Kim, MD, PhD**
Department of Pediatrics, Severance Hospital, Institute of Allergy, Institute for Innovation in Digital Healthcare, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea.
Tel: +82-2-2228-2050
Fax: +82-2-393-9118
Email: kwkim@yuhs.ac



**ORCID iDs**
Hamin Kim
https://orcid.org/0000-0002-0601-7300
Kyunguk Jeong
https://orcid.org/0000-0002-1261-4507
Mireu Park
https://orcid.org/0000-0003-4342-6143

## ABSTRACT

**Purpose:** Despite the risk of anaphylaxis, oral food challenges (OFCs) are performed clinically for various indications, particularly to confirm tolerance development. This study aimed to assess OFCs by relevant indications and build an outcome prediction model to help determine when to perform OFCs in children who are likely to have developed immune tolerance.
**Methods:** In total, 432 pediatric OFCs were retrospectively analyzed according to indications. Clinical characteristics, serum total immunoglobulin (Ig) E, blood eosinophils, and specific IgE and IgG4 levels for food allergens were noted and compared. Machine learning was utilized to select the most important variables in determining the passage of the OFCs, and prediction models were constructed using the selected variables.
**Results:** OFCs were most commonly performed to confirm tolerance development (number, %; 267, 61.8%). The most common food allergens tested were egg (191, 44.2%) and milk (135, 31.3%). Children who passed the egg challenges for confirming tolerance acquisition had significantly lower egg white-specific IgE level ($P = 0.008$). Similarly, those who passed milk challenges had significantly lower cow's milk-specific IgE ($P = 0.002$) and casein-specific IgE levels ($P = 0.005$). We developed a nomogram to predict the outcome of OFCs to determine the tolerance acquisition with the selected variables; lower food-specific IgE, higher total IgE, and younger age indicated a higher probability of passage. The area under the curve (95% confidence interval) was 0.623 (0.503–0.743) for egg and 0.734 (0.628–0.840) for milk.
**Conclusions:** Serum total IgE and food-specific IgE combined with age showed trends toward passing OFCs for confirming tolerance development. The constructed model may be used by clinicians as a practical guide for minimizing the risks of OFCs and a timely reintroduction for children with food allergies.

**Keywords:** Food hypersensitivity; milk hypersensitivity; egg hypersensitivity; machine learning

Yun Young Roh
https://orcid.org/0000-0002-8751-6784
Jae Hwa Jung
https://orcid.org/0000-0001-7443-9073
Soo Yeon Kim
https://orcid.org/0000-0003-4965-6193
Jong Deok Kim
https://orcid.org/0000-0002-4266-5655
Min Jung Kim
https://orcid.org/0000-0002-5634-9709
Yoon Hee Kim
https://orcid.org/0000-0002-2149-8501
Myung Hyun Sohn
https://orcid.org/0000-0002-2478-487X
Sooyoung Lee
https://orcid.org/0000-0003-1734-4101
Kyung Won Kim
https://orcid.org/0000-0003-4529-6135

**Disclosure**
There are no financial or other issues that might lead to conflict of interest.

## INTRODUCTION

Oral food challenge (OFC) is the gold standard for diagnosing food allergies; it is also used to confirm tolerance development, determine a safe ingestion quantity, or establish an initial dose for oral immunotherapy.[1,2] However, it involves risk-taking, particularly anaphylaxis, which can lead to severe complications and death.[3] Therefore, 95% predictive reaction decision points of food-specific immunoglobulin (Ig) E levels have been suggested in certain foods, facilitating a diagnosis without an OFC.[4,5] However, some patients still require an OFC in real-world clinical settings.[6] In addition, evidence of food-specific IgE levels is insufficient to substitute OFC for purposes other than diagnosis.

Determining the appropriate time to reintroduce food is critical for children with food allergies because it minimizes dietary restrictions. Whereas previous studies have identified the risk factors and predictors of resolution, such as allergen-specific IgE levels, reactions to food allergies vary across children.[7-10] Some children may present with reduced clinical reactivity even without reaching the cut-offs, potentially enabling an earlier reintroduction of allergenic food. Therefore, clinicians must consider multiple factors carefully and thoughtfully before deciding upon an OFC to confirm tolerance acquisition. This decision-making process can be burdensome and daunting for clinicians. Examining the contribution of associated factors to the likelihood of an OFC passage can aid a clinician's decision-making process.

The application of machine learning (ML) in medicine has extended to predicting clinical outcomes or classifying pertinent features in certain diseases.[11,12] In food allergies, studies have utilized ML to predict outcomes of milk, egg, peanut allergies held for diagnostic purposes.[13,14] ML enables identifying and selecting key variables from intricate datasets, a process sometimes too complex for traditional statistical methods. Factors that influence the passage of OFCs for tolerance confirmation are more intricate than those for diagnosis, and ML's feature ranking techniques emerge as appropriate tools for an effective analysis.

This study investigated OFC outcomes from three institutions over the last ten years. Initially, we examined OFCs according to various indications and food allergens. To predict tolerance development for the timely reintroduction of allergenic foods, we used ML to assess the outcome of OFCs. After identifying the key variables, we developed a prediction model in our cohort and validated it in an independent cohort.

## MATERIALS AND METHODS

### Study population

This retrospective study analyzed the data of all pediatric patients who underwent OFCs at Severance Children's Hospital, Gangnam Severance Hospital, and Yongin Severance Hospital, Republic of Korea, between January 2010 and June 2021. Patients who underwent OFCs were either suspected or diagnosed with food allergies. Their sex, age, history of allergic comorbidities (asthma, atopic dermatitis, allergic rhinitis), history of anaphylaxis, and food allergy other than the tested food allergen were collected from medical records. An external validation cohort included 100 pediatric patients who underwent OFCs at the Ajou University Hospital, Suwon, Republic of Korea. The study protocol was approved by the Institutional Review Boards of Severance Hospital, Gangnam and Yongin Severance Hospital,

and Ajou University Hospital (No. 4-2021-1296, No. 3-2021-0389, No. 9-2021-0159, and AJOUIRB-MDB-2022-040, respectively). The requirement for informed consent was waived owing to the retrospective nature of the study.

## OFCs

Open OFCs were performed according to Korean guidelines.[15] The OFC indications were to confirm diagnosis or tolerance development, determine the quantity for safe intake, or determine the starting dose for oral immunotherapy.[2] OFCs to confirm diagnosis or tolerance development were primarily based on the aforementioned guidelines, with amendments based on the patient's clinical history. For OFCs to determine the initial dose for oral immunotherapy, starting and incremental doses were customized based on the patient's allergic history. Food allergens were given incrementally at 30-minute intervals. Challenges were terminated with an allergist's confirmation if a patient reported signs (*e.g.*, dyspnea, abdominal pain, and wheezing) or symptoms. When a patient reported subjective symptoms that can be considered questionable clinical reactions, the identical dose was retried after waiting for 15 minutes. OFCs were considered nonpassed when three consecutive consumptions of suspected food allergens triggered subjective symptoms. Medical attention was provided as needed. Challenges were defined as passed when the patient consumed all given food allergens without any definitive symptoms, as confirmed by an allergist. For the oral egg challenge, the participant started with 1/8 of the boiled egg, followed by 1/4 and 1/2. For the oral milk challenge, the participant began with 10 mL of fresh milk, followed by 20 mL, 40 mL, 50 mL, and 80 mL at 30-minute intervals. Egg and milk OFCs were considered passed when the patient consumed one boiled egg (approximately 53 g) or 200 mL of fresh milk, respectively, without any symptoms following 2 hours after consumption. We classified the clinical reactions into five grades for non-passed OFCs according to Cox *et al.*[16] According to the grading scale, reactions involving symptoms or signs related to one organ system are grade 1, those related to multiple organ systems are grade 2, respiratory symptoms that are unresponsive to bronchodilators are grade 3, reactions involving respiratory failure or hypotension are grade 4, and reactions that result in death are grade 5.[16]

## Laboratory examinations

Immunologic parameters such as serum total IgE, blood eosinophils, and specific IgE and IgG4 levels for food allergens (measured within 3 months before the OFC) were collected and compared. All clinical laboratory examinations were conducted at the Department of Laboratory Medicine at Severance Hospital. Total IgE, allergen-specific IgE, and IgG4 levels were measured using the ImmunoCAP® 250 system (Phadia, Uppsala, Sweden). Blood eosinophils were assessed using an XN9000 hematology system (Sysmex, Kobe, Japan).

## Selection of variable of importance via ML processing

Using the dataset of 129 egg OFCs and 86 milk OFCs for confirmation of tolerance development, we performed ML modeling to identify significant variables in predicting outcomes of OFCs for tolerance development. The patient's sex, age, history of allergy to multiple foods, allergic comorbidities (asthma, atopic dermatitis, and allergic rhinitis), anaphylaxis history, serum total IgE, and food-specific IgE were included while selecting important variables. Four different feature ranking techniques were used: gradient boosting machine, Extreme Gradient Boost (XGBoost), random forest, and extremely randomized trees (extra trees). The dataset—randomly split into 70%-training and 30%-validation sets—underwent three-fold stratified cross-validation. Random and grid search techniques were applied for hyperparameter tuning. The model's performance was evaluated using the


https://doi.org/10.4168/aair.2024.16.2.179

test accuracy, F1-score, and area under the receiver operating characteristic curve (AUC) for the pass group. The averaged value and 95% confidence intervals (CIs) were calculated via bootstrap resampling of the test dataset with replacement of 1000 times. The feature ranking of each ML model was evaluated using permutation-based variable importance measures; each importance value represented the mean decrease in the model for the prediction of passing OFCs if the variable values were permuted randomly. Among the four ML models, feature ranking with the best prediction performance (AUC) was selected for nomogram development. ML modeling was implemented in Python, using the scikit-learn library (Python 3.9.0, scikit-learn 1.1.2).

### Statistical analyses

Statistical analyses were conducted using SPSS version 25.0 for Windows (IBM Corp., Armonk, NY, USA) and R version 3.3.3 (The R Foundation for Statistical Computing, Vienna, Austria). For inter-group comparisons, the Mann–Whitney test and $\chi^2$ test were used. Missing values were imputed with the median values of the variable. A $P$ value < 0.05 was considered statistically significant.

Weighted scatterplots (multi-class hexbins) were employed to visualize the relationship between OFC results and factors that could affect the challenge results. The size of each hexbin was considered proportional to the observed frequency of the challenge; the distribution of the OFC results was visualized by dividing up each hexbin.

Nomograms were constructed by considering factors that may affect tolerance development in order to provide a prediction method for OFC outcomes. The variables for nomogram development were selected via ML processing, as described earlier. An upward vertical line was drawn from each variable to the points bar to calculate points; subsequently, a downward vertical line was drawn from the total points to represent the probability of passing OFCs for confirmation of tolerance. After construction, we validated the nomograms in the external validation cohort. The AUC of the nomogram was used to evaluate the discriminative ability.[17]

## RESULTS

### Patient demographics and clinical characteristics of the OFCs

In total, 432 OFCs in 334 patients were analyzed, including 268 boys (62.0%). The participants' median (minimum–maximum) age was 38.0 (5.0–228.0) months. During the OFCs, patients in the pass group were younger than those in the non-pass group (34.0 vs. 45.5 months, respectively, $P$ = 0.002). Anaphylaxis was more prevalent in the non-pass group (27.5%) than in the pass group (17.2%, $P$ = 0.014). More than half of the patients had atopic dermatitis, and less than one-third had asthma or a history of allergic rhinitis. Almost two-thirds of patients had multiple food allergies; proportions were comparable between groups. Regarding food-related symptoms in the patients, anaphylaxis was more prevalent in the non-pass group (27.5%) than in the pass group (17.2%, $P$ = 0.014) (**Table 1**).

Among the various indications for OFCs, the most common was tolerance confirmation (n = 267, 61.8%), followed by diagnosis (n = 114, 26.4%), determination of the quantity for safe intake (n = 34, 7.9%), and determination of the dose for oral immunotherapy (n = 17, 3.9%). The pass rate was highest among OFCs for diagnosis confirmation (n = 83, 72.8%), followed by those for tolerance confirmation (n = 179, 67.0%). OFCs for determination of


https://doi.org/10.4168/aair.2024.16.2.179

**Table 1.** Demographic characteristics of patients who underwent OFCs

| Characteristics | Passed OFCs (n = 290) | Non-passed OFCs (n = 142) | *P* value |
|---|---|---|---|
| Age at OFC (mon) | 34.0 (5.0–206.0) | 45.5 (7.0–228.0) | **0.002** |
| Male sex | 183 (63.1) | 85 (59.9) | 0.514 |
| Allergic comorbidities | | | |
| Asthma | 76 (26.2) | 41 (28.9) | 0.558 |
| Atopic dermatitis | 164 (56.6) | 79 (55.6) | 0.857 |
| Allergic rhinitis | 82 (28.3) | 40 (28.2) | 0.982 |
| Multiple food allergies | 185 (63.8) | 93 (65.5) | 0.729 |
| Food-related symptoms | | | |
| Urticaria | 211 (72.8) | 90 (63.4) | 0.058 |
| Angioedema | 34 (11.7) | 24 (16.9) | 0.138 |
| Respiratory symptoms | 10 (3.4) | 7 (4.9) | 0.457 |
| Gastrointestinal symptoms | 23 (7.9) | 9 (6.3) | 0.553 |
| Anaphylaxis | 50 (17.2) | 39 (27.5) | **0.014** |
| Immunologic parameters | | | |
| Total IgE (IU/mL) (n = 427) | 189.5 (2.52–5,471.0) | 281.0 (7.50–6,383.0) | **0.047** |
| Blood eosinophils (/mm$^3$) (n = 413) | 310.0 (0.0–2,340.0) | 340.0 (0.0–2,340.0) | 0.663 |

Data are presented as number (%) or median (minimum–maximum). Statistically significant *P* values ($P < 0.05$) are in bold.
OFC, oral food challenge; IgE, immunoglobulin E.

safe intake quantity or dose for immunotherapy tended to have a lower pass rate. The most common food allergens tested were egg (n = 187, 43.3%) and milk (n = 132, 30.6%). The pass rate was highest for OFCs with peanuts (n = 30, 76.9%), followed by eggs (n = 145, 77.5%) (**Supplementary Table S1**). Among 142 non-passed OFC cases, 84 were grade 1, 46 were grade 2, 7 were grade 3, 5 were grade 4, and 0 were grade 5. The reacting dose varied between the patients, from a lip smear to a full dose.

## OFCs for confirmation of tolerance development

We performed further analyses on OFCs to confirm tolerance with the two most common food allergens, egg and milk. In total, 129 egg OFCs were performed to confirm tolerance development, and the participants passed 103 (79.8%). Further, egg white-specific IgE was significantly lower ($P = 0.008$), and egg white IgG4/IgE was significantly higher ($P = 0.023$) in the pass group. Allergic comorbidities (*e.g.*, history of asthma, atopic dermatitis, and allergic rhinitis) and multiple food allergies were comparable between groups. Total IgE and blood eosinophils showed no statistically significant difference ($P = 0.321$ and 0.742, respectively) (**Table 2**).

As for milk allergen, 86 OFCs were performed to confirm tolerance development. The participants passed 49 (57.0%) of these OFCs. Age was significantly different between the pass and non-pass groups (median age: 25.0 months versus 38.0 months, respectively, $P = 0.029$; **Table 3**). The median values of cow's milk IgE ($P = 0.002$) and casein-specific IgE ($P = 0.005$) were significantly lower in the pass group than in the non-pass group. As for IgG4, the casein-specific IgG4/IgE ratio was significantly higher in the pass group ($P = 0.048$) than in the non-pass group. The incidence of allergic comorbidities and history of multiple food allergies were comparable between groups.

## Weighted scatterplots between age, food-specific IgE, and the results of the challenge

**Fig. 1** shows the OFC distribution according to age and food-specific IgE, accounting for the challenge results. In egg OFCs for confirmation of tolerance, the distribution of non-passed OFCs tended to have high egg white-specific IgE. The distribution of egg OFC results showed no association with age. However, the proportion of non-passed OFCs for participants aged < 60


https://doi.org/10.4168/aair.2024.16.2.179

**Table 2.** Characteristics of the patients who underwent egg OFCs to confirm tolerance development

| Characteristics | Passed OFCs (n = 103) | Non-passed OFCs (n = 26) | *P* value |
|---|---|---|---|
| Age (mon) | 32.0 (10.0–145.0) | 36.5 (20.0–146.0) | 0.318 |
| Male sex | 67 (65.0) | 13 (50.0) | 0.158 |
| Comorbidities | | | |
| Asthma | 23 (22.3) | 5 (19.2) | 0.732 |
| Atopic dermatitis | 60 (58.3) | 18 (69.2) | 0.306 |
| Allergic rhinitis | 29 (28.2) | 4 (15.4) | 0.182 |
| Multiple food allergy | 56 (54.4) | 15 (57.7) | 0.761 |
| Food-related symptoms | | | |
| Urticaria | 79 (76.7) | 23 (88.5) | 0.281 |
| Angioedema | 12 (11.7) | 2 (7.7) | 0.562 |
| Respiratory symptoms | 3 (2.9) | 0 (0.0) | 0.379 |
| Gastrointestinal symptoms | 8 (7.8) | 1 (3.8) | 0.483 |
| Anaphylaxis due to egg consumption | 4 (3.9) | 0 (0.0) | 0.307 |
| Immunologic parameters | | | |
| Total IgE (kU/L) (n = 128) | 154.0 (5.00–4,279.0) | 193.0 (28.1–5,001.0) | 0.321 |
| Blood eosinophils (/mm$^3$) (n = 120) | 250.0 (0.00–1,480.0) | 305.0 (0.00–1,110.0) | 0.742 |
| EW-specific IgE (kU/L) (n = 129) | 3.58 (0.14–57.80) | 6.25 (0.20–29.20) | **0.008** |
| EW-specific IgE/tIgE (n = 128) | 0.019 (0.00–0.31) | 0.293 (0.00–0.13) | 0.115 |
| EW-specific IgG4 (kU/L) (n = 62) | 1.08 (0.01–80.30) | 0.41 (0.08–10.40) | 0.242 |
| EW-specific IgG4/IgE (n = 62) | 0.31 (0.00–57.2) | 0.06 (0.01–1.41) | **0.023** |

Data are presented as number (%) or median (range). Statistically significant *P* values (*P* < 0.05) are in bold.
OFC, oral food challenge; IgE, immunoglobulin E; IgG4, immunoglobulin G4; tIgE, total IgE; EW, egg white.

**Table 3.** Characteristics of the patients who underwent milk OFCs to confirm tolerance development

| Characteristics | Passed OFCs (n = 49) | Non-passed OFCs (n = 37) | *P* value |
|---|---|---|---|
| Age (mon) | 25.0 (12.0–132.0) | 38.0 (11.0–155.0) | **0.029** |
| Male sex | 27 (55.1) | 21 (56.8) | 0.878 |
| Comorbidities | | | |
| Asthma | 13 (26.5) | 13 (35.1) | 0.390 |
| Atopic dermatitis | 32 (65.3) | 20 (54.1) | 0.291 |
| Allergic rhinitis | 8 (16.3) | 8 (21.6) | 0.532 |
| Multiple food allergy | 39 (79.6) | 30 (81.1) | 0.864 |
| Food-related symptoms | | | |
| Urticaria | 34 (69.4) | 22 (59.5) | 0.369 |
| Angioedema | 5 (10.2) | 6 (16.2) | 0.409 |
| Respiratory symptoms | 4 (8.2) | 4 (10.8) | 0.676 |
| Gastrointestinal symptoms | 6 (12.2) | 3 (8.1) | 0.535 |
| Anaphylaxis due to milk consumption | 5 (10.2) | 5 (13.5) | 0.635 |
| Immunologic parameters | | | |
| Total IgE (kU/L) (n = 86) | 177.0 (2.52–3,406.0) | 186.0 (8.80–2,891.0) | 0.631 |
| Blood eosinophils (/mm$^3$) (n = 83) | 255.0 (20.0–1,960.0) | 300.0 (0.00–1,110.0) | 0.915 |
| CM-specific IgE (kU/L) (n = 86) | 1.71 (0.04–19.60) | 3.75 (0.35–101.0) | **0.002** |
| CM-specific IgE/tIgE (n = 86) | 0.012 (0.00–0.07) | 0.024 (0.00–0.11) | **0.007** |
| Casein-specific IgE (kU/L) (n = 39) | 0.40 (0.00–7.46) | 3.87 (0.12–101.0) | **0.005** |
| Casein-specific IgG4 (kU/L) (n = 24) | 0.23 (0.08–3.98) | 0.68 (0.09–20.0) | 0.285 |
| Casein-specific IgG4/IgE (n = 24) | 0.69 (0.06–3.26) | 0.16 (0.02–1.13) | **0.048** |

Data are presented as number (%) or median (range). Statistically significant *P* values (*P* < 0.05) are in bold.
OFC, oral food challenge; IgE, immunoglobulin E; IgG4, immunoglobulin G4; tIgE, total IgE; CM, cow's milk.

months seemed to be higher in older than younger patients. As for milk, non-passed OFCs were associated with higher levels of cow's milk-specific IgE. The proportion of non-passed OFCs in patients older than 60 months was higher than in those younger than 60 months. For patients younger than 60 months, age seemed irrelevant; non-passed OFCs were distributed throughout all ages with a comparable proportion.


https://doi.org/10.4168/aair.2024.16.2.179

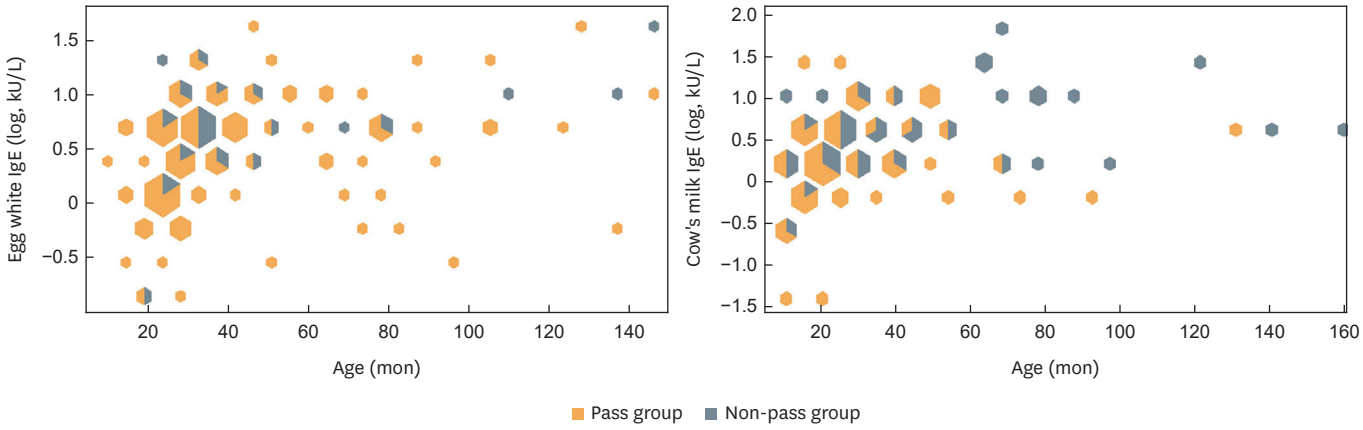


**Fig. 1.** Distribution of oral food challenge results based on age and food-specific immunoglobulin E for egg white and cow's milk. These weighted scatterplots (multi-class hexbins) visualize the relationship between OFC results in association with the age and allergen-specific IgE levels. The size of each hexbin is proportional to the observed frequency of the challenge at a certain age and IgE level. Within the hexbin, yellow represents the proportion of passed OFCs, whereas grey represents that of the nonpassed ones.
IgE, immunoglobulin E; OFC, oral food challenge.

## Predicting OFC outcomes for confirmation of tolerance development

Among the techniques for selection of variables of importance, XGBoost produced the highest AUC (95% CI) of 0.856 (0.699–0.974) for egg and 0.832 (0.662–0.966) for milk (**Supplementary Table S2**). Among the included variables, the top three important features were egg white-specific IgE, total IgE, and age for egg, and cow's milk-specific IgE, age, and total IgE for milk.

Further, we constructed a nomogram for predicting outcomes of OFCs to confirm tolerance development by using the top three important features selected via ML processing. Lower food-specific IgE was correlated with a higher probability of passing egg and milk OFCs. Additionally, younger age and higher total IgE were associated with a higher probability of passing. The AUCs (95% CI) for each nomogram were 0.623 (0.503–0.743) and 0.734 (0.628–0.840) for egg and milk, respectively (**Fig. 2**).

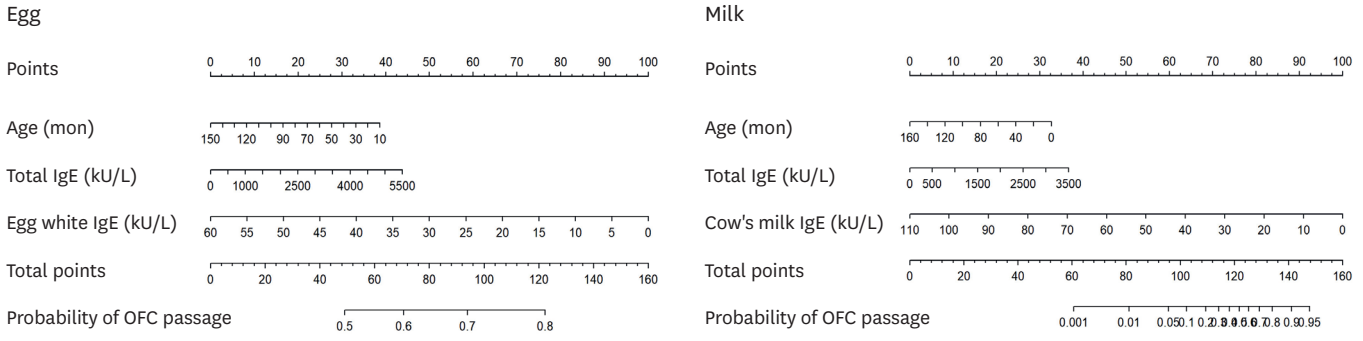


**Fig. 2.** Nomogram for patients of all ages. For each variable, a point is assigned by drawing an upward vertical line from the value on the variable to the "Points" axis. After identifying the points for each variable, these points are summed. The total sum is calculated on the "Total Points" axis, and a downward vertical line is drawn from this point to the bottom "Probability of OFC passage" axis.
IgE, immunoglobulin E; OFC, oral food challenge.


https://doi.org/10.4168/aair.2024.16.2.179

### External validation of the nomogram

We included 50 patients, each with egg allergy and milk allergy, for external validation of the nomogram to predict the outcome of OFCs for confirmation of tolerance development. The external validation cohort showed similar immunologic trends to the exploratory cohort. The pass group had lower egg white IgE ($P = 0.034$; **Supplementary Table S3**), cow's milk IgE ($P = 0.004$), and casein-specific IgE ($P = 0.002$) levels than the non-pass group (**Supplementary Table S4**). Finally, the validated nomogram had an AUC (95% CI) of 0.651 (0.494–0.808) for egg and 0.644 (0.487–0.802) for milk.

## DISCUSSION

This study analyzed OFCs to confirm tolerance development with the most common food allergens tested (egg and milk). The pass group from OFCs had lower food-specific IgE levels and higher food-specific IgG4/IgE ratios than the non-pass group for both food allergens. After selecting the relevant variables via ML, we developed a prediction model for passing OFCs to confirm tolerance development to food allergens. The nomograms encompassed age, the food-specific IgE and total IgE levels as predictive factors and were validated in an independent external cohort.

The data assessed included OFC status for over a decade, according to causative food allergens and indications, among patients from multiple referral institutions. The most common allergens tested were egg and milk, followed by peanut, walnut, and wheat, in accordance with the leading causes of food allergy in Korea.[18,19] The most common indication for OFCs was confirmation of tolerance development (61.8%). Indications can show a variable distribution because implementing OFCs is a clinical decision made by physicians related to patient factors, including age, food allergen, reaction severity, and caregiver-related factors. The severity of allergic reactions to OFCs depended on the indication; the reaction was significantly higher when determining threshold levels for oral immunotherapy, which might be inevitable.[2] The patients' demographics showed a lower median age in the pass group compared to the non-pass group. The timing of OFCs to confirm tolerance or determine safe intake and dosage for oral immunotherapy is at the discretion of the clinician, which may cause bias and delays in patients with a history of anaphylaxis, as OFC is relatively contraindicated in patients with a recent anaphylaxis history.[1]

The food-specific IgE level, specific IgE to total IgE ratio, and IgG4 level may be considered factors related to allergic reaction on ingestion.[4,5,20-24] The allergen-specific IgE levels were lower in the pass group than in the non-pass group, consistent with previous studies,[5,25] while IgG4/IgE ratios were higher in the pass group.[26,27] However, there were other inconsistencies and complexities regarding tolerance development. We investigated the trend in OFC results to confirm tolerance development via weighted scatterplots, which visualized the distribution of OFC results according to the participants' age and food-specific IgE level. Overall, 57.0% of the participants passed milk OFCs, while 79.8% passed egg OFCs. In egg OFCs, age and egg white-specific IgE were associated with OFC outcomes in children younger than 60 months, but did not show much association in older children. In milk OFCs, age seemed irrelevant in children under 60 months, whereas more children older than 60 months did not pass.

The weighted scatterplots revealed the need for a novel combination of associated factors. While many prior investigations have used specific variables to predict OFC outcomes,


https://doi.org/10.4168/aair.2024.16.2.179

few studies have evaluated the combination of important factors, particularly for the confirmation of tolerance development in food allergy.[5,21,28,29] ML was first utilized for predicting outcomes of the heated egg challenge, and a recent study with ensemble learning developed a prediction model for peanut, egg, and milk allergies.[13,14] Nevertheless, the aforementioned studies developed models for diagnosing food allergies. In real-world clinical settings, OFCs are also performed for the confirmation of tolerance development. Despite reports on the clinical implications of each factor, clinicians are expected to consider these variables collectively when deciding the timing of an OFC, which is a challenging task. There is a need for a ready-to-use prediction model that can aid clinicians in decision-making and minimize risks.

Therefore, we selected important factors via ML processing and constructed food-specific nomograms to predict OFC outcomes. We also validated these nomograms using an external independent cohort. The nomogram for egg OFCs to confirm tolerance showed that a younger age, higher total IgE level, and lower egg white-specific IgE level increased the likelihood of passing. Similarly, in the nomogram for milk OFCs, younger age, lower cow's milk IgE level, and higher total IgE level indicated a higher probability of passing. An increased total IgE level was reported to reduce allergic reactivity; patients with higher total IgE levels were significantly less responsive in egg and milk OFCs.[30] A possible explanation for this association is that higher nonspecific or low-affinity IgE levels suppress allergen-specific IgE-mediated activation of basophils *in vitro*.[31] To our knowledge, these nomograms are the first easy-to-use tool for predicting tolerance development in children with egg and milk allergies. The prediction from OFC outcomes can guide OFC enforcement timing, while minimizing associated risks.

Despite data collection spanning over a decade from multiple institutions, there are certain limitations. Pediatric OFCs are inherently resource-intensive and time-consuming, compounded by diverse allergenic foods and frequent natural tolerance development. Consequently, several cases are diagnosed and resolved without OFCs, leading to a limited sample size. In this study, we focused primarily on egg and milk, the most prevalent allergens in our dataset and those most associated with tolerance development. Allergens, such as peanuts and buckwheat, are more prone to systemic reactions, indicating a greater risk of anaphylaxis in OFCs. However, they have a lower rate of natural tolerance development and, thus, are less frequently used in OFCs for tolerance confirmation.[32] Further research with a larger sample size would enable predictive modeling for reducing systemic reactions for these allergens.

Although retrospective in nature, this study conducted a fine analysis using nomograms for egg and milk OFCs, with validation in an independent cohort. The clinical decision to implement OFCs depends on each clinician. We attempted to overcome clinician-related factors by conducting a multicenter study over 10 years and using a separate validation cohort comprising more than eight physicians. Our nomograms achieved an AUC (95% CI) of 0.623 (0.503–0.743) and 0.734 (0.628–0.840) for egg and milk OFCs, which were likely influenced by patient heterogeneity and a small sample size. Despite these challenges, the validation group demonstrated AUCs of 0.651 (0.494–0.808) and 0.644 (0.487–0.802) for egg and milk, respectively. This validation can be deemed comparable because the finding was achieved with a small sample size (n = 50) from a different institution with other environmental factors. Statistically, comparing AUC levels between the original and validation cohorts resulted in *P*-values of 0.787 and 0.361 for egg and milk, respectively, indicating a statistically insignificant difference. Furthermore, when evaluated using Area


https://doi.org/10.4168/aair.2024.16.2.179

Under the Precision-Recall Curve, which can be used in case of an imbalance between data used in modeling, the values exceeded the actual prevalence of pass outcomes, namely 0.840 and 0.790 for egg and milk, respectively. In addition, upon performing modeling with adjustments for data imbalance, the results exhibited comparable outcomes in terms of AUC (data not shown).[33] This aspect reinforces the potential of our nomograms as a novel and practical clinical tool, demonstrating promising utility despite the limitations.

Finally, our nomogram can guide OFC enforcement timing indirectly regarding safety. However, our results should be interpreted with caution. The majority of patients who undergo OFCs to confirm tolerance development are under diet restriction due to previous—mostly severe—allergic reactions. Therefore, our results should not be used as a predictive marker of tolerance development to food allergens, but as a tool to help clinicians make decisions for a safer OFC.

The results of this study indicated that combined age, total IgE, and food-specific IgE correlated with an increased likelihood of passing OFCs for tolerance confirmation in children with egg or milk allergies. Our prediction model for tolerance confirmation can guide clinicians regarding optimal timing for OFCs, while minimizing risks.

## ACKNOWLEDGMENTS

We are grateful to Yun Na Lee (Department of Dermatology, Yonsei University College of Medicine) for collaborating on the machine learning model and providing the necessary technical support for the study.
This study was supported by the National Research Foundation of Korea (NRF) grant (No. 2022R1A2C1010462) funded by the Korea government (MSIT).

## SUPPLEMENTARY MATERIALS

**Supplementary Table S1**
Distribution and results of OFCs

**Supplementary Table S2**
Performance of the machine learning models for egg and milk oral food challenges

**Supplementary Table S3**
Immunologic parameters of the patients in the external validation cohort who underwent egg OFCs to confirm tolerance development

**Supplementary Table S4**
Immunologic parameters of patients in the external validation cohort who underwent milk OFCs to confirm tolerance development

## REFERENCES

1. Nowak-Wegrzyn A, Assa'ad AH, Bahna SL, Bock SA, Sicherer SH, Teuber SS, et al. Work group report: oral food challenge testing. J Allergy Clin Immunol 2009;123:S365-83. PUBMED | CROSSREF

2. Itazawa T, Adachi Y, Takahashi Y, Miura K, Uehara Y, Kameda M, et al. The severity of reaction after food challenges depends on the indication: a prospective multicenter study. Pediatr Allergy Immunol 2020;31:167-74. PUBMED | CROSSREF
3. Upton J, Alvaro M, Nadeau K. A perspective on the pediatric death from oral food challenge reported from the Allergy Vigilance Network. Allergy 2019;74:1035-6. PUBMED | CROSSREF
4. Sampson HA. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. J Allergy Clin Immunol 2001;107:891-6. PUBMED | CROSSREF
5. Perry TT, Matsui EC, Kay Conover-Walker M, Wood RA. The relationship of allergen-specific IgE levels and oral food challenge outcome. J Allergy Clin Immunol 2004;114:144-9. PUBMED | CROSSREF
6. Bird JA, Leonard S, Groetch M, Assa'ad A, Cianferoni A, Clark A, et al. Conducting an oral food challenge: an update to the 2009 adverse reactions to foods committee work group report. J Allergy Clin Immunol Pract 2020;8:75-90.e17. PUBMED | CROSSREF
7. Beigelman A, Strunk RC, Garbutt JM, Schechtman KB, Jaenicke MW, Stein JS, et al. Clinical and laboratory factors associated with negative oral food challenges. Allergy Asthma Proc 2012;33:467-73. PUBMED | CROSSREF
8. Kim JD, Kim SY, Kwak EJ, Sol IS, Kim MJ, Kim YH, et al. Reduction rate of specific IgE level as a predictor of persistent egg allergy in children. Allergy Asthma Immunol Res 2019;11:498-507. PUBMED | CROSSREF
9. Ponce M, Diesner SC, Szépfalusi Z, Eiwegger T. Markers of tolerance development to food allergens. Allergy 2016;71:1393-404. PUBMED | CROSSREF
10. Jang H, Kim EG, Kim M, Kim SY, Kim YH, Sohn MH, et al. Metabolomic profiling revealed altered lipid metabolite levels in childhood food allergy. J Allergy Clin Immunol 2022;149:1722-1731.e9. PUBMED | CROSSREF
11. Haque F, Ibne Reaz MB, Chowdhury ME, Md Ali SH, Ashrif A Bakar A, Rahman T, et al. A nomogram-based diabetic sensorimotor polyneuropathy severity prediction using Michigan neuropathy screening instrumentations. Comput Biol Med 2021;139:104954. PUBMED | CROSSREF
12. Choi S, Kim J, Lee JH, Lee YN, Lee JH. Clinical and histological characteristics of localized morphea, generalized morphea and systemic sclerosis: a comparative study aided by machine learning. Acta Derm Venereol 2023;103:adv11953. PUBMED | CROSSREF
13. Kuniyoshi Y, Tokutake H, Takahashi N, Kamura A, Yasuda S, Tashiro M. Machine learning approach and oral food challenge with heated egg. Pediatr Allergy Immunol 2021;32:776-8. PUBMED | CROSSREF
14. Zhang J, Lee D, Jungles K, Shaltis D, Najarian K, Ravikumar R, et al. Prediction of oral food challenge outcomes via ensemble learning. Inform Med Unlocked 2023;36:101142. CROSSREF
15. Song TW, Kim KW, Kim WK, Kim JH, Kim HH, Park YM, et al. Guidelines for the oral food challenges in children. Pediatr Allergy Respir Dis 2012;22:4-20.
16. Cox L, Larenas-Linnemann D, Lockey RF, Passalacqua G. Speaking the same language: the World Allergy Organization subcutaneous immunotherapy systemic reaction grading system. J Allergy Clin Immunol 2010;125:569-74, 574.e1-574.e7. PUBMED | CROSSREF
17. Muller MP, Tomlinson G, Marrie TJ, Tang P, McGeer A, Low DE, et al. Can routine laboratory tests discriminate between severe acute respiratory syndrome and other causes of community-acquired pneumonia? Clin Infect Dis 2005;40:1079-86. PUBMED | CROSSREF
18. Park M, Kim D, Ahn K, Kim J, Han Y. Prevalence of immediate-type food allergy in early childhood in Seoul. Allergy Asthma Immunol Res 2014;6:131-6. PUBMED | CROSSREF
19. Kim M, Lee JY, Jeon HY, Yang HK, Lee KJ, Han Y, et al. Prevalence of immediate-type food allergy in Korean Schoolchildren in 2015: a nationwide, population-based study. Allergy Asthma Immunol Res 2017;9:410-6. PUBMED | CROSSREF
20. Shek LP, Soderstrom L, Ahlstedt S, Beyer K, Sampson HA. Determination of food specific IgE levels over time can predict the development of tolerance in cow's milk and hen's egg allergy. J Allergy Clin Immunol 2004;114:387-91. PUBMED | CROSSREF
21. Gupta RS, Lau CH, Hamilton RG, Donnell A, Newhall KK. Predicting outcomes of oral food challenges by using the allergen-specific IgE-total IgE ratio. J Allergy Clin Immunol Pract 2014;2:300-5. PUBMED | CROSSREF
22. Ishizaka A, Sakiyama Y, Nakanishi M, Tomizawa K, Oshika E, Kojima K, et al. The inductive effect of interleukin-4 on IgG4 and IgE synthesis in human peripheral blood lymphocytes. Clin Exp Immunol 1990;79:392-6. PUBMED | CROSSREF
23. Platts-Mills T, Vaughan J, Squillace S, Woodfolk J, Sporik R. Sensitisation, asthma, and a modified Th2 response in children exposed to cat allergen: a population-based cross-sectional study. Lancet 2001;357:752-6. PUBMED | CROSSREF

24. Tomicić S, Norrman G, Fälth-Magnusson K, Jenmalm MC, Devenney I, Böttcher MF. High levels of IgG4 antibodies to foods during infancy are associated with tolerance to corresponding foods later in life. Pediatr Allergy Immunol 2009;20:35-41. PUBMED | CROSSREF

25. Montesinos E, Martorell A, Félix R, Cerdá JC. Egg white specific IgE levels in serum as clinical reactivity predictors in the course of egg allergy follow-up. Pediatr Allergy Immunol 2010;21:634-9. PUBMED | CROSSREF

26. Okamoto S, Taniuchi S, Sudo K, Hatano Y, Nakano K, Shimo T, et al. Predictive value of IgE/IgG4 antibody ratio in children with egg allergy. Allergy Asthma Clin Immunol 2012;8:9. PUBMED | CROSSREF

27. Foong RX, Santos AF. Biomarkers of diagnosis and resolution of food allergy. Pediatr Allergy Immunol 2021;32:223-33. PUBMED | CROSSREF

28. Rolinck-Werninghaus C, Niggemann B, Grabenhenrich L, Wahn U, Beyer K. Outcome of oral food challenges in children in relation to symptom-eliciting allergen dose and allergen-specific IgE. Allergy 2012;67:951-7. PUBMED | CROSSREF

29. DunnGalvin A, Daly D, Cullinane C, Stenke E, Keeton D, Erlewyn-Lajeunesse M, et al. Highly accurate prediction of food challenge outcome using routinely available clinical data. J Allergy Clin Immunol 2011;127:633-639.e1-3. PUBMED | CROSSREF

30. Horimukai K, Hayashi K, Tsumura Y, Nomura I, Narita M, Ohya Y, et al. Total serum IgE level influences oral food challenge tests for IgE-mediated food allergies. Allergy 2015;70:334-7. PUBMED | CROSSREF

31. Christensen LH, Holm J, Lund G, Riise E, Lund K. Several distinct properties of the IgE repertoire determine effector cell degranulation in response to allergen challenge. J Allergy Clin Immunol 2008;122:298-304. PUBMED | CROSSREF

32. Savage J, Sicherer S, Wood R. The natural history of food allergy. J Allergy Clin Immunol Pract 2016;4:196-203. PUBMED | CROSSREF

33. Elreedy D, Atiya AF. A comprehensive analysis of synthetic minority oversampling technique (SMOTE) for handling class imbalance. Inf Sci 2019;505:32-64. CROSSREF