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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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Machine learning approach and oral food challenge with heated egg

To the Editor.

Serum levels of allergen-specific IgE (sIgE) are among the tools used to diagnose hen's egg allergy. However, sIgE levels may lead to false-positive results and reliable diagnostic cutoff levels are currently unclear.¹ Recently, machine learning (ML) techniques have been applied to predict clinical diagnoses and prognoses in many fields of medicine.^{2,3} To the best of our knowledge, there are no published studies that have applied ML methods to issues related to outcomes from heated egg oral food challenge (OFC). We hypothesized that an ML approach may help clinicians to make clinical decisions regarding the need for and conduct of OFC in the clinical setting. We aim to construct a ML method that will reliably predict the outcome of heated egg OFC using routinely available laboratory data.

We retrospectively evaluated clinical records of patients who underwent an OFC with heated hen's egg at Tsugaruhoken Medial

COOP Kensei Hospital between January 2014 and December 2019. The Ethics Committee of Tsugaruhoken Medial COOP Kensei Hospital reviewed and approved this study. Written informed consent was obtained from the patient's guardians. The following data were collected: age (year), gender, total IgE (tIgE), egg white (EW)-sIgE, egg yolk (EY)-sIgE, and ovomucoid (OM)-sIgE. Serum IgE levels were measured using the ImmunoCAP assay system. Ratios of sIgE/tIgE ratio were calculated for each measurement.

OFC was performed openly with heated egg administered in one of the following forms: baked pumpkin cake containing either one whole egg or a half of egg, well-cooked scrambled eggs (one whole egg or one half of one egg), or hard-boiled EWs alone (16 g or 32 g). The challenge foods were administered in increments of 1/16, 1/16, 1/8, 1/4, and 1/2 of the full challenge at 30-minute intervals. No further challenges were administered if allergic reactions appeared.

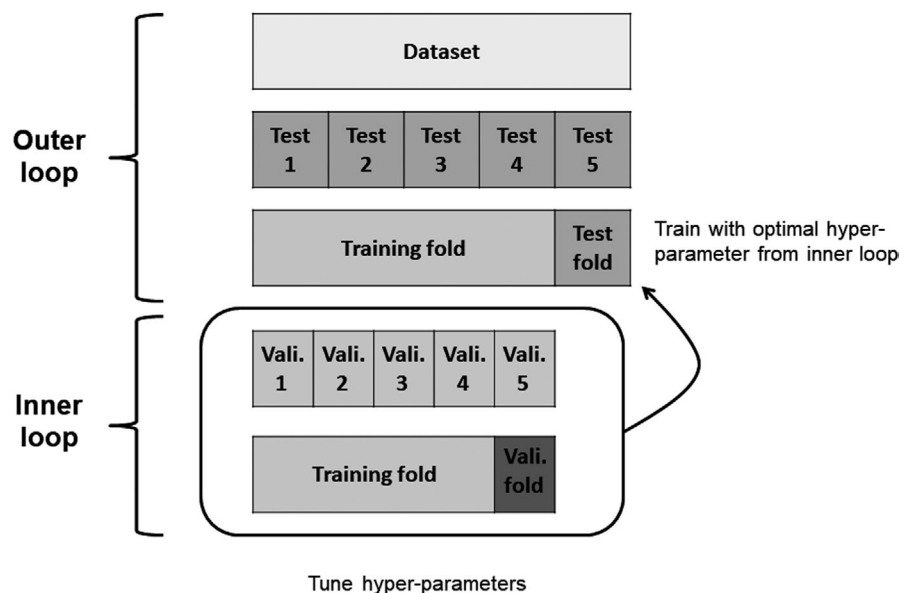


FIGURE 1 Flow chart demonstrating the fivefold nested cross-validation method. Abbreviation: vali.; validation

TABLE 1 Clinical and laboratory characteristics between positive and negative oral food challenge

	OFC-positive (n = 31)	OFC-negative (n = 36)	p-Value
Age in years, mean, median (IQR)	3.7, 3 (1–5.5)	2.1, 1 (1–2.3)	
<1 year old, n (%)	0 (0)	2 (6)	.012
1 year old, n (%)	10 (32)	17 (47)	
≥2 year old, n (%)	21 (68)	17 (47)	
Gender, male, n (%)	15 (48)	25 (69)	.13
Egg formulation for OFC			
Boiled egg white, n	18	12	.093
Pumpkin cake with whole egg, n	10	21	
Scrambled egg with whole egg, n	3	3	
Total IgE (kU _A /L), mean, median (IQR)	886, 130 (39–490)	807, 87 (26–305)	.28
Specific IgE (kU _A /L)			
Egg white, mean, median (IQR)	26, 14.2 (5.5–34.1)	13, 6.6 (2.0–16.1)	.016
Egg yolk, mean, median (IQR)	6.0, 2.5 (0.7–9.8)	5.6, 1.1 (0.3–5.1)	.091
Ovomucoid, mean, median (IQR)	15, 5.3 (0.9–12.4)	6.2, 0.8 (0.2–9.0)	.021
Specific IgE/total IgE ratio			
Egg white, (×10 ⁻²), mean, median (IQR)	14, 12 (5.2–23)	8.8, 7.1 (2.3–12.7)	.082
Egg yolk, (×10 ⁻²), mean, median (IQR)	2.7, 2.0 (1.0–3.2)	2.1, 1.3 (0.6–3.1)	.29
Ovomucoid, (×10 ⁻²), mean, median (IQR)	6.6, 3.6 (1.0–8.5)	2.8, 1.2 (0.3–2.4)	.021

Abbreviation IQR; interquartile range.

All children were observed in the hospital for 4 hours after the final ingestion. We identified a patient as OFC positive if he or she experienced an immediate allergic reaction, which included either one clear objective sign or multiple persistent subjective symptoms⁴ in response to ingestion of less than one half of one egg or 16 g of EW.

Statistical analysis was carried out in Python version 3.6 (Python Software Foundation). We used Mann-Whitney U tests for continuous variables and chi-square tests for categorical variables. We evaluated the predictive performance of the three supervised ML classifiers. Specifically, we trained using logistic regression (LR) with L2 regularization, linear support vector machine (SVM), and eXtreme gradient boosting (XGB), which are commonly used supervised classification ML models, using the scikit-learn and XGBoost packages. Previous studies reported that XGB achieved

better performance for clinical prediction than other ML models.^{5,6} The predictive performance was evaluated by area under the receiver operator characteristic curve (AUC), accuracy, sensitivity, and specificity. Three ML models were produced with following variables: age (years), gender, tIgE, EW-sIgE, EY-sIgE, OM-sIgE, EW-sIgE/tIgE ratio, EY-sIgE/tIgE ratio, and OM-sIgE/tIgE ratio. For preprocessing, we standardized variables by rescaling data to have a mean of 0 and a standard deviation of unit variance. To evaluate the predictive performance of three ML models and algorithms, we performed the nested fivefold cross-validation (CV)⁷ with “GridSearchCV” for hyper-parameter optimization (Figure 1). In this study, we repeated the nested CV a total of 10 times in separate splits and averaged the result to avoid sampling bias and data overfitting. Additionally, to assess the relative usefulness of the ML models, we compared their predictive performance with that determined using previously proposed cutoff levels for EW-sIgE and OM-sIgE, which were reported by Komata et al,⁸ Ando et al,⁹ and Haneda et al¹⁰ Komata et al⁸ proposed a 95% positive predictive value (PPV) cutoff level for EW-sIgE as ≥ 13 kU_A/L for < 1 year of age, ≥ 23 kU_A/L for 1 year of age, and ≥ 30 kU_A/L for ≥ 2 years of age. Ando⁹ proposed a cutoff level for OM-sIgE as ≥ 10.8 kU_A/L. Haneda¹⁰ proposed a cutoff level for OM-sIgE as ≥ 26.6 kU_A/L.

The initial patient group underwent 84 OFC trials with heated hen's egg preparations. Of these, 17 OFC trials were excluded, because one or more of the following values could not be found in their medical records: tIgE, EW-sIgE, EY-sIgE, and/or OM-sIgE. The demographic and laboratory data of 67 patients are summarized in Table 1.

As shown in Table 2, AUCs for the LR and linear SVM models exceeded 0.80. The AUC for XGB was lower than for the other two models. The results of accuracy (mean ± SD) were 0.72 ± 0.024, 0.72 ± 0.022, and 0.59 ± 0.035 in LR, linear SVM, and XGB, respectively. Accuracy using any one of the previously proposed cutoff levels was about 0.60.

We present here the predictive performances of three ML models (LR, linear SVM, and XGB) for determining the outcome of a heated egg OFC in a retrospective analysis of food-allergic children. ML models may have significant advantages toward these ends because multiple variables from a single patient are considered simultaneously. ML is flexible and can be applied to many tasks and clinical problems.

To our best knowledge, this is the first study to compare the predictive performances of ML models for the outcome of OFCs to heated egg. The ML approach is straightforward and the models can be easily retrained and updated with the newest data available. By contrast, there were several limitations associated with this study. First, the dataset used to train and validate the ML models was relatively small. However, we used nested CV to obtain an unbiased estimate of the true error and we also repeated nested CV 10 times and averaged the validation error to reduce sampling bias. Second, the entire dataset came from retrospective findings from a single hospital. Accordingly, our results may not

TABLE 2 Predictive performances of the three machine learning models vs. clinical data alone

	AUC	Sensitivity	Specificity	Accuracy
LR	0.82 ± 0.018	0.70 ± 0.048	0.73 ± 0.040	0.72 ± 0.024
SVM	0.83 ± 0.027	0.68 ± 0.029	0.74 ± 0.044	0.72 ± 0.022
XGBoost	0.63 ± 0.056	0.51 ± 0.057	0.66 ± 0.038	0.59 ± 0.035
Komata ⁸ (95%PPV)		0.29	0.83	0.58
Ando ⁹				
(Positive DP)		0.29	0.83	0.58
(Negative DP)		0.71	0.53	0.61
Haneda ¹⁰ (95%PPV)		0.13	0.94	0.57

Note Abbreviations: AUC, area under the receiver operator characteristic curve; LR, logistic regression; SVM, support vector machine; XGB, eXtreme gradient boosting, PPV, positive predictive value; DP, decision point

be completely generalizable to other populations. However, the findings from hospital-specific model are meaningful and valuable only as a starting point. Further investigations are required to determine the prediction performance of our ML model in other settings. Third, we did not include clinical information, such as history of immediate reaction, comorbid allergic disease, and the results of skin tests, in our prediction model. Addition of these factors in future studies may improve the prediction performance of the models.

In conclusion, we evaluated the performance of ML models for predicting the outcomes of heated egg OFCs. Models using LR and linear SVM had reliable performance. Ultimately, clinically validated predictions based on the recommendations from ML models will be available to inform the clinical practice of food allergy.

KEYWORDS

area under curve, egg allergy, logistic regression, machine learning, nested cross-validation, oral food challenge, predictive model, support vector machine

CONFLICT OF INTEREST

None.

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