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Assessment of egg and milk allergies among Indians by revalidating a food allergy predictive model

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ABSTRACT

Background: The recent upsurge in food allergy indicates the need for accurate medical diagnostics. The application of predictive diagnostic models can envisage the outcome of oral food challenge (OFC), reducing cost and time. A logistic regression model was developed by Dunn-Galvin for children predicting OFC outcome using six predictors viz: sex, age, history, specific IgE, total IgE minus specific IgE, and skin prick test. This model was later updated by Klemans, reducing the number of predictors enhancing the calibration and discrimination of outcome.

Objective: Our aim was to revalidate both the models for assessment of egg and milk allergies among Indians in the age group 0–19 years and to determine regression coefficients for our study population.

Methods: Revalidation was done at the allergy clinic using OFC outcomes of egg and milk allergic patients. Precise values of the predictors were set up for which calibration (predicted against observed outcome) and discrimination (area under curve [AUC] of receiver operator characteristic curve [ROC]) would be better.

Results: The Klemans model with reduced number of predictors showed better accuracy, calibration and discrimination than the DunnGalvin. Best calibration for egg allergy was achieved in the Klemans model with correlation coefficient (r^2) of 0.90 and accuracy of 97%. The AUC of ROC was 0.90. For milk allergy, the coefficient was 0.94 with accuracy of 98%. The AUC was 0.91.

Conclusion: The present study showed that mathematical models are non-invasive and can be successfully used as appropriate alternative to OFC in Indian population after proper validation.

Keywords: Oral food challenge, DunnGalvin model, Klemans model

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INTRODUCTION

Clinical studies worldwide reported that incidence of milk and egg allergies have been increased during last 2 decades[1–3] including cases from India.[4–7] Milk and egg are the most common allergens that cause food allergy mainly in infants and young children.[8,9] Recent evidence suggests that both allergies to some extent could persist during adolescence.[10,11] Both allergies are defined as adverse immune reactions triggered by specific allergenic proteins. Reactions might be either IgE-based, non-IgE-based, or mixed, whereas IgE-based allergy was prevalent.[8,12] The public awareness in any food allergy, which was little known before, has also grown rapidly. The diagnostics tools eg, oral food challenge (OFC), specific IgE (sIgE) test, skin prick test (SPT), component resolved diagnostics (CRD), etc, remain same today but their correlations with food allergy allow the achievement of adequate diagnosis of food allergy.[13,14] Under this scenario, new hopes rekindled with predictive diagnostic models that can envisage the outcome of OFC using sIgE, Total IgE (tIgE), SPT, and so forth. DunnGalvin et al, 2011 showed that a combination of diagnostic test results such as sIgE, SPT, tIgE minus sIgE, and so forth, along with patients' demographic characteristics like age, sex, and history of allergic symptoms could predict OFC results.[15] They used nonlinear logistic regression, which was set up with the data of 239, 110, and 80 patients of peanut, milk, and egg allergies and validated on 23, 14, and 13 patients, respectively. The receiver operator characteristics (ROC) curves showed area under the curve (AUC) of 0.97, 0.94, and 0.95 respectively for peanut, milk ,and egg allergies. This promising diagnostic model was revalidated by Klemans et al[16] in peanut allergy reducing number of predictors, which showed good discrimination (88%) but poor calibration ($P < 0.001$).

Therefore, we feel both the models are needed to be revalidated with data from different geographical locations to make the predictive mathematical model successful and more powerful alternative diagnostic tool than existing OFC in the Indian population. In the present study, both models were rigorously tested using the data of egg and milk allergies collected from the allergy clinic. This is, to the best of our knowledge, unique in Asia.

MATERIALS AND METHODS

Inclusion and exclusion criteria

The study included 91 and 98 patients (Fig. 1) with self-reported egg and milk allergies respectively, coming from rural and urban areas of West Bengal, India, both male and female in the age group 0-19 years, seeking treatment at the allergy clinic during the months of February to November, 2020. All were reported to be suffering from different food allergic manifestations such as itching, nausea, abdominal pain, diarrhoea, shortness of breath, angioedema, and urticarial rash, either alone or in different combinations. The demographic and clinical features of individual patient including age, sex, height, weight, presence of urticaria, atopic dermatitis, gastrointestinal problems, oral allergy syndrome, asthma etc, were recorded in a well-prepared questionnaire. A suspected history of egg/milk allergy referred to an allergic reaction occurred immediately or within 2 h after consumption of responsible food or food-based products. Patients residing temporarily in West Bengal, suffering from systemic diseases such as diabetes and thyroid disorders or were unwilling to participate in the study, were excluded ($n = 29$).

Skin prick test

All the suspected egg and milk allergic patients were subjected to SPT against respective allergens. The SPT solutions with egg and milk allergen extracts were supplied by Credisol®, Mumbai, India. The test was done on the flexor side of forearms using sterile lancet separately for each allergen. Histamine (10 mg/mL of histamine phosphate) and 0.9% sterile saline were used as positive and negative controls, respectively. The wheal diameter (mean of the longest diameter and its perpendicular) was measured after 20 min of allergen-antibody reactions.

Measurement of allergen specific IgE

Egg-white and milk specific IgE were measured using Pharmacia Immuno CAP 100 system. This test was calibrated as per World Health Organization (WHO) standard with a range of 0.35–100 kU/L.

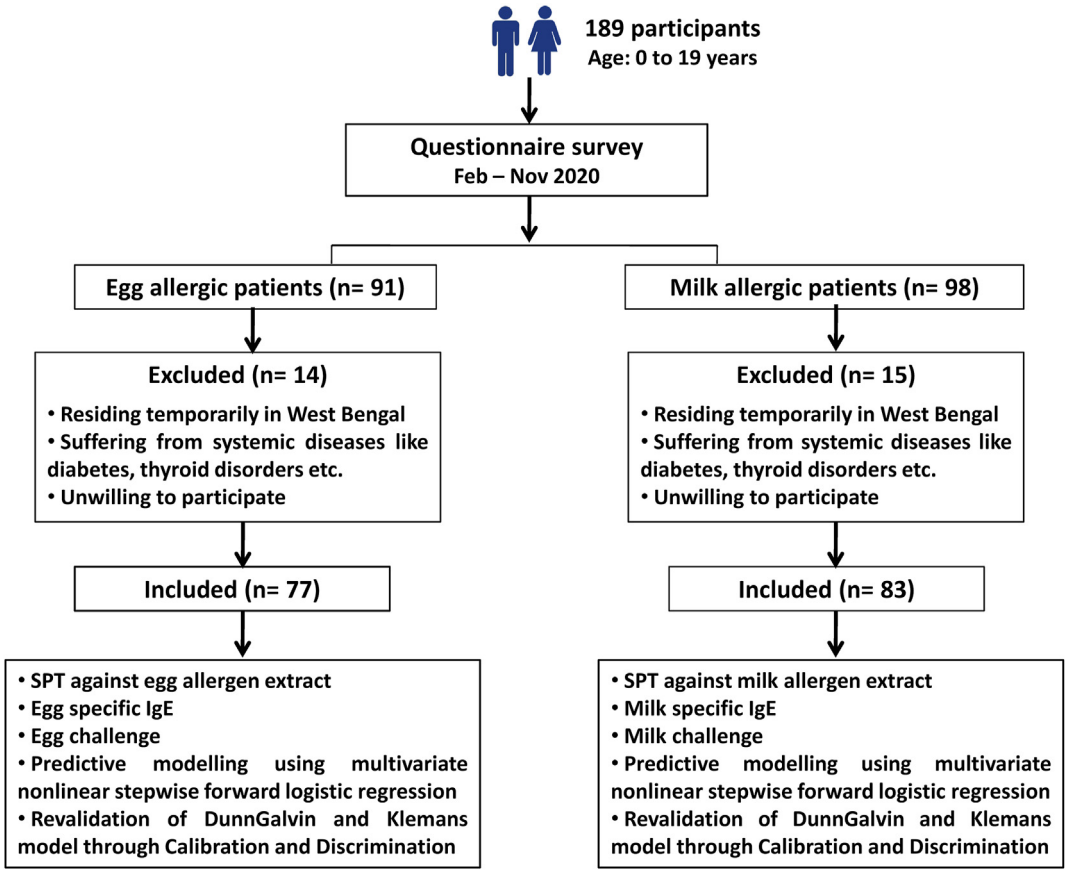

Fig. 1 The consort study diagram

Oral food challenge

Single blinded OFC was performed on 77 egg and 83 milk allergic patients depending on clinical decision given by the physician, with consideration of clinical history, results of SPT and/or food-specific IgE. The guidelines given in the article by Bird et al[17] were followed in the present study. OFC was conducted without placebo and foods were provided every time with a masking vehicle (Supplementary Table 1) to reduce bias. Only the physician was not blinded about the food being tested. Verbal or written consent was taken from all participants or from their parents. Only healthy patients, whose allergic status was under optimal control at the time of OFC, were selected for the test. The tested food items were eliminated from patients diets for 2 weeks before OFC. The tests were started at normal breakfast time in fasting condition of the participants and continued for 3 h under supervision of a physician. Before the start of the test, pulse rate, respiratory rate, oxygen saturation in blood (sPO_2) and peak expiratory flow rate (PEFR) of the patients were recorded. At every 30 min, dose of the selected food items was increased and patients were re-examined for the above health parameters. Epinephrine, antihistamines, or intravenous steroids were used as the treatment of allergic reactions during the test. OFC was stopped and considered positive according to the following criteria: i) Objective signs like rhino-conjunctivitis, angioedema, urticaria, emesis, diarrhoea, hoarseness, stridor, and wheezing; ii) Subjective symptoms like oral swelling/itching, nausea, abdominal pain, or throat tightness occurred at 3 subsequent doses; iii) Changes in vital signs viz pulse rate (>110/min), respiratory rate (>25/min), sPO_2 (<90%) and PEFR (≥20% reduction from predicted value). The predicted values of PEFR (L/min) were calculated using the following formula:[18]

$$\text{For male} = -1.807 \times \text{age in years} + 3.206 \times \text{Height in cm}$$

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$$\text{For female} = -1.454 \times \text{age in years} + 2.368 \times \text{Height in cm}$$

Data analysis

The outcome of egg and milk allergies was calculated using the following formula:

$$\text{Allergy probability} = \frac{e^{a+\sum_i b_i x_i}}{1+e^{a+\sum_i b_i x_i}}$$

Here, a = intercept, x_i is the clinical predictors such as sex, history, groups 1, 2, 3, and 4, SPT, sIgE to a particular food allergen, tIgE minus sIgE and age; with $i = 1, 2, 3, 4, \ldots, 9$. Similarly b_i is estimator or regressor of the corresponding value of x_i. Histories 1, 2, 3 and 4 denote skin or oral or gastrointestinal or upper respiratory tract only or 1 system problems; upper respiratory tract and gastrointestinal or 2 systems problems; lower respiratory tract or 3 system problems and cardiovascular or 4 system problems, respectively. No symptoms would make the score 0. All predictors were dichotomized; SPT and sIgE were defined as positive (above decision point) or negative (below decision point) on the basis of published decision points for allergen types:[19-21] egg (≥7 mm; ≥7 kU/L) and milk (≥8 mm; ≥15 kU/L); history of reaction (yes/no).

The formulas of both DunnGalvin and Klemans were tested by calibration and discrimination. Calibration indicates agreement between predicted and observed OFC outcomes. This is tested using calibration (observed vs predicted probabilities) plot. As the plot is nearer to a straight line passing through the origin of X-Y axis with the slope of 1, calibration is better. Besides, Hosmer-Lemeshow test result with $P < 0.05$ indicates better calibration. On the contrary, discrimination means degree of distinction between positive and negative outcomes, studied with ROC curve and corresponding AUC was calculated. Better discrimination indicates higher value of AUC. AUC less than 0.5 indicates no discrimination and 1 indicates perfect discrimination.

Six different variables such as sex, age, history, sIgE, tIgE minus sIgE, and SPT were used in the DunnGalvin model, whereas the Klemans model showed that instead of using all the variables if only 4 (sex, SPT, sIgE, tIgE minus sIgE) of them had been kept, the DunnGalvin formula could predict food allergy better. In the present study, a multivariate nonlinear stepwise forward logistic regression was carried out and regression coefficients were calculated for all the variables. sIgE values were subtracted from tIgE so that sIgE would be accounted for only once. All analyses were done using Prism ver. 7 (GraphPad Prism, San Diego, CA). The calibration plot was drawn in Sigma plot ver. 10.0 (Systat Software Inc, USA).

RESULTS

Demographic and clinical attributes of the patients

Out of 77 and 83 potential cases of egg and milk allergies, respectively as per clinical diagnosis, 3 egg and 2 milk allergic patients had inconclusive OFC because they had refused to ingest the food, hence excluded from analyses. Therefore, we included 74 egg and 81 milk allergic patients with OFC results (Table 1a and b).

In egg allergy, 26 patients gave positive results, whereas 48 patients were found as egg-tolerant (Table 1a). 43% of the patients showed severe ie, above 7 mm reaction in SPT and 36% had specific IgE level of 7 kU/L or above in serum. We considered symptoms of 1 system as the reference for odds ratio (OR) calculation. Egg allergic and tolerant groups differed significantly in the following parameters: tIgE minus sIgE [OR = 1.16, 95% confidence interval (CI) = 1.03–1.30, p = 0.01], tolerance to baked egg (OR = 2.64, 95% CI = 1.05–6.61, p = 0.04), patients bearing 2 symptoms (OR = 1.77, 95% CI = 1.07–2.94, p = 0.03) or 3 symptoms (OR = 2.88, 95% CI = 1.59–5.24, p = 0.0005) (Supplementary Fig. 1(a)).

For milk, the study group comprised of 34 milk-allergic and 47 milk-tolerant patients (Table 1b). Severe SPT reactions (≥8 mm) were shown by 53% patients; whereas specific IgE level of 15 kU/L or above was found in 48% patients. Milk allergic and tolerant group were compared with 1 system problem as the reference and showed significant differences on the basis of OR in the following parameters: tIgE minus sIgE

(a) Egg allergy			
	Egg allergic (n = 26)	Egg tolerant (n = 48)	P value
Males, n (%)	15 (58)	26 (54)	0.96
Females, n (%)	11 (42)	22 (46)	
Median age (y)	6 (0–17)	9 (3–19)	0.75
Median weight (kg)	27 (4–69)	45 (14–72)	0.84
Median height (cm)	112 (54–173)	126 (94–178)	0.64
Median SPT (mm)	7.06 (3.55–10.95)	6.15 (3.06–7.95)	0.58
Median sIgE (KU/L)	25.02 (0.01–46.5)	4.67 (0.001–16.5)	0.06
Median tIgE – sIgE	4191.21 (49.76–7447.5)	2038.52 (146–5362)	0.01*
Tolerance to baked egg[a], n (%)	18 (69)	15 (31)	0.004*
1 system, n (%)	23 (88)	38 (79)	0.49
2 systems, n (%)	18 (69)	17 (35)	0.01*
3 systems, n (%)	16 (61)	9 (19)	0.0005*
4 systems, n (%)	9 (34)	0	–
	Reactions at challenge		
Subjective, n (%)	17 (65)	Nil	–
Objective, n (%)	20 (77)	Nil	–
Both, n (%)	11 (42)	Nil	–

(b) Milk allergy			
	Milk allergic (n = 34)	Milk tolerant (n = 47)	P value
Males, n (%)	21 (62)	18 (56)	0.06
Females, n (%)	13 (38)	29 (44)	
Median age (y)	9 (0–15)	10 (2–17)	0.60
Median weight (kg)	30 (3–63)	37 (13–69)	0.87
Median height (cm)	113 (50–172)	133 (86–173)	0.94
Median SPT (mm)	8.44 (3.04–12.91)	6.21 (3.11–8.92)	0.51
Median sIgE (KU/L)	30.99 (0.12–116)	6.80 (0.001–44.3)	0.64
Median tIgE – sIgE	2883.15 (51.3–5363)	3630.32 (49.71–7446.5)	<0.001*
Tolerance to baked milk[a], n (%)	26 (76)	11 (23)	<0.0001*
1 system, n (%)	32 (94)	42 (89)	0.73
2 systems, n (%)	27 (79)	14 (30)	<0.0001*
3 systems, n (%)	23 (68)	6 (13)	<0.0001*
4 systems, n (%)	16 (47)	0	–

(continued)

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(b) Milk allergy			
	Milk allergic (n = 34)	Milk tolerant (n = 47)	P value
	Reactions at challenge		
Subjective, n (%)	29 (85)	Nil	-
Objective, n (%)	25 (73)	Nil	-
Both, n (%)	12 (35)	Nil	-

Table 1. (Continued) Demographic and clinical characteristics of allergic and tolerant patients at OFC (a) egg (b) milk (*P value significant). *[a]Tolerance to baked egg and milk were analysed from questionnaire survey of the patients; hence it refers to the past reactions to baked egg/milk prior to single blinded OFC as reported by the patients*

(OR = 1.41, 95% CI = 1.25–1.59, $p < 0.0001$), tolerance to baked milk (OR = 2.36, 95% CI = 1.04–5.39, $p = 0.04$), patients bearing 2 symptoms (OR = 2.49, 95% CI = 1.50–4.15, $p = 0.0005$) or 3 symptoms (OR = 4.95, 95% CI = 2.56–9.59, $p < 0.0001$) (Supplementary Fig 1(b)). Although tIgE + sIgE and tIgE/sIgE were both significant when evaluated, tIgE minus sIgE had the best predictive ability, adding 13% egg and milk allergic cases accurately diagnosed as positive or negative.

OFC outcomes in allergic and tolerant groups

The average ingested dose of OFC-positive patients was 15 mg for egg and 10 mg for milk. 35% of patients developed symptoms immediately after the consumption of initial dose in OFC, whereas the tolerant group had no effect till the end of OFC. No late allergic reactions were observed at home after the completion of challenges. The rate of positive OFC was higher in milk (42%) than that in egg (35%).

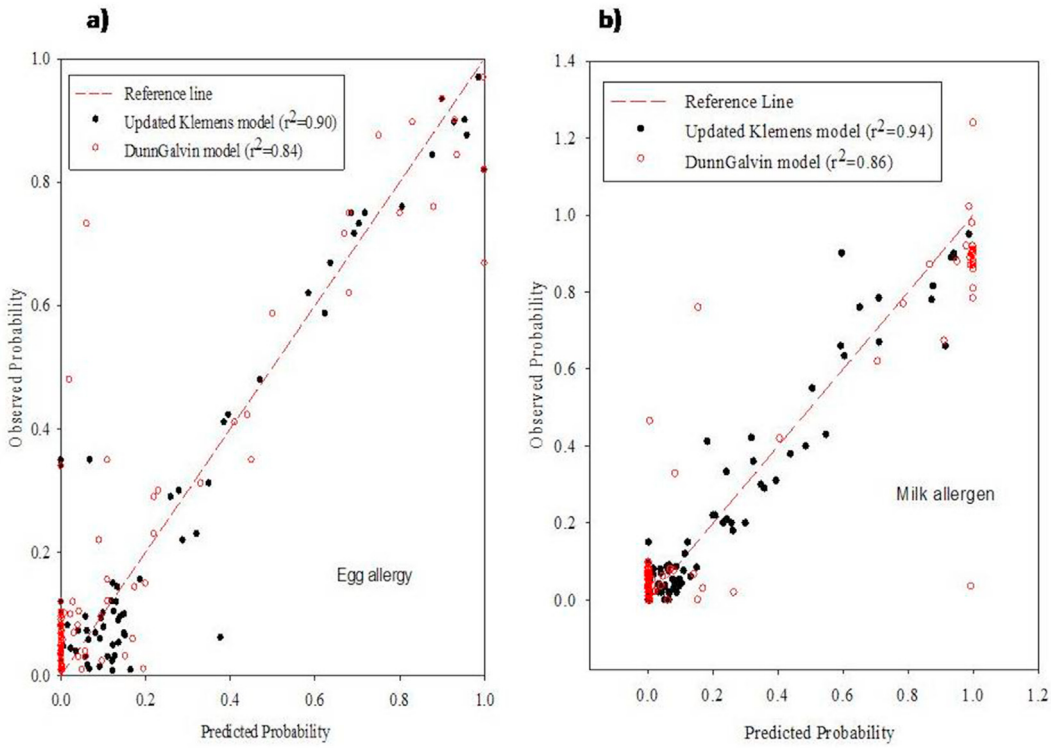

Fig. 2 Calibration plot for DunnGalvin and Klemans models for (a) egg and (b) milk allergy

Revalidation of the DunnGalvin & Klemans models

Calibration

The calibration plots of the DunnGalvin and Klemans models are shown in Fig. 2(a) and (b) for egg and milk allergies respectively. The observed against predicted probability is shown by red dashed reference line. Open red circles were calculated from the DunnGalvin formula, which gives correlation coefficient (r^2) of 0.84 and 0.86 respectively for egg and milk allergies. The calibration intercepts were 0.070 ± 0.017 and 0.054 ± 0.023 whereas the slopes found to be 0.848 ± 0.043 and 0.822 ± 0.039 respectively. In the Klemans model, predicted data points (black filled circles) give $r^2 = 0.90$ and 0.94 respectively. Here the intercepts and slopes were 0.017 ± 0.001 and 0.925 ± 0.035 for egg allergy while for milk allergy these were 0.010 ± 0.002 and 0.944 ± 0.039 respectively. It is clear that the Klemans model prediction gives better calibration. The coefficients of the Klemans model varied rigorously until best fits were available. Residual plots were also checked and the points lie randomly on two sides of $y = 0$, indicating logistic regression model is fine. Hosmer-Lemeshow test also indicated significant result ($P < 0.001$).

Discrimination

Fig. 3(a) and (b) show ROC curves for egg and milk allergens, respectively. The prediction of the Klemans model (red dashed line) comes much better than that of the DunnGalvin (blue continuous line) model, as is evident from the AUC of ROC curves. For egg allergen, the AUC of the Klemans model was 0.90 (95% CI: 0.81–0.95) compared to 0.78 (95% CI: 0.71–0.84) in the DunnGalvin model (Fig. 3(a)). In milk allergen, similar results were found; 0.91 (95% CI: 0.82–0.95) vs. 0.80 (95% CI: 0.73–0.82) (Fig. 3(b)).

Determination of regression coefficients

The multivariate stepwise forward logistic regression was performed with probability of entering and removing a variable was 0.05 and 0.06, respectively. Table 2(a) and (b) indicate values of regression coefficients for egg and milk allergic patients, respectively calculated from the Klemans model. The corresponding standard errors (SE), OR (calculated from the exponential of parameter values) and 95% CI are also shown

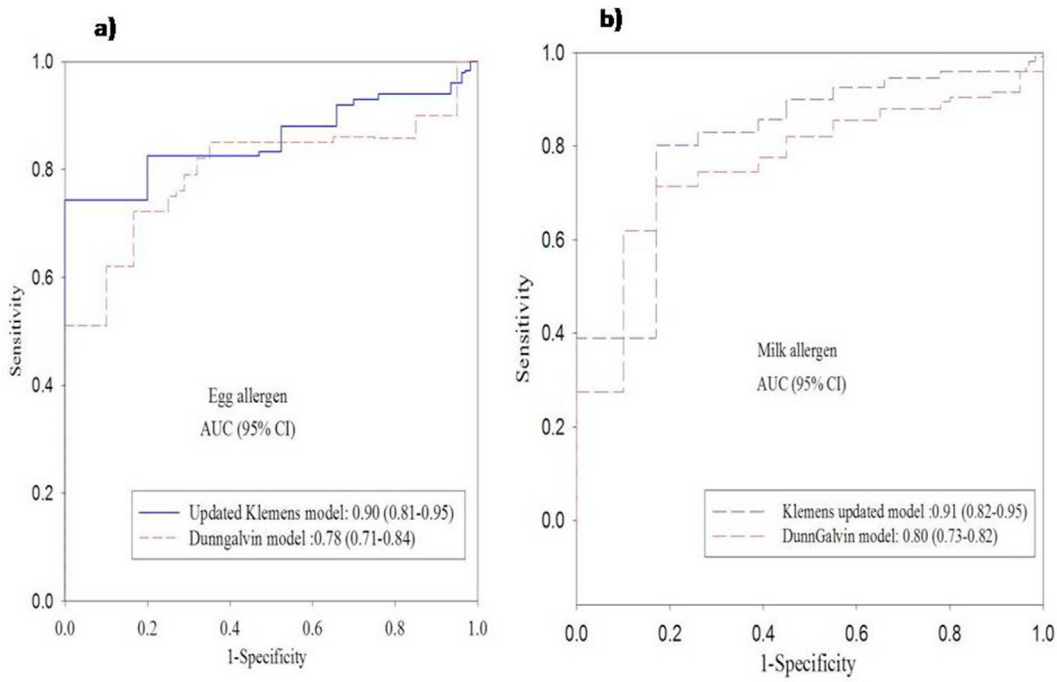

Fig. 3 ROC curves of DunnGalvin and Klemans model for (a) egg and (b) milk allergen

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(a) Egg allergy				
Predictors	DunnGalvin model	Klemans model	Standard errors*	Odd ratio (95% CI)*
Sex	1.70	−1.70	0.53	0.25 (0.06–0.54)
History 1	1.40	–	–	–
History 2	2.08	–	–	–
History 3	2.74	–	–	–
History 4	3.76	–	–	–
SPT (mm)	0.29	0.29	0.09	1.28 (1.15–1.4)
tIgE-sIgE	−0.004	−0.0024	0.001	0.99 (0.9–1.06)
sIgE (kU/L)	0.20	0.25	0.01	1.16 (1.05–1.22)
Age (year)	−0.15	–	–	–
Intercept	−2.42	−1.42	0.29	0.17 (0.10–0.24)
(b) Milk allergy				
Predictors	DunnGalvin model	Klemans model	Standard errors*	Odd ratio (95% CI)*
Sex	0.59	−1.37	0.63	0.25 (0.12–0.44)
History 1	0.48	–	–	–
History 2	2.36	–	–	–
History 3	7.92	–	–	–
History 4	8.51	–	–	–
SPT (mm)	0.35	0.19	0.10	1.20 (0.9–1.40)
tIgE-sIgE	−0.006	−0.004	0.002	0.99 (0.90–1.16)
sIgE (kU/L)	1.8	0.20	0.03	1.22 (1.05–1.32)
Age (year)	−0.15	–	–	–
Intercept	−14.61	−1.04	0.29	0.35 (0.10–0.39)

Table 2. Predictors of DunnGalvin & Klemans models, corresponding standard errors & odds ratio (95% CI) for (a) egg and (b) milk allergy (*Calculated on basis of Klemans formula)

in both the tables. Higher OR was achieved for SPT [1.28; 95% CI: 1.15–1.4 and 1.20; 95% CI: 0.9–1.40] and sIgE [1.16; 95% CI: 1.05–1.22 and 1.22; 95% CI: 1.05–1.32] in egg and milk allergies, respectively.

Outcome of the revalidated model in terms of specificity, sensitivity, positive and negative predictive values, and accuracy of predictions

The outcome of the revalidated model was assessed on a probability scale from 0 to 1 (cut-off points). The probability of the outcome being accurate was increased as we moved higher up in the scale. The specificity, sensitivity, positive (PPV) and negative predictive values (NPV), accuracy of predictions for the different cut off-points are given in Table 3(a) and (b). For egg allergy, we got the highest sensitivity of 94% and NPV of 90%, but specificity and PPV were lowest (79% and 89%, respectively) at cut-off point of the predicted probability of ≥0.5 (Table 3a). This means 94% egg allergic (n = 24) and 90% egg-tolerant (n = 43) patients in our study with a score of less than 0.5

(a) Egg allergy					
Cut-off point (probability)	Specificity (%)	Sensitivity (%)	PPV (%)	NPV (%)	Accuracy (%)
≥0.5	79	94	89	90	95.00
≥0.6	80	85	95	86	97.20
≥0.7	86	82	96	82	97.20
(b) Milk allergy					
Cut-off point (probability)	Specificity (%)	Sensitivity (%)	PPV (%)	NPV (%)	Accuracy (%)
≥0.5	80	95	90	91	96.00
≥0.6	82	87	96	84	98.00
≥0.7	85	83	97	80	98.00

Table 3. Outcome of Klemans model at different cut-off points of predicted probabilities for (a) egg and (b) milk allergy

were accurately predicted (ie, had a positive and negative OFC, respectively). A cut-off point of the probability of ≥0.7 achieved the best diagnostic accuracy (97.20%) with reference to PPV and NPV (96% and 82%, respectively). In milk allergy, the trend was similar, where the best accuracy level was slightly higher (98%) with respect to PPV and NPV (97% and 80%, respectively) at the cut-off point of probability of ≥0.7 (Table 3b).

DISCUSSION

Food allergy is known to show variation with different ethnicity and races. The distribution of genetic factors that causes food allergy varies across the ancestral groups.[22] One possible reason behind these differences is that there may be ethnocultural factors, such as variation in diet and feeding habits during childhood which may be more significant than genetic factors for egg and milk allergy. The present study showed new data as well as the first time application of existing mathematical models in Asian region with egg and milk allergy.

Milk is an essential supplement in the diet of children and adolescents, since it has a balanced composition of nutrients with optimal digestibility, resulting in a product with high biological value. Milk proteins can be classified into 2 groups: whey and casein.[23] Casein accounts for 80% of the total milk protein and is more heat stable,[24] hence causing greater sensitivity.[25] OFC is necessary to make proper diagnosis while reducing the burden to patient and family. The present study reported 42% positive milk challenge. This indicates that milk is one of the dominant food allergens among children, confirming the results of the previous sensitization study in West Bengal.[7] In this study, egg was the second most common food giving positive challenge (35%). Egg white is the major sensitizer in egg[26] and Ovomucoid has been reported to be the dominant allergen in egg white.[27] Its allergenicity depends on its resistance to heat and digestive enzymes,[28] which is why we have used raw freeze-dried egg-white powder to assure maximal allergenicity. However, the rate of both egg and milk positive OFC was lower than open challenges reported from Japan (61% and 72% respectively).[29] A possible reason for this relatively low rate of positive food challenge in our study might be the inclusion criteria of a clinical history of convincing egg or milk allergy. A positive SPT or specific IgE was not always co-related. Our findings suggest that systemic reactions from milk are quite serious than that of egg. For example, 79% of patients with milk sensitivity have developed symptoms to more than 1 body system, some of which have been severe reactions. However, anaphylactic reactions were absent with both egg and milk challenges. The present study also revealed that the eliciting dose of OFC had been varied between egg and milk. Patients reacted at low doses of milk (mean final dose 10 mg) while they reacted at higher doses for egg (mean final dose 15 mg).

In Asia, aside from China, Japan, Korea, and Singapore, limited information was available regarding OFC.[30–33] In our country, patients with suspicion of having food allergy are commonly advised for diet elimination by the clinicians from all the foods potentially causing allergic reactions without a proper medical evaluation. Such practice can cause undue stress to the families (frustration, apprehension) and difficulties in acquiring food substitutes. Hence, there is an urgent need for conducting a proper diagnostic evaluation for food allergy to ensure that avoidance is limited to only those with true allergy to foods. The majority of the studies focused on the prevalence on basis of SPT[4,6] and specific IgE result or both,[7] while patients with a history of milk or egg allergy after the ingestion were not taken into account. Skin testing or IgE only establishes sensitization; it does not always relate with clinical reactivity to the food.[34] Moreover, for those who continue to suffer, OFC is the only diagnostic tool in order to ascertain non-IgE mediated food allergy and accomplishment of tolerance in them.[35] The strength of our study is that all the patients suspected of having an allergy were offered an OFC for confirmation.

For the present study, 6 predictors viz age, sex, history of reaction, SPT, sIgE and tIgE minus sIgE were taken for validation of the DunnGalvin model, among them 4 predictors (sex, SPT, sIgE, tIgE minus sIgE) were selected for the Klemans model. A recent study showed that IgE level in serum declined with increase in age.[7] In this respect, age adjustments of tIgE and sIgE values were performed in the present study to withstand their confounding potential before revalidation of both the models.

However, the present study has some limitations. Our study depends on single blind challenges instead of double blind placebo controlled food challenges (DBPCFC) because these are typically not used in routine clinical practices in India. The sample size of the present study was kept small because high dose intakes may cause severe anaphylaxis in children and adolescents;[36] although the size was quite comparable to that of the DunnGalvin model. Many previous studies regarding OFC have been reported with small number of patients.[37–39] In the present study, calibration of risk prediction may be distorted due to several possible sources. According to previous reports, patient characteristics and disease incidence or prevalence rates differ according to region and countries, and even by health centers.[40] In our work, the data were collected at the allergy clinic where on average 50 patients per day visit for the various allergic complains. Thus the homogeneity between patients' settings could be maintained. Besides, the nature of food may be another source of error. It was previously seen that most of the patients with milk and egg allergy have developed tolerance to baked products.[41–44] In our case, non-baked food was supplied, which is essential to compare with the results of earlier baked milk and egg challenges.[9] It is indeed true that predictive model results may be biased towards the setting of disease incidence. If the algorithm is developed in a place with high disease incidence, there will be a systematic error which will result error prone risk estimates.[45,46] Therefore, the validation of this model is needed in places other than the study area. However, this error has been lowered as the patients represented from different areas of the state West Bengal in India.

Although the DunnGalvin and Klemans models were developed for children, we have demonstrated that these can also be used in adolescents. Klemans et al[16] opined that their model, which was modified from that of DunnGalvin, could be used in different populations and age groups after proper validation in new population. Klemans updated the model for peanut allergy, while the present study proved universality of the Klemans model by applying for egg and milk allergy.

The success of the mathematical models lies in their predictive power; especially the Klemans model where high level of sensitivity (~82–83%) was achieved at the cut-off of probability $\geq$0.7. The present study accurately predicted 24 of 26 positive cases and 43 of 48 negative cases of egg allergy; 32 of 34 positive cases and 43 of 47 negative cases of milk allergy. Although the DunnGalvin model gave high discrimination (AUC ~0.94–0.95), our data demonstrated poor discrimination (AUC ~0.78–0.80). The Klemans model showed high level of calibration as well as discrimination (AUC 0.94) for peanut allergy. In the present study, a similar kind of calibration and discrimination

(AUC ~0.90–0.91) was achieved for egg and milk allergy using the Klemans model.

CONCLUSION

The present study indicated that the Klemans model may be suitable for using in our study area if the model parameters are modified suitably, even though the original model was constructed in different countries. Application of the predictive model may assist physicians in the diagnosis of food allergy in a non-invasive way that could save money and time. Moreover, this could become a highly important confirmatory test of food allergy. However, universal validity of these models requires testing with larger datasets which could be possible with Artificial Intelligence (AI)/machine learning algorithms in near future.

Abbreviations

AI, Artificial Intelligence; AUC, Area Under Curve; CI, Confidence Interval; DBPCFC, Double-Blind Placebo-Controlled Food Challenge; EIA, Enzyme Immune Assay; GERD, Gastro-Esophageal Reflux Disease; NPV, Negative Predictive Value; OFC, Oral Food Challenge; OR, Odds Ratio; PEFR, Peak Expiratory Flow Rate; PPV, Positive Predictive Value; ROC, Receiver Operator Characteristic Curve; SE, Standard Error; sIgE, Specific IgE; SPT, Skin Prick Test; tIgE, Total IgE; WHO, World Health Organization.

Potential competing interests

The authors report no competing interests.

Consent for publication

All the authors confirm their consent for publication.

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Ethics statement and consent to participate

The study protocol was approved by the Clinical Research Ethics Committee, Allergy and Asthma Research Center, West Bengal, India (CREC-AARC Ref: 004/17). All the procedures performed in the present study involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written informed consents were also taken from the selected patients or from their parents.

Authors' contributions

All the authors have made substantial contributions. Arghya Laha contributed to data collection and wrote first draft of the manuscript. Srijit Bhattacharya did the mathematical modeling and critically revised the manuscript. Saibal Moitra diagnosed the disease and provided the sample. Nimai Chandra Saha, Himani Biswas and Sanjoy Podder conceived the study design, supervised the work and made the final draft. All the authors approved the final manuscript and agree with all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.waojou.2022.100639.

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Supplementary Table 1: Single blind food challenge protocol.

Vehicle	Challenge food form	Protein in 10 mg challenge food	Dose of tested food item
Fruit smoothie (250 ml)	Freeze-dried egg-white powder	7.5mg	@ 5mg, 10mg, 15mg, 20mg, 25mg, 30mg respectively at every 30 minutes
Fruit juice (250ml)	Skim milk powder	3.6mg	