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Melek Yorgun Altunbas[1,2,3], Ezgi Yalcin Gungoren[1,2,3], Salim Can[1,2,3], Razin Amirov[1,2,3], Necmiye Ozturk[1,2,3], Selcen Bozkurt[1,2,3], Sevgi Bilgic Eltan[1,2,3], Safa Baris[1,2,3], Ahmet Ozen[1,2,3], Elif Karakoc-Aydiner[1,2,3]

Early markers of baked milk and egg tolerance in young children with IgE-mediated immediate reactions

[1]Division of Allergy and Immunology, Department of Pediatrics, Marmara University, School of Medicine, Istanbul, Türkiye
[2]The Istanbul Jeffrey Modell Diagnostic Center for Primary Immunodeficiency Diseases, Istanbul, Türkiye
[3]The Isil Berat Barlan Center for Translational Medicine, Istanbul, Türkiye

Key words

Baked milk; baked egg; early tolerance; IgE-mediated immediate-type allergy; infant.

Corresponding author
Elif Karakoc-Aydiner
Division of Allergy and Immunology
Department of Pediatrics
School of Medicine
Marmara University
Fevzi Çakmak, Muhsin Yazıcıoğlu
Street No:10, 34899
Pendik, Istanbul, Türkiye
ORCID: 0000-0003-4150-5200
E-mail: elifaydiner@gmail.com

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Impact statement

The study focuses on a unique particular subset. It identifies prognostic markers during the initial reactions and delineates the group for whom a very early reduction of dietary restrictions may be feasible.

Summary

Background. *Children with milk and egg allergies have outcomes in which three-quarters are tolerant to baked forms of the allergenic food. Identifying predictors of tolerance to baked foods for IgE-mediated immediate-type reactions may guide the early introduction of baked allergens to diet and tolerance development. This study explores factors associated with early tolerance to baked foods.* ***Methods.*** *We retrospectively analyzed patients with IgE-mediated immediate-type food allergy in infancy who either became tolerant to the baked form before two years or remained reactive after two years.* ***Results.*** *We examined 143 patients solely with IgE-mediated immediate-type egg and/or milk allergies excluding those with atopic dermatitis. 76 (42 egg-allergics; 34 milk-allergics) achieved tolerance, and 67 (38 egg-allergics; 29 milk-allergics) were reactive beyond the age of two. Receiver operating characteristic analysis determined cut-off values for specific-Immunoglobulin E (sIgE) levels (kU/L) predicting mild phenotype at first admission: egg white-sIgE ≤ 7.39, milk-sIgE ≤ 5.99, and casein-sIgE ≤ 4.99, with AUC values of 0.703, 0.716, and 0.749, respectively.* ***Conclusions.*** *This study identifies key prognostic factors for tolerance to baked allergen for IgE-mediated immediate-type reactions, providing valuable insights to determine the patients who need more intensive care versus the ones who don't need baked allergen avoidance early in their life from their initial admission at infancy.*

Introduction

Milk and egg are the leading causes of food allergy in infants and young children. The estimated prevalence rates range from 0.9% to 3.8% for milk and 1% to 2% for egg, respectively, although these numbers vary across different populations (1-4). Food allergies pose a significant public health concern due to their frequency in the population and potential to cause life-threatening reactions. Although many patients outgrow their food allergies within the first few years of life, a significant subset continues to experience allergic reactions into adolescence and even adulthood. This refractory course necessitates ongoing management and vigilance to prevent and treat potential allergic reactions (5-10). Predicting whether and when an allergy will resolve spontaneously is often challenging. Various factors have been linked to the persistence of food allergies, including a history of anaphylaxis, the severity of reactions, the age at symptom onset, family history of atopy, specific immunoglobulin E (sIgE) levels, skin prick test wheal sizes, the presence of multiple food allergies, and the involvement of multiple systems. These factors contribute to

the complexity of managing food allergies and highlight the need for tailored approaches to patient care (6, 7, 9).
In recent years, IgE-mediated milk and egg allergies have been graded based on the tolerability of baked products containing these allergens. Approximately three-quarters of the affected population can tolerate baked products and are more likely to outgrow their allergies. Conversely, those who react to baked milk (BM) and baked egg (BE) are more likely to have persistent allergies (11-16). The structure of milk and egg proteins can be altered by heat and the food matrix. Incorporating the offending food into the dough and baking it changes the antigenic structures. Children with IgE antibodies directed against 3D conformational epitopes are likely to tolerate the antigenic food after it undergoes this cooking process (17-19). This tolerability offers significant social, practical, and nutritional benefits to children by allowing a less restricted diet. In addition to these advantages, continuous consumption of the tolerated form of the allergenic food (baked milk or baked egg) may promote immunological tolerance to the unbaked forms, thus enhancing the overall patient experience. This approach can lead to an improved quality of life and potentially expedite the resolution of the allergy (20).
Upon diagnosing a food allergy, the standard practice is to eliminate all forms of the allergenic food, including its baked variants, from the diet until a physician-supervised challenge can be conducted (21). Predicting whether a patient will tolerate baked foods in the future remains challenging, but various diagnostic approaches have been proposed. The potential utility of skin prick testing and specific IgE measurements has been explored, typically focusing on results obtained closer to the time of an oral food challenge (OFC) (13, 22-32). These methods aim to improve the accuracy of predicting baked food tolerability and guiding patient management strategies (13, 22-31).
The first two years of life represent a crucial window during which infants can develop tolerance to previously allergenic foods. However, data on the rates of tolerance to baked forms within this period is limited. Research has primarily focused on whether tolerating baked foods impacts the resolution of allergies to their native forms (9, 11). In this study, we investigate the natural history of infants admitted solely with immediate-type hypersensitivity to milk and/or egg with a specific focus on their tolerability to baked forms of these foods by the age of two in addition to their predicting factors for baked allergen tolerability at initial admission.

Materials and methods

The study retrospectively analyzed medical records of patients diagnosed with food allergy at the Pediatric Allergy and Immunology Unit of the University Hospital between January 2020 and January 2023. The study was conducted per good clinical practice rules and received ethical approval from the Marmara University Ethical Committee (Protocol ID: 09.2024.222). The ethics committee did not deem it necessary to obtain informed consent from participants for this study.
We reviewed data from 564 patients diagnosed with milk and/or egg allergies. Eligibility criteria included the onset of an allergic reaction to the offending food within the first 12 months of life. Inclusion criteria encompassed a clear history of an immediate reaction within two hours of ingestion of milk or egg, presenting with symptoms such as urticaria and/or angioedema, wheezing, coughing, dyspnea, stridor, vomiting, anaphylaxis (33, 34), or a positive oral food challenge (OFC) under physician supervision. A positive sIgE test was defined as milk-sIgE or egg white-sIgE $\geq$ 0.35 kU/L to the trigger food within three months of the initial reaction.
Following these criteria, out of 564 patients whose records were screened, exclusions were made for the following reasons: absence of an immediate type reaction (n = 308), history of a first IgE-mediated rapid reaction occurring after the age of one year (n = 31), lack of evidence for a positive sIgE to the trigger food in the medical records within three months of the initial reaction (n = 25), missing regular outpatient clinic records every 3-6 months until at least two years of age (n = 37), and presence of moderate or severe atopic dermatitis (AD) at the time of diagnosis (n = 20) (35). These patients were excluded to ensure the integrity and specificity of the study cohort.

Data collection and oral food challenge test (OFC)

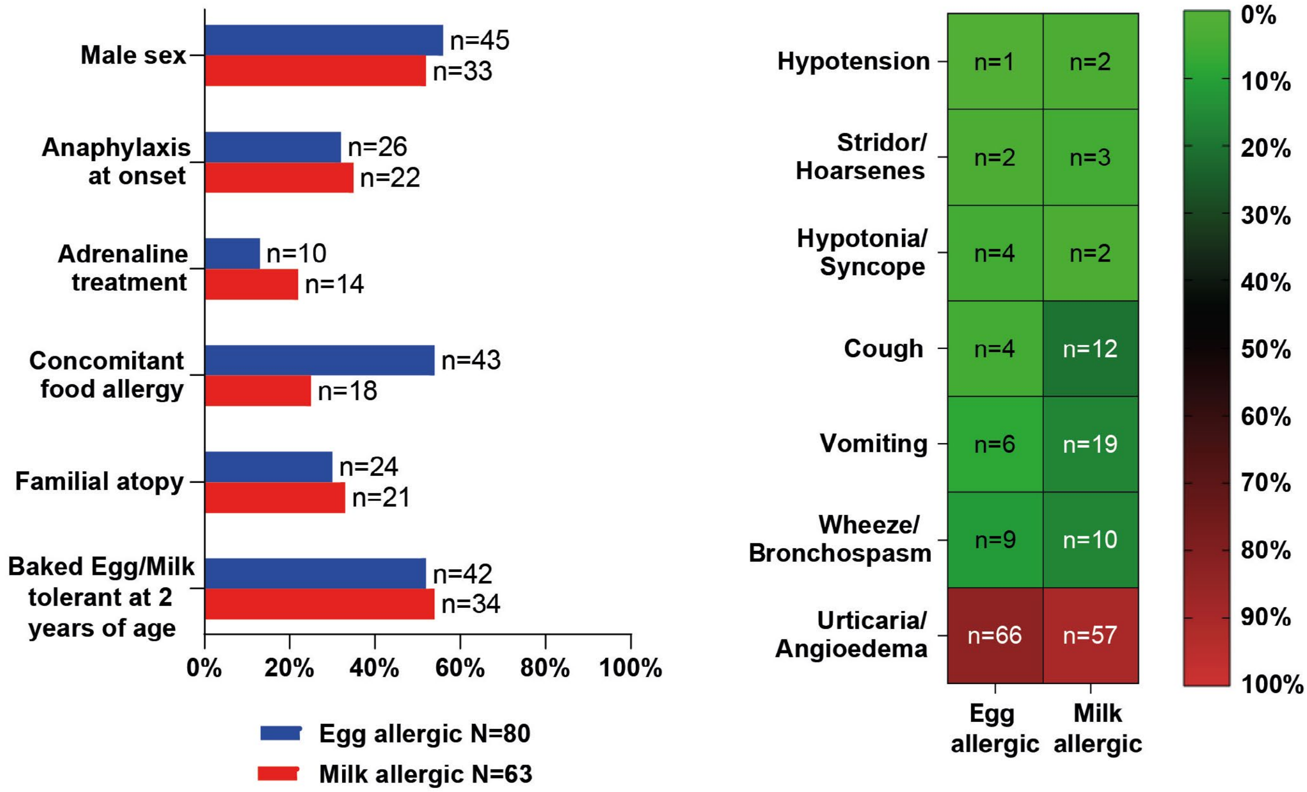
Patients' demographic, clinical, and laboratory data were collected from medical records. This data included gender, age, age at onset, type of initial reaction, presence of other food allergies identified before or at the time of the first reaction, and family history of atopy (diagnosed by a physician). Initial laboratory values were also gathered, including milk-sIgE, casein-sIgE, egg white-sIgE, total IgE, and eosinophil count within three months of the initial reaction. For analysis, patients were classified into two groups based on whether they developed tolerance to baked forms of the offending food before the age of two years. Patients were classified as baked food-tolerant if they had a negative OFC test to a baked form of the allergenic food or if they consumed a baked form of the allergen in an amount equivalent to an OFC every day for at least a week without any symptoms. The baked food-reactive group consisted of patients who, after the age of two, had either a positive oral food challenge (OFC) under the supervision of a physician or a documented history of an immediate reaction following the accidental ingestion of baked trigger food containing protein amounts equal to or less than those used in the OFC.
The OFC was conducted as an open challenge under physician supervision using the recipes formulated by the Jaffe Institute of

Food Allergy (New York) (36) for both BM and BE challenges. This involved administering a cumulative dose of 1.6 grams of milk protein for milk allergy and a cumulative dose of 2 grams of egg (yolk and white) protein for egg allergy.

Statistics

For the comparison between the baked food-tolerant and baked food-reactive groups, we employed the χ^2 test for categorical variables and the Mann-Whitney U test for continuous variables. The potential prognostic factors analyzed included sex, family history of atopy, age at the initial reaction, severity of the initial reaction (dichotomized as anaphylaxis or not), presence of concomitant food allergy at presentation, total IgE levels, eosinophil count, and allergen-specific IgE levels at the time of the first reaction. The effect of each prognostic factor was examined in a univariate analysis. P-value < 0.05 was considered to indicate a statistically significant result. The risk factors for BE/BM tolerance were determined by logistic regression analysis. For milk and egg allergies, logistic regression analysis was conducted using variables that were statistically significant in univariate analysis in terms of tolerance/reactivity and those that were not statistically significant but could be clinically meaningful with $p < 0.2$. We decided to include five variables for egg-allergic patients and six variables for milk-allergic patients in the potentially multivariable logistic regression model. The contributions of each variable included in the model using the hierarchical block method were evaluated with the Akaike information criterion (AIC), Bayesian information criterion (BIC), and Nagelkerke R^2. For milk-allergic patients, the variables of sex and milk-sIgE levels, and for HE-allergic patients, eosinophil count, were excluded from the models, as they did not contribute significantly to the model fit. Regarding multicollinearity, all variables were assessed using correlation analyses, VIF, and tolerance values. Residual and Cook's distance values were checked. Although there were a few cases with residual values > 3, none of them had Cook's distance > 1, so no case was removed from the dataset. Ultimately, 4 variables (female sex, no family history of atopy, no anaphylaxis at onset, and HE white-sIgE level) were included in the model for the egg-allergic group; while 4 variables (no family history of atopy, not anaphylaxis at onset, no concomitant food allergy at onset, casein-sIgE

Figure 1 *- Demographic and clinical characteristics of patients with egg and milk allergies at presentation.*



(A) Demographic and clinical characteristics are shown; **(B)** Symptoms and signs during the initial reaction are shown. Data are presented as numbers and percentages. n: number.

level) were included for the cases with milk allergy. The omnibus test confirmed the models' overall fit ($p < 0.01$). Receiver operating characteristic curve (ROC) analysis was used to determine initial sIgE levels that distinguished patients with BE/BM reactive and tolerant with the highest sensitivity and specificity. Statistical analysis was conducted by Jamovi 2.3.26 version (The Jamovi Project, Australia) and graphs are produced by GraphPad Prism 9 (GraphPad Software Inc., San Diego, California).

Results

Among the 143 patients enrolled, 78 were male and 65 were female; 80 were allergic to egg, and 63 were allergic to milk. The median (interquartile range, IQR 25%-75%) age at onset and at the last visit for participants was 6 (3-6) months and 45 (32-72) months for egg allergy, and 5 (3-6) months and 48 (36-76) months for milk allergy, respectively. The demographic and clinical characteristics of the patients are presented in **figure 1** and **table I**. Among the 80 patients with egg allergy, 41 (51%) had concomitant milk allergy, 1 (2%) had peanut allergy, and 1 (2%) had tree nut allergy. Among the 63 patients with milk allergy, 18 (29%) had concomitant egg allergy.

Seventy-six patients (53%) were found to be baked-food tolerant by the age of two years; 52 (68%) were confirmed with a negative open OFC test, and 24 (32%) were confirmed based on a history of tolerating baked food at home without any reactions. Sixty-seven patients (47%) had ongoing reactivity to baked food after two years; this reactivity was confirmed in 43 (64%) with a positive open OFC and in 24 (36%) with a convincing history of an immediate type reaction after reintroduction of baked food at home. The demographic, clinical, and laboratory features of the study group at the time of the first reaction were comparatively analyzed between the baked-food tolerant and reactive groups for both milk-allergic and egg-allergic children (**table II** and **figure 2**). The fitness of the multivariate logistic regression model for egg-allergic patients, which included four variables (female sex, no family history of atopy, no anaphylaxis at onset, and egg white-sIgE level), was confirmed by the omnibus test ($p < 0.001$). The model explained 33% of the variance (Nagelkerke $R^2 = 0.330$). In the multivariate logistic regression model, no anaphylaxis at onset was found to be an independent predictor of tolerance to baked egg. According to the likelihood ratio (LR) analysis, no anaphylaxis at onset and male sex contributed the most to the

***Table I** - Demographic and clinical characteristics of patients with egg and milk allergies.*

	All (n = 143) (100%)	**Egg allergy (n = 80) (56%)**	**Milk allergy (n = 63) (45%)**
Sex n (%)			
Male	78 (54.5%)	45 (56%)	33 (52%)
Female	65 (44.5%)	35 (44%)	30 (48%)
Age at last visit (mo) median (IQR 25%-75%)	46 (33-73)	45 (32-72)	48 (36-76)
Age at onset (mo) median (IQR 25%-75%)	5 (3-6)	6 (3-6.3)	5 (3-6)
Age at diagnosis (mo) median (IQR 25%-75%)	6 (5-8.5)	6.8 (5-9)	6 (4-8)
Reaction at onset			
No anaphylaxis n (%)	95 (66%)	54 (68%)	41 (65%)
Anaphylaxis n (%)	48 (34%)	26 (32%)	22 (35%)
Use of adrenaline	24(17%)	10 (13%)	14 (22%)
Use of antihistamines/steroids	24(17%)	16 (20%)	8 (13%)
Concomitant food allergy n (%)*	61 (43%)	43 (54%)	18 (25%)
Family atopy n (%)	45 (31%)	24 (30%)	21 (33%)
Outcome for baked food consumption by the age of 2			
Tolerant n (%)	76 (53%)	42 (52%)	34 (54%)
Proven by OFC	52 (68%)	31 (66%)	22 (65%)
Safely reintroduced at home	24 (32%)	10 (24%)	12 (35%)
Reactive n (%)	67 (47%)	38 (48%)	29 (46%)
Proven by OFC	43 (64%)	27 (71%)	16 (55%)
Safely reintroduced at home	24 (36%)	11 (29%)	13 (45%)

IQR: interquartile range; mo: months; n: number; OFC: oral food challenge. *Represents concomitant egg allergy for milk allergic patients and concomitant milk allergy for egg allergic patients.

***Table II** - Predictive factors at infancy for the tolerance development for baked egg (BE) and/or baked milk (BM) at the age of two years.*

Predictors*	Egg allergy (n = 80) (100%)			Milk allergy (n = 63) (100%)		
	BE tolerant n = 42	**BE reactive n = 38**	**P-value**	**BM tolerant n = 34**	**BM reactive n = 29**	**P-value**
Sex						
Male	18 (43%)	27 (71%)	**0.011**	14 (41%)	19 (65%)	0.054
Female	24 (57%)	11 (29%)		20 (59%)	10 (35%)	
Age at onset (mo)	5.5 (3-7)	6(3-6)	0.763	5 (3-6)	6 (3-6)	0.606
Anaphylaxis at onset						
No	36 (86%)	18 (47%)	**< 0.01**	29 (85%)	12 (41%)	**< 0.001**
Yes	6 (14%)	20 (53%)		5 (15%)	17 (59%)	
Familial atopy						
No	34 (80%)	22 (58%)	**0.025**	28 (74%)	14 (48%)	**0.004**
Yes	8 (20%)	16 (42%)		6 (26%)	15(52%)	
**Concomitant Food allergy						
No	17 (40%)	20 (53%)	0.268	28 (82%)	17 (65%)	**0.038**
Yes	25 (60%)	18 (47%)		6 (18%)	12 (35%)	
Eosinophil count/mm³	355 (225-613)	625 (300-960)	0.055	475 (300-700)	400 (200-800)	0.934
Total IgE (IU/ml)	75 (27-135)	87 (34-216)	0.350	83 (45-142)	79 (33-204)	0.874
Egg white-sIgE (kU/L)	5.1 (2.4-18.6)	12.1 (6.4-44.2)	**0.002**			
Milk-sIgE (kU/L)				4.9 (3.1-9.3)	8.8 (6-18.5)	**0.003**
Casein-sIgE (kU/L)				3.3 (1.6-6.1)	8.2 (4.9-17.2)	**< 0.001**

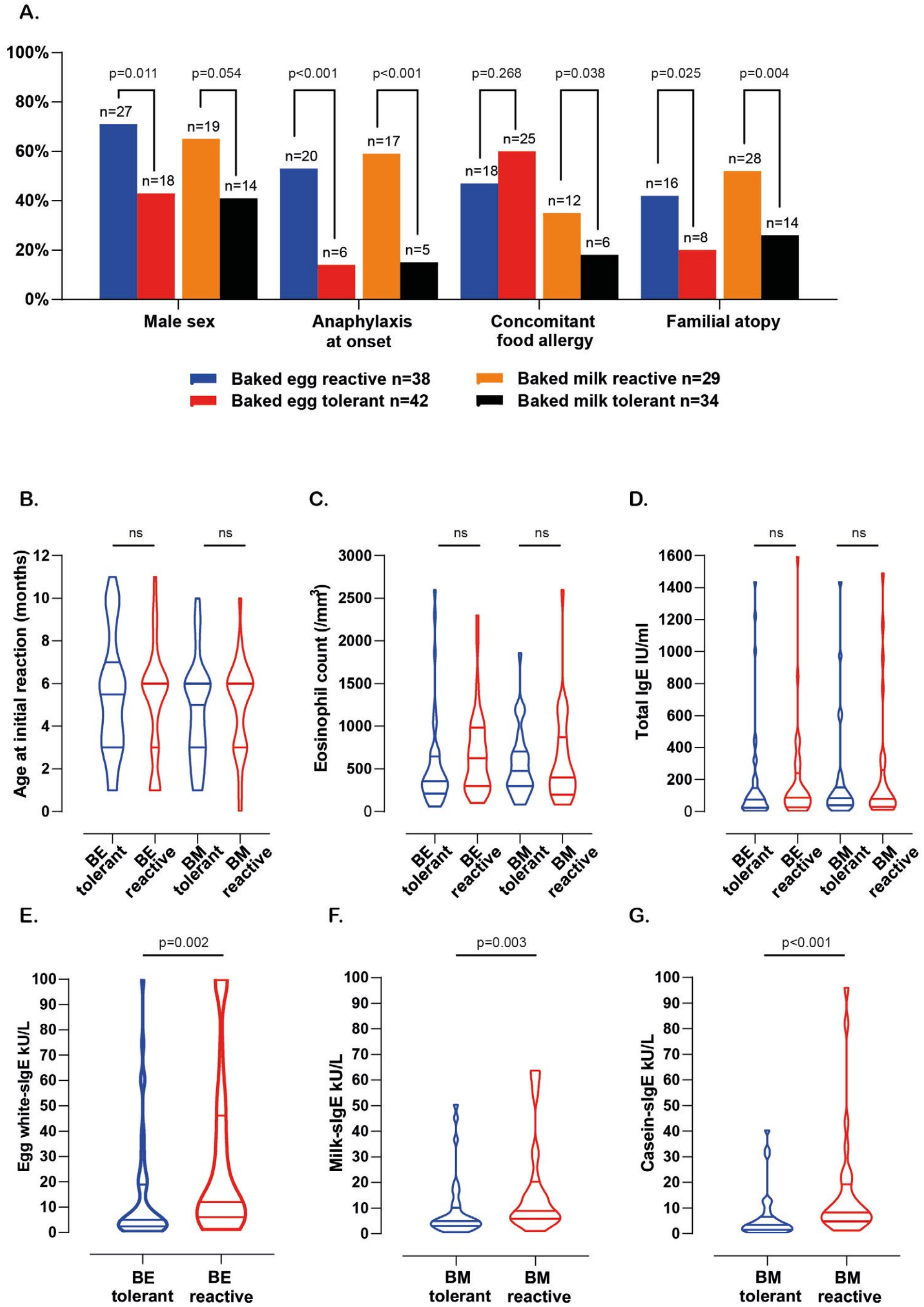
*Data presented with n (%) for categorical data and median (IQR 25-75%) for non-parametric continuous data Statistical comparisons were made by χ^2 test for categorical variables and Mann-Whitney U test for continuous variables. **Represents concomitant egg allergy for milk allergic patients and concomitant milk allergy for egg allergic patients; BE: baked egg; BM: baked milk: IgE: immunoglobulin E; IQR: interquartile range; mo: months; n: number; sIgE: specific IgE.

model, while egg-sIgE contributed the least (LR test χ^2 values 7.94, 3.95, and 1.79; p = 0.005, p = 0.047, and p = 0.180, respectively). The results of the logistic regression analysis for egg allergic patients are shown in **table III**. The model demonstrated an AUC of 0.788 with a sensitivity of 60.5%, a specificity of 60.5%, and an accuracy of 73.8%, respectively.

The fitness of the multivariate logistic regression model for milk allergy cases including 4 variables (no family history of atopy, no anaphylaxis at onset, no concomitant food allergy at onset, casein-sIgE level) was confirmed by omnibus test ($p < 0.001$). The model explained 49% of the variance (Nagelkerke $R^2 = 0.487$). In the multivariable logistic regression model, no anaphylaxis at onset, no family history of atopy, and no concomitant food allergy were found to be independent predictors of tolerance to baked milk. According to LR analysis, no anaphylaxis at onset and no family history of atopy contributed the most to the model, while casein-sIgE level contributed the least (LR test X^2 values 12.6, 7.6, 2.9, $p < 0.01$, p = 0.06, p = 0.089, respectively). The results of the logistic regression analysis for Milk allergy cases are shown in **table III**. The model demonstrated an AUC of 0.859 with a sensitivity of 79.4%, a specificity of 72.45%, and an accuracy of 76.2%, respectively.

The optimal sIgE cut-offs predicting baked allergenic tolerance from the time of initial reaction at the onset by ROC analysis was 7.39 kU/L for egg white-sIgE, 5.99 kU/L for milk-sIgE and 4.02 kU/L for casein-sIgE. Furthermore, we identified cut-off points with 100% positive predictive value for egg white-sIgE and 100% positive and 100% negative predictive value for milk-

Figure 2 *- Comparison of initial characteristics of egg/milk allergic patients with and without tolerance to baked allergen in the first 2 years of life.*



(A) Demographic, clinical characteristics at presentation. Data are presented as numbers and percentages, and the statistical comparison of the baked egg/milk tolerant *vs* reactive group was made by using χ^2 test; significance was set at $p < 0.005$; **(B)** Age at onset; **(C)** Eosinophils counts; **(D)** Total IgE levels; **(E)** Egg white-sIgE levels; **(F)** Milk-sIgE levels; **(G)** Casein-sIgE levels. **(B-G)** Data are presented as median (IQR 25-75%), and the statistical comparisons of baked egg/milk tolerant *vs* reactive groups were made by Mann-Whitney U test; significance was set to $p < 0.05$. BE: baked egg; BM: baked milk; IgE: immunoglobulin E; IQR: interquartile range; n: number; ns: not significant; sIgE: specific IgE.

Table III *- Predictors for early tolerance at age two by logistic regression analysis of baked eggs or milk allergies.*

	Predictor	Estimate	Wald	P-value	OR (95%CI)
Egg allergy	Intercept	-1.9320	-2.48	0.013	0.145 (0.0315-0.667)
	Female gender	1.0362	1.95	0.051	2.818 (0.9959-7.976)
	No familial atopy	1.0374	1.72	0.085	2.822 (0.8651-9.205)
	No anaphylaxis at onset	1.5961	2.71	**0.007**	4.934 (1.5542-15.662)
	Egg white-sIgE value	-0.0139	-1.32	0.187	0.986 (0.9660-1.007)
Milk allergy	Intercept	-3.5128	-2.80	0.005	0.0298 (0.00255-0.348)
	No familial atopy	1.9795	2.55	**0.011**	7.2392 (1.57688-33.234)
	No anaphylaxis at onset	2.4948	3.13	**0.002**	12.1198 (2.54524-57.711)
	*No concomitant allergy at onset	1.6040	1.97	**0.049**	4.9729 (1.00655-24.569)
	Casein-sIgE value	-0.0595	-1.63	0.103	0.9422 (0.87724-1.012)

The statistical analysis employed the binomial logistic regression. Estimates represent the log odds of "baked tolerant" *vs* "baked reactive". OR: odds ratio; CI: confidence intervals; IgE: immunoglobulin E; sIgE: specific IgE. *Represents concomitant egg allergy for milk allergic patients.

sIgE and casein-sIgE as shown in **table IV**. Furthermore, the optimal sIgE cut-offs predicting baked food-reactive from the time of initial reaction at the onset by ROC analysis was 7.39 kU/L for egg white-sIgE 5.99 kU/L for milk-sIgE and 4.02 kU/L for casein-sIgE.

Discussion and conclusions

The current study evaluated the outcomes of patients with IgE-mediated allergies to egg and milk that began in the first year of life, specifically focusing on their tolerability of baked food by the age

Table IV *- Specific IgE cut-off values indicate the outcome being tolerant to baked milk/ baked eggs by ROC analysis.*

		Cut-off (kU/L)	AUC	Sensitivity (%) (95%CI)	Specificity (%) (95%CI)	PPV (%) (95%CI)	NPV (%) (95%CI)	Accuracy (%) (95%CI)
Egg white-sIgE	Optimal	≤ 7.39	0.703	67 50-80	74 57-80	67 56-77	74 57-80	70 59-80
	100% PPV	≤ 1.2	0.703	12 4-26	100 91-100	100	51 48-53	54 42-65
Milk-sIgE	Optimal	≤ 5.99	0.716	65 47-82	76 57-90	76 61-86	65 53-75	70 57-81
	100% PPV	≤ 1	0.716	6 1-19	100 88-100	100	48 45-50	49 36-62
	100% NPV	≤ 54	0.716	100	14 4-32	58 54-61	100	60 47-72
Casein-sIgE	Optimal	≤ 4.02	0.749	62 44-78	86 68-96	84 67-93	66 55-75	73 60-83
	100% PPV	≤ 1.2	0.749	21 9-38	100 88-100	100	52 48-56	57 44-70
	100% NPV	≤ 43.4	0.749	100 90-100	10 2-27	57 54-60	100	59 46-71

AUC: area under curve; CI: confidence intervals; IgE: immunoglobulin E; NPV: negative predictive value; PPV: positive predictive value; ROC: Receiver Operating Characteristic; sIgE: specific IgE.

of two years. Given that egg and milk allergies are the most prevalent food allergies and that the co-existence of these two allergens is common in our population, we concentrated our attention on these clinically significant allergens.

For patients with egg allergy, using continued BE reactivity beyond age two as a reference, BE tolerability before age two years was linked to female sex, absence of anaphylaxis at presentation, no family history of atopy, and lower egg white-sIgE levels. However, logistic regression analysis revealed that the absence of anaphylaxis during the initial reaction was the only independent predictor of BE tolerability, increasing the likelihood of tolerance before two years by fivefold.

Similar analyses for patients with milk allergy showed that BM tolerability before age two was associated with the absence of anaphylaxis during the initial reaction, no family history of atopy, absence of concomitant egg allergy, low baseline milk-sIgE, and casein-sIgE levels. In a multivariate analysis, we found that no anaphylaxis as the initial reaction, no familial atopy, and no concomitant egg allergy were independent predictors of tolerability to BM before age two.

Previous studies from other groups have investigated factors associated with BE/BM tolerability at an early age in milk- and egg-allergic children. Cogurlu *et al.* (11) reported that male sex was the sole risk factor for BM reactivity, while multiple food allergies and urticaria as the first reaction were independent factors for BE reactivity. Sirin Kose *et al.* (13) found that gender, age, and the nature of symptoms at presentation were not risk factors for BE and BM reactivity at a later point.

We propose that the eligibility criteria in different studies, including the current one, may be an important factor in explaining the heterogeneous results. Our study included children with IgE-mediated immediate-type food allergy that began in the first year of age and excluded those patients with atopic dermatitis. These criteria differed from the other studies. Another potential factor could be the rate of anaphylaxis at presentation, which was higher in our study.

In a recent study examining a similar population with immediate-type reactions before the age of one year, anaphylactic episodes, atopic dermatitis before the age of one year, and high egg white-sIgE levels were identified as poor prognostic factors for egg allergy. Similarly, for milk allergy, anaphylactic episodes, concomitant egg allergy, atopic dermatitis before the age of one year, and high milk-sIgE levels were found to be poor prognostic factors. While the results of our study align with these findings, the discrepancies may be attributed to differences in study design. The previous study did not report on familial atopy (35), whereas our study excluded patients with moderate to severe atopic dermatitis. While there is no consensus on the prognostic factors of IgE-mediated egg and milk allergy (6, 37-44), numerous factors have been identified that vary depending on the population, age group of patients, and clinical characteristics of the examined patients. These factors for egg allergy include onset age, the initial symptom being a systemic reaction, accompanying asthma, atopic dermatitis (7, 45), high sIgE levels in the first reaction, family history of atopy (46), and the size of the skin prick wheal (47). History of systemic reactions (48, 49), and comorbidities such as asthma and allergic rhinitis (48) are risk factors for persistent milk allergy. In addition to these known facts, we think that we have presented an important contribution by elucidating the prognostic factors for food allergy tolerance *vs* persistence at the age of 2 depending on the data-driven at the time of the first reaction in a well-defined, younger and more specific group of patients with milk and/or egg allergy. This information will assist physicians in the evaluation of similar patients in the primary care setting in determining, at the time of diagnosis, which patients should be referred to reference centers for treatment, such as immunotherapy, if necessary, and which patients can be safely followed up in terms of tolerance development.

Efforts to find a reliable clinical or laboratory predictor to determine BE/BM tolerance have been ongoing. Among the tests, it has been suggested that egg white-sIgE is one of the laboratory parameters that best predicts BE tolerance (31, 50, 51), but some claim otherwise (41, 52). Although it has often been suggested that milk-sIgE and casein-sIgE levels are higher in BM-reactive patients than in BM-tolerant (14, 32, 36, 53), there are also studies suggesting that there is no difference in milk-sIgE or casein-sIgE (11, 29). Studies investigating the cut-off value of egg white-sIgE that distinguishes BE-tolerant from BE-reactive subjects have generally examined final values just before OFC testing (31, 50-52, 54). The sIgE cut-off values to differentiate between BM-tolerant and reactive groups have been investigated mainly in patients > 2 years of age and different values have been found (12, 53, 55). Studies reporting initial sIgE cut-off values have aimed to distinguish between those whose allergy resolves and those whose allergy persists. Nevertheless, the threshold for the baseline sIgE level varies according to the study design, including whether it is population-based, single-center, or tertiary center, as well as the clinical characteristics of the participants (37, 56, 57). On the other hand, in cohort studies of patients with egg and milk allergy, especially those with immediate-type reactions, although baseline sIgE levels were higher in the persistent group than in the tolerant group, no discriminative cut-off value was determined (46, 58). Although our results support these studies, we have additionally determined egg white-sIgE, milk-sIgE and casein-sIgE cut-off values as both optimal and 100% positive predictive values, distinguishing the BE/BM tolerant group from the reactive group. However, these values are not sufficient to replace OFC yet. It is crucial to note that the sIgE cut-offs are specific to our population and may vary in other populations. Therefore, it is essential that each center establishes its own sIgE cut-offs for its respective area or population, taking into account the methodology employed for sIgE detection.

One of the limitations of our study is its retrospective design. However, we attempted to mitigate this limitation by excluding patients with incomplete data or follow-up. Another limitation is that our study may not reflect the general population, given that it was conducted in a tertiary clinic where severe cases are often referred. Despite these limitations, the study's key strengths lie in its inclusion of a unique cohort of patients diagnosed during infancy, particularly those with IgE-mediated rapid-type reactions, and its analysis of the initial laboratory tests conducted on all patients during their first year of life.

In conclusion, physicians need guidelines to predict whether young infants with egg or milk allergies will tolerate baked forms of these foods later in life. This study provides valuable insights into the management strategies of food-allergic children. We propose that the identified risk factors could help determine which patients might be candidates for an OFC with baked foods within the specified age periods and who should be referred to a specialized center for future management.

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Contributions

EK-A, MYA: conceptualization, supervision. MYA, EYG, SC, RA, NO, SeBo, SBE, SaBa, AO, EK-A methodology, data curation. MYA, EK-A: formal analysis. MYA, E.K-A, AO: writing – original draft. All authors: writing – review & editing.

Conflict of interests

The authors declare that they have no conflict of interests.

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