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Phenotyping of immediate-type food allergies based on 10 years of research: A latent class analysis

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Abstract

Background: Food allergy is a disease with a diverse and variable natural history, and some patients may react to two or more food antigens. This study aimed to classify and characterize the long-term prognosis of infantile-onset, immediate-type food allergies, focusing on three major antigens in Japan: egg, milk, and wheat.

Methods: All children who visited our hospital with food allergies, including suspected cases, were prospectively registered in our medical database. Among the children in this database, subjects registered by the age of 1 year with immediate-type symptoms or sensitization to the above three antigens were included. The course of the subjects up to the age of 6 years was analyzed. Cox regression analysis and repeated-measures latent class analysis (LCA) were performed to reveal risk factors and tolerance patterns for food allergies.

Results: We included 915 patients with immediate-type food allergy symptoms and 276 sensitized asymptomatic patients in this study. The number of patients with immediate-type symptoms to egg, milk, and wheat was 609, 443, and 235, respectively. The number of patients with multiple food allergies was 302. The proportion of patients with tolerance to egg, milk, and wheat at 6 years of age was 74%, 69%, and 75%, respectively. LCA revealed 7 classes of prognosis for food allergies. The largest class was *transient egg allergy alone* (19.6%), and there were severe cases of *multiple food allergies* (6.5%).

Conclusions: This study demonstrated the prognosis of food allergy classes in Japan, including multiple food allergies, with 7 classes with its own characteristics.

KEYWORDS

food allergy, latent class analysis, natural history

1 | INTRODUCTION

Food allergy is a disease with diversity and variable natural history. Most patients acquire tolerance as they mature, whereas some patients have persistent symptoms. For example, 70%–80% of patients

with allergy to hen's egg naturally acquire tolerance by the age of 6 years.¹ In addition, some patients may have food allergy to two or more antigens concomitantly. Among atopic disease patients, 57% reacted to two or three foods in oral food challenges (OFCs).² Patients can develop symptoms from accidental ingestion,³ and their

growth may be affected by lack of necessary nutrients due to food allergies⁴; therefore, early management is important. Food allergies can be burdensome on patients and their guardians, especially in patients with multiple antigens⁵; hence, knowing how many patients have multiple food allergy and their clinical courses is important. However, little is known about the prognosis when multiple food allergies are considered simultaneously.

Latent class analysis (LCA) is a statistical technique for identifying potential subgroups from patterns of observed data. Recently, several articles have been published that classify phenotypes of allergic disease, asthma,⁶⁻⁹ atopic dermatitis,¹⁰ and sensitization patterns, using LCA. There have been some reports about multiple sensitizations to food allergens and subsequent allergic disease.^{11,12} However, to the best of our knowledge, there are currently no reports analyzing the clinical course and remission of food allergy using LCA.

In Japan, hen's egg, cow's milk, and wheat account for 95% of foods that cause immediate-type symptoms in infants.¹³ These three foods are extremely important in infantile-onset food allergies. In addition, since compulsory education in Japan begins at age 6, it is important to check the progress up to that age. This study aimed to classify and characterize the long-term course of infantile-onset, immediate-type food allergies of these three antigens in children.

2 | METHODS

2.1 | Study design and subjects

This was a longitudinal study performed in the Department of Pediatrics, Sagami National Hospital. Our hospital is one of the central base hospitals in Japan as stipulated in the Basic Law on Measures Against Allergic Diseases, and many children with allergic diseases visit our hospital. Since 2010, we have operated a comprehensive database for food allergy patients in cooperation with Hitachi Solutions Create (iAnet), in which all children with food allergies, including suspected cases, were prospectively registered. Patient information (sex, date of birth, food allergy, physician's diagnosis of allergic complications, family history, etc.) obtained at the time of the initial visit is stored. Details of the food allergy are recorded for each causative food, including the time of diagnosis, reason for elimination of the causative food, history of anaphylaxis, current food allergy status (acquired tolerance, partial elimination, complete elimination), results of oral food challenge tests, and blood test results. Blood test results include total IgE and specific IgE (sIgE) (Appendix S3). Allergy complications and food intake status are updated prospectively at a monthly granularity.

Patients who had first visited our hospital before the age of 1 year and had a food allergy (including suspected allergy) to hen's eggs, cow's milk, or wheat were included in this study. The diagnosis of food allergy was performed by a convincing history of immediate reaction to causative foods and confirmation of sensitization, or positive OFC results. After the diagnosis of food allergy, the patients

Key Message

Our study is the first to demonstrate the clinical course of multiple allergens simultaneously. The latent class analysis categorizes our subjects into 7 classes, each with its own characteristics. There is one severe class with persistent allergies to three major allergens. The simulation software developed from the results of this study may be useful in verifying food allergy prognosis, and it is more applicable to each facility or population. Further study is needed to determine the relationship with other comorbid allergic diseases and how the class may change over time.

were considered to be tolerant when they were able to take the indicated amount of food without symptoms. (Details in Appendices S4 and S7). The course of the subjects up to the age of 6 years was analyzed. Data after the interruption of a visit were treated as missing and the appropriate data analysis method was used.

The exclusion criteria for patients were described in Appendix S2.

2.2 | Statistical analysis

All statistical analyses were performed using R version 4.2.1 (2022; The R Foundation). Cox regression analysis was performed to determine the effect of variables on the resolution of food allergies. Repeated-measures LCA was used to reveal tolerance patterns of patients with food allergy. Manifest variable used in the model was the presence of food allergy to three major antigens in Japan (hen's egg, cow's milk, and wheat) at 6-month intervals. Sex and comorbid atopic dermatitis at age 1 were used as covariates. More details are described in Appendix S5.

2.3 | Simulation software

From pseudo-observations in the statistical analysis, simulation software for the prognosis of food allergy was developed. The parameters used in Cox regression analysis were used for developing the software. Source codes for this software are available in the public domain.

3 | RESULTS

3.1 | Patients

Of 2830 patients registered in the database from 2010 to 2014, we excluded patients with: age above 1 year at first visit ($n = 1613$), non-immunoglobulin E (IgE)-mediated food allergy ($n = 6$), no symptoms or sensitization to eggs/milk/wheat ($n = 10$), and missing clinical data

($n = 10$). Finally, we included 915 patients with immediate-type food allergies to the three antigens and 276 asymptomatic patients (sensitization only) in this study (Figure 1). Median age at the first visit was 0.67 (interquartile range [IQR]: 0.50–0.83) years, and median length of the observation period was 5.01 (3.23–7.00) years. Atopic dermatitis was comorbid in 836 (70%) patients. Patients underwent three OFCs (IQR: 1.0–6.0) during this observation period (Table 1).

The number of patients allergic to eggs, milk, and wheat was 609 (51%), 443 (37%), and 235 (20%), respectively; 302 (25%) patients had multiple food allergies (Figure S1).

3.2 | Prognosis of egg allergy

Of the 915 patients with immediate-type food allergies, 609 (67%) were allergic to eggs, of which 149 (24%) had anaphylactic episodes during their clinical course. The median levels of total IgE, egg white- and ovomucoid-sIgE were 115 (IQR: 43.7–288) IU/L, 12.9 (5.01–32.4) kU_A/L, and 4.46 (<0.35–15.1) kU_A/L, respectively (Table 2). Egg white- and ovomucoid-sIgE levels plateaued at ages 6 months and 1 year, respectively (Figure S2a,b). The number of patients with negative ovomucoid-sIgE (<0.35 kU_A/L) before 1 year of age was 166; however, of the 147 patients who underwent blood testing after 1 year of age, the ovomucoid-sIgE level of 133 (90.5%) patients turned positive (median: 2.1 kU_A/L, IQR: 2.1–9.14).

The median age of acquiring tolerance was 3.42 (95% confidence interval [CI]: 3.17–3.65) years, and 74.1% (70.1%–77.6%) of subjects acquired tolerance at the age of 6 years (Figure 2a). We performed Cox regression analysis for the time to remission of hen's egg allergy; hazard ratios (HR) greater than 1.0 mean acquiring tolerance faster, and factors with HRs less than 1.0 are related to persistent symptoms. Risk factors for prolonged egg allergy were atopic dermatitis (HR [95% CI]: 0.59 [0.47–0.73], $p < .001$), episodes of anaphylaxis

(HR: 0.71 [0.56–0.91], $p = .006$), comorbid wheat allergy (HR: 0.56 [0.42–0.74], $p < .001$), total IgE (HR: 0.84 [0.64–0.91], $p = .008$), Egg white-sIgE (HR: 0.71 [0.56–0.91], $p = .006$), and ovomucoid-sIgE (HR: 0.85 [0.74–0.98], $p = .023$) (Table 2). Table S1 displays the results of the sensitivity analysis.

3.3 | Prognosis of milk allergy

Of the patients with immediate-type food allergy, 443 (48%) were allergic to milk, of which 154 (35%) had anaphylactic episodes. The median levels of total IgE and milk-sIgE were 151 (IQR: 56.2–389) IU/L and 5.24 (1.58–15.8) kU_A/L, respectively (Table 2). Milk-sIgE level plateaued at 6 months of age (Figure S2c).

The median age of acquiring tolerance was 3.67 (IQR: 3.41–4.09) years, and 69.1% (64.1%–73.4%) of subjects acquired tolerance at the age of 6 years. (Figure 2b). Risk factors for prolonged milk allergy were atopic dermatitis (HR: 0.53 [0.41–0.70], $p < .001$), anaphylactic episodes (HR: 0.49 [0.37–0.65], $p < .001$), comorbid egg allergy (HR: 0.59 [0.46–0.76], $p < .001$), and milk-sIgE (HR: 0.50 [0.39–0.64], $p < .001$) (Table 2).

3.4 | Prognosis of wheat allergy

Of the patients with immediate-type food allergy, 235 (26%) were allergic to wheat, of which 54 (23%) had anaphylactic episodes. The median levels of total IgE, wheat-sIgE, and omega-5 gliadin (Tri a 19)-sIgE were 166 (IQR: 72.4–389) IU/L, 6.02 (1.78–20.4) kU_A/L, and 1.12 (0.36–3.39) kU_A/L, respectively (Table 2). The wheat-sIgE level plateaued at 6 months of age. (Figure S2d).

The median age of acquiring tolerance was 3.24 (IQR: 2.92–3.76) years, and 75.0% (68.4–80.3%) of the subjects acquired tolerance at the age of 6 years. (Figure 2c). Risk factors for prolonged

FIGURE 1 Study design and enrolled subjects. Of the 4588 patients in our database, 915 subjects with immediate-type food allergies to hen's egg, cow's milk, and wheat as well as 276 asymptomatic patients (sensitization only) were included in the study.

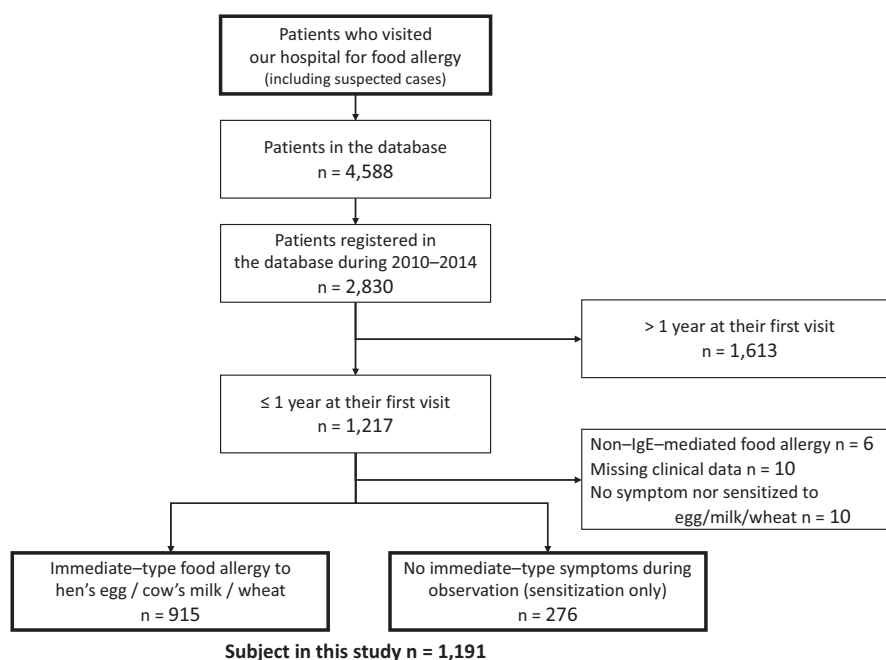


TABLE 1 Demographic and clinical observations of patients enrolled in this study

	Subjects, <i>n</i> = 1191	Immediate-type food allergy to eggs, milk, wheat, <i>n</i> = 915	Sensitization only, <i>n</i> = 276
Sex (male:female)	735 (62%):456 (38%)	570 (62%):345 (38%)	165 (60%):111 (40%)
Age at first visit (year)	0.67 (0.50–0.83)	0.67 (0.50–0.92)	0.50 (0.33–0.75)
Atopic dermatitis (at 1 year)	836 (70%)	615 (67%)	221 (80%)
Observation period (year)	5.01 (3.23–7.00)	5.58 (3.46–7.29)	3.98 (2.63–5.91)
Number of OFCs	3.0 (1.0–6.0)	3.0 (1.0–6.0)	3.0 (1.0–6.0)
Total IgE (IU/L)	100 (40.7–263)	112 (43.7–288)	64.6 (26.3–186)
Egg white-sIgE (kU _A /L)	11.5 (3.71–29.5)	12.3 (4.36–31.6)	7.94 (1.74–20.42)
Ovomucoid-sIgE (kU _A /L)	2.34 (<0.35–11.7)	2.81 (<0.35–12.9)	0.93 (<0.35–8.51)
Milk-sIgE (kU _A /L)	1.41 (<0.35–7.76)	1.86 (<0.35–8.71)	0.48 (<0.35–2.75)
Wheat-sIgE (kU _A /L)	0.81 (<0.35–6.17)	1.05 (<0.35–7.41)	0.19 (<0.35–1.86)
Omega-5 gliadin-sIgE (kU _A /L)	0.35 (<0.35–1.48)	0.42 (<0.35–1.74)	<0.35 (<0.35–0.66)
Hen's egg allergy	609 (51%)	609 (67%)	0 (0%)
Anaphylaxis to hen's egg	149 (13%)	149 (16%)	—
Cow's milk allergy	443 (37%)	443 (48%)	0 (0%)
Anaphylaxis to cow's milk	145 (12%)	145 (16%)	—
Wheat allergy	235 (20%)	235 (26%)	0 (0%)
Anaphylaxis to wheat	54 (4.5%)	54 (5.9%)	—
Peanut allergy	69 (5.8%)	59 (6.4%)	10 (3.6%)
Anaphylaxis to peanuts	26 (2.2%)	23 (2.5%)	3 (1.1%)
Soybean allergy	46 (3.9%)	35 (3.8%)	11 (4.0%)
Anaphylaxis to soybeans	2 (0.2%)	2 (0.2%)	2 (0.2%)

Note: Data are expressed as the number (%) or median value (interquartile range). Total IgE as well as egg white-, ovomucoid-, milk-, wheat-, and omega-5-specific IgE at 1 year of age were available for 1147, 1134, 1068, 928, 820, and 396 cases, respectively.

Abbreviations: OFC, oral food challenge; sIgE, specific IgE.

wheat allergy included anaphylactic episodes (HR [95% CI]: 0.38 [0.21–0.69], *p* = .002), comorbid egg allergy (HR: 0.60 [0.40–0.91], *p* = .018), wheat-sIgE (HR: 0.68 [0.42–0.96], *p* = .031), and omega-5 gliadin-sIgE (HR: 0.54 [0.32–0.91], *p* = .021) (Table 2).

3.5 | Latent class analysis

The Bayesian information criterion was lowest with 7 classes (Table S2). We identified one class without food allergy and six classes with food allergies (Table 3 and Figure 3).

Class 1 Sensitization only (28.4%): Patients who were sensitized, but no immediate symptoms were observed in OFCs or during their clinical course. This class was treated as a reference for the softmax regression.

Class 2 Transient egg allergy alone (19.6%): Patients with a favorable prognosis of egg allergy who acquired tolerance at the age of 3 years. They had a lower prevalence of comorbid atopic dermatitis. Egg white-sIgE levels were similar to those of Class 1 but had higher ovomucoid-sIgE levels. This constituted the largest class of food allergies.

Class 3 Milk ± transient egg allergy (17.5%): Patients with milk allergy, about half of whom acquired tolerance at the age of 4 years. Approximately a quarter of this class had transient egg allergies. Egg

white-sIgE levels were higher than those of Class 1 and 2, and had higher milk-sIgE levels.

Class 4 Prolonged egg allergy (13.1%): Patients with egg allergy, half of whom were still allergic to eggs at the age of 6 years. They had higher egg white- and ovomucoid-sIgE levels, and a higher prevalence of comorbid AD than those of Class 2.

Class 5 Wheat ± transient milk allergy (7.8%): Patients with wheat allergy and approximately a quarter of this class had transient milk allergies. Male sex and higher wheat-sIgE levels were correlated with this class. They had high egg white-sIgE levels but low ovomucoid-sIgE levels.

Class 6 Persistent egg and milk allergy (7.2%): Patients with persistent egg and milk allergies. Higher egg white-, and milk-sIgE levels tended to belong to this class.

Class 7 Multiple food allergy (6.5%): Patients allergic to eggs, milk, and wheat. They had higher egg white-, milk-, and wheat-sIgE levels.

3.6 | Simulation software

We developed interactive web-based simulation software for food allergy prognosis. This application is available at <https://link.kcrt.net/iAnetLCA>.

TABLE 2 Cox regression analysis for patients with egg, milk, and wheat allergies

	Egg allergy ^b , n = 609	Adjusted HRs (95% CI)	p Values	Milk allergy ^c , n = 443	Adjusted HRs (95% CI)	p Values	Wheat allergy ^d , n = 235	Adjusted HRs (95% CI)	p Values
Sex									
Male	376 (62%)	1.00 [Reference]	.205	279 (63%)	1.00 [Reference]	.137	161 (69%)	1.00 [Reference]	.257
Female	233 (38%)	0.88 (0.71–1.08)		164 (37%)	0.82 (0.64–1.06)		74 (31%)	1.27 (0.84–1.92)	
Atopic dermatitis (at 1 year)	418 (69%)	0.59 (0.47–0.73)	<.001	308 (70%)	0.53 (0.41–0.70)	<.001	178 (76%)	0.87 (0.56–1.35)	.535
Episode of anaphylaxis	149 (24%)	0.71 (0.56–0.91)	.006	145 (33%)	0.49 (0.37–0.65)	<.001	54 (23%)	0.38 (0.21–0.69)	.002
Hen's egg allergy	–	–	–	211 (48%)	0.59 (0.46–0.76)	<.001	120 (51%)	0.60 (0.40–0.91)	.018
Cow's milk allergy	211 (35%)	0.85 (0.68–1.07)	.164	–	–	–	111 (47%)	0.83 (0.55–1.24)	.359
Wheat allergy	120 (20%)	0.56 (0.42–0.74)	<.001	111 (25%)	0.82 (0.61–1.11)	.195	–	–	–
Total IgE (IU/L) ^a	115 (43.7–288)	0.84 (0.64–1.08)	.173	151 (56.2–389)	0.97 (0.72–1.31)	.843	166 (72.4–389)	1.40 (0.92–2.12)	.113
Egg white-sIgE (kU _A /L) ^a	12.9 (5.01–32.4)	0.71 (0.55–0.91)	.008	–	–	–	–	–	–
Ovomucoid-sIgE (kU _A /L) ^a	4.46 (<0.35–15.1)	0.85 (0.74–0.98)	.023	–	–	–	–	–	–
Milk-sIgE (kU _A /L) ^a	–	–	–	5.24 (1.58–15.8)	0.50 (0.39–0.64)	<.001	–	–	–
Wheat-sIgE (kU _A /L) ^a	–	–	–	–	–	–	6.02 (1.78–20.4)	0.63 (0.42–0.96)	.031
Omega-5 gliadin-sIgE (kU _A /L) ^a	–	–	–	–	–	–	1.12 (0.36–3.39)	0.54 (0.32–0.91)	.021

Note: Missing values were handled using multiple imputations. Variables not in the models are left blank. Hazard ratios are adjusted with all variables in the models.

Abbreviations: CI, confidential interval; HR, hazard ratio; IgE, immunoglobulin E; sIgE, specific IgE.

^aHazard ratios are expressed for every 1.0 unit increase in the decimal logarithm.

^bTotal IgE as well as egg white- and ovomucoid-specific IgEs at 1 year of age were available for 577, 591, and 561 cases, respectively.

^cTotal IgE and milk-specific IgE at 1 year of age were available for 420 and 418 cases, respectively.

^dTotal IgE and wheat- and omega-5-specific IgEs at 1 year of age were available for 224, 223, and 156 cases, respectively.

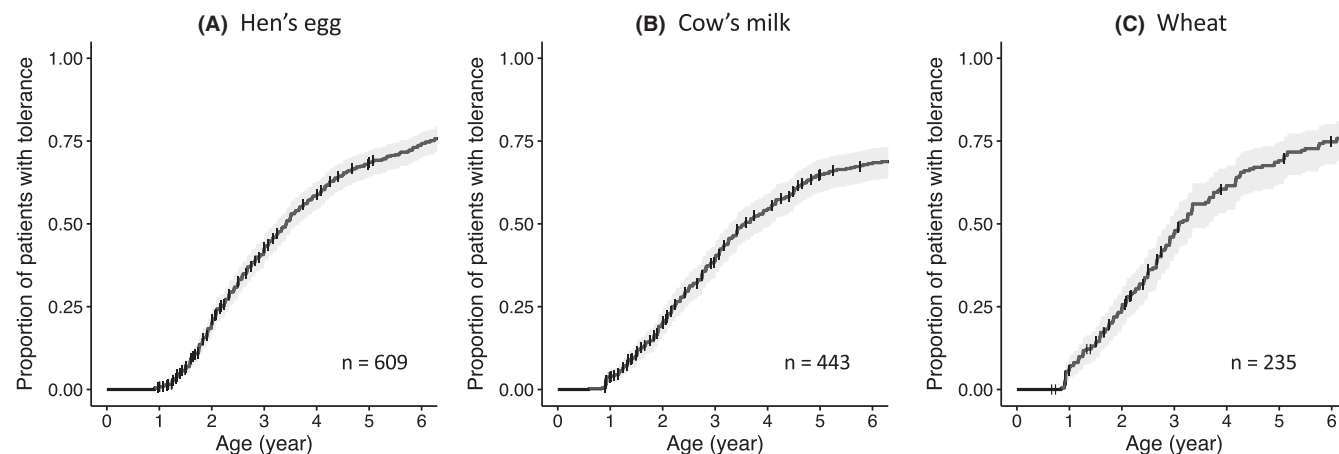


FIGURE 2 Kaplan-Meier curve for tolerance acquisition for infantile-onset, immediate-type food allergy. Gray area indicates 95% confidence interval. Resolution of hen's egg allergy, $n = 609$. Resolution of cow's milk allergy, $n = 443$. Resolution of wheat allergy, $n = 235$.

4 | DISCUSSION

In this study, we investigated the clinical courses of patients with food allergies, including those with multiple allergies. There are some reports on multiple foods^{14–16} and LCA of food allergies.^{17,18} To the best of our knowledge, this is the first study to examine the clinical course of multiple food allergies simultaneously. These results augment our understanding of the course of infantile-onset food allergy and provide a method for early identification of severe cases, allowing clinical allergists to consider different approaches, such as oral immunotherapy.

Among our egg allergy patients, the proportion of patients with tolerance at the age of 6 years is consistent with previously reported results.^{1,19} Egg white^{19,20} and ovomucoid-sIgE^{20–22} levels have reportedly correlated with persistent egg allergy. We reported that ovomucoid-sIgE predicted tolerance of heated eggs,²³ and contrastingly, tolerance of less heated foods, such as a scrambled egg, correlated with egg white-sIgE. In our study, these two sIgEs were both significant, even when simultaneously considered as parameters, because our goal of egg tolerance was consuming scrambled eggs after passing the heated egg OFC. Furthermore, ovomucoid-sIgE level plateaued at approximately 1 year of age. Ovomucoid-sIgE levels measured before this age may have been unreliable and needed retesting. Although milk allergy is not associated with prolonged egg allergy, comorbid wheat allergy is a risk factor. Wheat can reduce egg antigenicity²⁴ and aid in daily egg intake, helping induce tolerance.²⁵ This may explain the potential association between wheat allergy and egg tolerance.

In our study, 69% of the subjects acquired tolerance to milk at the age of 6 years. Although factors associated with tolerance were similar, the reported proportion of children acquiring milk tolerance at 6 years varied widely,^{26–29} ranging 12%²⁶–92%.²⁹ This was influenced by subject differences between studies; therefore, we believe that our simulation software will be useful in providing exploratory information to patients.

The wheat-tolerance rate was similar to that in previous reports.^{30–32} Wheat- and omega-5-sIgEs correlated with tolerance. Unlike egg and milk allergies, atopic dermatitis was not associated with wheat-allergy resolution, although the proportions of patients with atopic dermatitis were not low. This result is consistent with those of previous studies on natural history.^{31–33} Although the reason for this is unknown, the sensitization pattern of wheat may be different from that of eggs and milk.

From our results, the largest food allergy class was *Class 2: Transient egg allergy alone*, which accounted for 19.6% of our subjects. Considering the large size of this class, it will be necessary to establish a system for family doctors to manage these patients appropriately. Although higher ovomucoid-sIgE levels at 1 year of age were associated with this class, the egg white-sIgE level was not useful in distinguishing this class from *Class 1: Sensitization only*. Contrastingly, egg white-sIgE levels were associated with *Class 4: Prolonged egg allergy*. This result is consistent with that of the Cox regression analysis.

Patients in one severe class, *Class 7: Multiple food allergy*, had persistent allergies to three major allergens. Prolonged food allergy can significantly affect the quality of life, so it is important to identify these cases early. Patients considered to belong to this class should be referred to an allergist at an early age for early intervention.

There have been several reports on the association between antigen sensitization and allergic disease. From the data of two cohorts, Hose et al.¹¹ found latent classes from patterns of sensitization to various antigens, including food antigens, and described the association with asthma and other diseases. Havstad et al.¹² analyzed sensitization to 10 antigens at 2 years of age using LCA and found 4 classes and differences in the presence of asthma at age 10. However, these reports did not include food allergies in their analysis. Gabet et al.³⁴ also analyzed sensitization to food and inhalant antigens at 18 months and the development of allergic disease at 6 years of age, but only 6% of the subjects had food allergies, and the authors did not explain which antigens produced immediate-type symptoms.

Classify analyze, n (%) or median (interquartile range)

Sex (male) 189 (58%)

Year	1990	2000	2010	2020
1990	100%	100%	100%	100%
2000	100%	100%	100%	100%
2010	100%	100%	100%	100%
2020	100%	100%	100%	100%

MILK AN 0 (1.8%)

Total IgE 61.7 (26.9-177.8)

OVM-sIgE 0.52 (<0.35–6.61)

Wheat-sIgE 0.24 (<0.35-2.19)

Sex (male)	Reference
1	1
2	2
3	3
4	4
5	5
6	6
7	7
8	8
9	9
10	10
11	11
12	12
13	13
14	14
15	15
16	16
17	17
18	18
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86	86
87	87
88	88
89	89
90	90
91	91
92	92
93	93
94	94
95	95
96	96
97	97
98	98
99	99
100	100

25

EW-SigE

Milk-sIgE

Abbreviations: AD, atopic dermatitis; An, anaphylaxis; E

E—hen's egg; M—cow's milk; W—wheat. Cells with con-

* $p < .001$ ** $p < .01$ *** $p < .05$

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The predicted class population was calculated using modal posterior probabilities.

PF—hen's egg: M—cow's milk: W—wheat. Cells with conditional probabilities greater

Odds ratios are adjusted with all variables in the models. Class 1 was used as reference

*** $p < .001$ ** $p < .01$ * $p < .05$

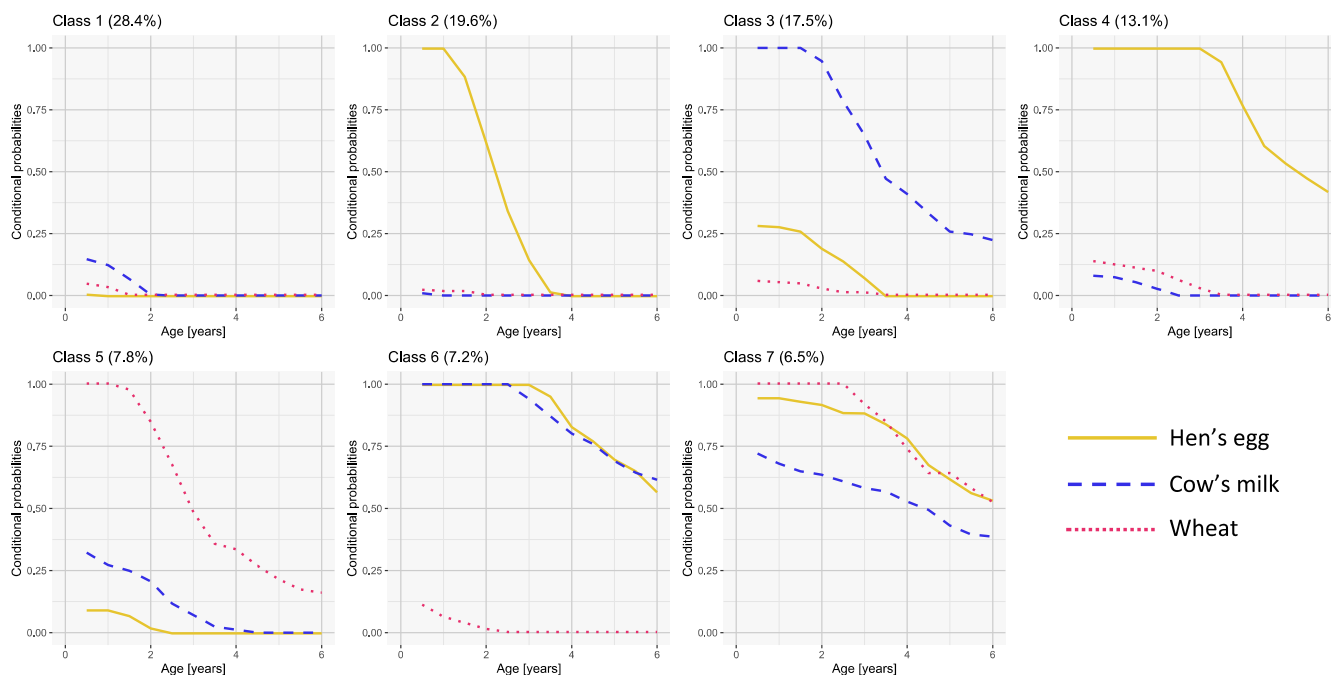


FIGURE 3 Conditional probabilities for food allergies to three major antigens. The yellow solid, blue dashed, and red dotted lines indicate conditional probabilities of hen's egg, cow's milk, and wheat allergies, respectively. Class 1: sensitization only (28.4%), Class 2: transient egg allergy alone (19.6%), Class 3: milk $\pm$ transient egg allergy (17.5%), Class 4: prolonged egg allergy (13.1%), Class 5: wheat $\pm$ transient milk allergy (7.8%), Class 6: persistent egg and milk allergy (7.2%), Class 7: multiple food allergy (6.5%).

In recent years, LCA has been also used in the field of food allergy. Tran et al.¹⁸ revealed three food-introduction patterns from a birth cohort study in Canada. They reported that delaying food introduction significantly increased the risk of sensitization to egg white and peanuts. Peters et al.¹⁷ identified five distinct phenotypes of allergic diseases from the HealthNuts study. They reported a single egg allergy as the most dominant class in food allergy, which is consistent with our results. However, they did not discuss food allergy prognosis. This study is novel in that we simultaneously observed and classified the progression of food antigens until tolerance was acquired.

In our study, the male sex was not identified as a factor for food allergy classes. This is inconsistent with the HealthNuts study results,¹⁷ possibly due to the study target selection. Since 62% of the subjects in our study were male, it is clear that the subjects are different from those in the birth cohort. In other words, when considering risk factors for children who visit a hospital, the data from this study may be more applicable than the results obtained from the birth cohort.

We developed simulation software to depict patient prognosis. This software helps identify patients requiring more attention. Although probability curves and Kaplan–Meier curves are often used in the field of food allergy, it is difficult to fit only one curve to a diverse group of patients. The implementation code of this software is open source, so that other researchers will be able to easily create their own versions.

Our study has several limitations. First, this study was conducted only at our institution, and large multi-centric studies are necessary to obtain more generalized results. Second, due to the small number of peanut-allergy cases, we could not examine peanut allergy. Only 2.8% of patients developed peanut allergies during observation, possibly due to its low prevalence and uncommon peanut consumption during

infancy in Japan.¹³ Third, the prediction of prognosis was based only on data at 1 year of age. Methods for more accurate long-term prediction by using the patients' progress during the course are required.

In conclusion, we demonstrated the prognosis of egg, milk, and wheat in Japan and identified food allergy classes, including multiple food allergies, with their individual characteristics. Characteristics tend to vary from one target population to another; therefore, studies on different populations are imperative. The relevance between the classes found in the present study and the improvement/development of comorbid allergic disease also needs to be analyzed. In addition, how the proportions of these classes change over time needs to be examined in future.

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CONFLICT OF INTEREST

Sakura Sato and Motohiro Ebisawa received speaker honoraria from Mylan EPD. The other authors declare that they have no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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