Predicting Severe Reactions in Oral Food Challenge from Blood Test Results in Children Who have Never Eaten the Suspected Food

Izumi Kato[1,2], Osamu Takahashi[1]

[1] Graduate School of Public Health, St. Luke's International University

[2] Department of Pediatrics, Chiba Kaihin Municipal Hospital

Final Report for Capstone Project

February 18, 2020

Acknowledgements

I would like to thank *Dr. Osamu Takahashi*, my adviser, for his guidance in conducting this research and valuable suggestions.

I am indebted to *Dr. Edward Barroga*, Medical Editor and Professor of Academic Writing at St. Luke's International University, for carefully reviewing and editing the manuscript.

Abstract

In daily practice of food allergies, it is common to see food elimination in children despite an incomplete diagnosis, for example, diagnosis made by the results of the blood test alone. Oral food challenge (OFC) is the most reliable test to diagnose food allergies. However, OFC also carries the risk of severe anaphylaxis. Factors that predict the outcomes of OFC have been reported. However, those specific to children who are on an elimination diet but have never eaten the suspected food have been scarcely investigated. This study aimed to identify factors that may help in predicting severe reactions in OFC from blood test results in children who have never eaten the suspected food.

OFC performed in children from April 2013 to March 2018 in Chiba Kaihin Municipal Hospital was analyzed. The inclusion criteria to the OFC were children aged 0 to 15 years, children in whom eggs have been eliminated despite the use of limited diagnostic tests, and children who have never eaten the suspected food before the OFC. Age, sex, total IgE (tIgE), egg white-sIgE, and ovomucoid (OVM)-sIgE were analyzed in the severe reaction group [Total Score/Egg Protein (TS/Pro) ≥ 31] and non-severe reaction group (TS/Pro < 31). A total of 156 OFCs were analyzed. The OVM-sIgE level was significantly higher in the severe reaction group than in the non-severe reaction group. OVM-sgE may be useful for predicting severe reactions in OFC, particularly in those who have never eaten eggs.

Keywords: Oral food challenge, hen’s eggs, ovomucoid-specific IgE

Background

Food allergy is “a phenomenon in which adverse reactions are caused by antigen-specific immunological mechanisms after exposure to a given food” as defined in the Japanese guidelines for food allergy 2017 (Ebisawa et al., 2017). An IgE-mediated response is the major antigen-specific immunological mechanism in food allergies. Food allergy is very common among children, and the number of patients has been increasing worldwide (Sicherer & Sampson, 2017). The prevalence rates of food allergy in Japan are 5%-10% in infants, 5% in young children, and 4.5% in school children. The major causative foods are hen’s eggs, cow’s milk, wheat, peanuts, fruits, fish roe, crustaceans, nuts, buckwheat and fish, with hen’s eggs accounting for 39% of the food allergies among children (Ebisawa et al., 2017).

The diagnosis of food allergy is made in three steps. The first step is to take the full dietary history. The second step is to conduct tests for antigen-specific IgE to assist in the diagnosis. These include blood tests [egg white-specific IgE (EW-sIgE) and ovomucoid-specific IgE (OVM-sIgE) for hen’s eggs] and skin prick tests (SPTs). However, it should be noted that specific IgEs indicate the presence of IgE sensitization to a specific food, which is not always associated with a clinical reaction to that food.

The third step is to perform an oral food challenge (OFC). This is the most reliable test and the gold standard for diagnosing food allergy (Ebisawa et al., 2017; Sicherer & Sampson, 2017). OFC is defined as "an examination to investigate the presence or absence of induced symptoms in a subject following the administration of an ascertained or suspected causative food in a single or multiple doses" (Ebisawa et al., 2017). Although OFC is the gold standard for diagnosing food allergies, it also has risks of acute allergic reactions, including life-threatening anaphylaxis. Thus, factors that predict positive results and severe reactions during OFC have been reported. These include high specific IgEs, positive SPTs, past history of severe reactions such as anaphylaxis, symptoms induced by a small amount of the causative food, age 5 years and older, complete avoidance of eggs, and low tIgE (Ebisawa et al., 2017; DunnGalvin et al., 2011; Sugiura et al., 2016).

There are several reasons for diagnosing food allergy. *First*, eliminating certain food(s) will have an effect on the nutritional status of a child. *Second*, a small and safe amount of the allergy-inducing food may help overcome the food allergy (Okada et al., 2015). In addition, eliminating certain foods has been shown to affect the QOL of children. Some examples of how food allergy affects people's lives are as follows: 30%-40% of children with food allergy get bullied, and children with food allergy were twice as likely to get bullied as their peers without food allergy. Moreover, various social activities are missed as follows: 16% of parents avoid letting their child go to restaurants, 11% of parents avoid letting their child go to school parties and sports, 10% avoid letting their child go to birthday parties, and 26% avoid letting their child go to camp (Walkner et al., 2015).

OFC is reported to play a positive role in the QOL of children with food allergies. In their systematic review, Kansen et al. (2018) described that most reports have indicated the favorable effects of OFC on all emotional impact, anxiety towards food, and social/dietary impact (Kansen et al., 2018).

In daily practice of food allergies, it is common to see food elimination in children based only on a blood test. As stated above, it is important to have a balance between the need of diagnosing food allergy and the risk of OFC. However, factors that predict the outcomes of OFC specifically in children who are on an elimination diet but have never eaten the suspected food have been scarcely investigated.

Objectives

This study aimed to identify factors that may help in predicting severe reactions in OFC from blood test results in children who have never eaten the suspected food.

Methods

Design and sample population

The research study design was a retrospective cohort study. The sample population was composed of children living around Chiba City and children suspected of having food allergy to eggs. All OFCs were performed for whole eggs at the Department of Pediatrics in Chiba Kaihin Municipal Hospital. This is a 293-bed municipal hospital in Chiba City and is a regional core center for pediatrics. Approximately 600 OFCs are conducted in this hospital per year.

Inclusion / exclusion criteria and dataset

OFC performed from April 2013 to March 2018 was analyzed in this study. The inclusion criteria were children aged 0 to15 years, children in whom eggs have been eliminated despite an incomplete diagnosis, namely, blood test alone, and children who have never eaten the suspected food before the OFC. The exclusion criteria were children who have eaten eggs before the OFC, regardless of their allergic reactions, and children who could not complete the OFC. During the study period, 1266 OFCs for eggs were performed during the study period. Of these, 1109 cases were excluded because they had already eaten the suspected food. One was excluded because he/she could not complete the OFC, resulting in 156 OFCs for analysis (Figure 1).

Oral food challenge

All OFCs were performed by physicians in the Department of Pediatrics in Chiba Kaihin

Municipal Hospital using the same protocol. The protocol involved two dosages of well-cooked scrambled eggs challenged at an interval of one hour according to the Japanese guidelines for food allergy 2017 (Ebisawa et al., 2017). The actual challenge dosages of the scrambled eggs were 0.5 g and 1 g, 3 g and 6 g, or 13 g and 27 g depending on each case. The test was completed when the two challenge dosages were fully administered. The test was stopped when allergic reactions occurred or when the child could not eat the food. The symptoms were scored using the Anaphylaxis Scoring Aichi (ASCA) (Hino et al., 2013). The allergic reactions were treated promptly according to the severity of the symptoms.

Outcome

The outcome of this study was the severe reactions during the OFC. Severe reaction is defined as Total Score (TS)/Egg protein (Pro) ≥ 31, and non-severe reaction is defined as TS/Pro < 31 according to a previous study (Sugiura et al., 2016). As stated earlier, ASCA was used for scoring, and TS indicates the total sum of the ASCA score, which is divided into five organ symptoms, namely, respiratory skin/mucosal, gastrointestinal, psychoneurological, and cardiovascular symptoms, from 0 to 60 points each. The score ranges from 0 (no symptoms) to a maximum of 240. Pro represents the total amount of egg protein challenged during the OFC, and TS/Pro is calculated by dividing TS by Pro.

Factors analyzed

Age, sex, tIgE, EW-sIgE, and OVM-sIgE were selected as variables for analysis. Age, tIgE, EW-sIgE, and OVM-sIgE are known to be predictors of severe reactions during OFC (Ebisawa et al., 2017; Sugiura et al., 2016). For the results of EW-sIgE and OVM-sIgE, the classification of sIgE, which is classified into seven classes (classes 0 to 6), was used for analysis. The classification was as follows: class 0 < 0.35 U_A/ml, class 1 0.35 U_A/ml – 0.69 U_A/ml, class 2 0.70 U_A/ml – 3.49 U_A/ml, class 3 3.5 U_A/ml – 17.49 U_A/ml, class 4 17.5 U_A/ml – 49.99 U_A/ml, class 5 50 U_A/ml – 99.99 U_A/ml, and class 6 ≥ 100 U_A/ml.

Statistical analysis

The OFC cases were divided into two groups: severe reaction group (TS/Pro ≥ 31) and non-severe reaction group (TS/Pro < 31). For univariate analysis, the T-test was used for continuous variables, and the chi-square test was used for categorical variables. The seven classes of EW-sIgE and OVM-sIgE were divided into three groups for analysis: group 1 for classes 0 to 1, group 2 for classes 2 to 3, and group 3 for classes 4 to 6. Thereafter, logistic regression analysis was used for multivariate analysis. A P-value of $< .05$ was considered to indicate a statistically significant difference. Based on the results, a receiver operating characteristic (ROC) curve was analyzed to evaluate the performance of the diagnostic tests. All statistical analyses were conducted using Stata (version IC/16; StataCorp. LLC, College Station, TX, USA).

Ethical statement

This study was approved by the institutional review board of Chiba Kaihin Municipal Hospital (IRB no. 2019-05). All OFCs were explained and agreed to by the patient and/or caregivers of the patient.

Results

Characteristics of the analyzed cases

Table 1 shows the characteristics of the 156 cases. The median age was one year, with a range of 0 to 12 years. Graph 1 shows the distribution of the ages. The range was from 0 to 12 years, but most of the cases were between 0 to 6 years (n = 154), with one year being the most frequent (n = 91). There were 55.8% male patients (n = 87). A TS/Pro above 31, which is considered severe, was seen in 29.5% of the cases (n = 46). Allergic reactions during OFC were treated using adrenaline injection in 6% of the cases (n = 10). The median IgE level was 134 IU/ml (range 2-16203 IU/ml).

Graph 2 shows the distributions of EW-sIgE and OVM-sIgE. Even though both OVM and EW are specific IgEs for hen's eggs, OVM-sIgE showed a different distribution from that of EW-sIgE, having quite a number of class 0s. Graph 3 demonstrates the correlation between EW-sIgE and OVM-sIgE (R = 0.45), which shows that a high EW-sIgE level does not always mean a high OVM-sIgE level.

Univariate analysis

Table 2 shows the results of the univariate analysis. As for age and sex, there were no significant differences between the severe reaction group and the non-severe reaction group. As for IgE, EW-sIgE and OVM-sIgE, significant differences were seen between the two groups in which the severe reaction group had a significantly higher tIgE level ($p = .03$) and significantly higher EW-sIgE and OVM-sIgE groups ($p < .01$ for both variables).

Multivariate analysis

All five variables, namely, age, sex, IgE, EW-sIgE, and OVM-sIgE were included in the multivariate logistic regression analysis. Table 3 shows the results of the logistic regression analysis. The odds ratios for IgE (OR 1.00, 95% CI 1.00 to 1.00) and EW-sIgE (OR 0.26 for group 2, 95% CI 0.02 to 3.55 and OR 0.80 for group 3, 95% CI 0.06 to 10.30) were not significant. The ORs for OVM-sIgE were significant. The OR was 19.00 for group 2 compared with group 1 (95% CI 3.75 to 96.36), and 26.18 for group 3 compared with group 1 (95% CI 4.59 to 149.42). The range of the confidence interval was broad.

ROC curve for OVM-sIgE

Based on the results of the logistic regression analysis, an ROC curve was obtained for OVM-sIgE (Graph 4). The area under the curve (AUC) was 0.787.

Discussion

In daily practice of food allergies, it is usual for children to have blood tests before eating specific foods, and to subsequently eliminate a certain food despite an incomplete diagnosis such as a blood test alone, leading to unnecessary food elimination. OFC is needed to definitively diagnose these children, although severe reactions may simultaneously occur during the test. The present study was conducted to identify and evaluate these children who have never eaten the suspected food but are on a strict elimination diet. As they have not yet eaten the suspected food, the important factors associated with severe symptoms during OFC or the history of anaphylaxis is unknown. Factors that could easily be adopted in the general hospital were selected for analysis.

In the present study, OVM-sIgE was the only factor that showed significant differences in the multivariate analysis. In contrast, EW-sIgE showed no significant differences. Children with a low OVM-sIgE level, despite the EW-sIgE level, are eligible for OFCs. In contrast, children with a high OVM-sIgE level, regardless of the EW-sIgE level may have a high risk of severe reaction during OFCs, necessitating careful thought about pending the test. Sugiura et al. (2016) have reported that OVM-sIgE shows a better correlation with TS/Pro than EW-sIgE. Nomura et al. (2014) have reported that OVM-sIgE can be used for predicting severe reactions in OFCs. Although our present data were limited to children who have never eaten hen's eggs, the effectiveness of OVM-sIgE for predicting severe reactions in OFC was similar to that reported in the previous studies.

In our study, the ORs for age, sex, and tIgE were not significant. In contrast, Sugiura et al. (2016) showed that an age of five years or more was one of the risk factors for severe reactions. This discrepancy may be due to the nature of our study. As the data were limited to children who have never eaten hen's eggs, the number of children over five years old was very small. Children with no history of eating eggs at the age of over 5 years can easily be imagined as having more severe food allergies. Thus, if there are a sufficient number of older children for analysis, the results may differ from those of the present study.

Strength of the study

The present study showed similar results to previous studies, that is, OVM-sIgE in particular plays an important role in predicting severe reactions during OFCs. In addition, the present study showed that OVM-sIgE is useful specifically for children who have never eaten hen's eggs. The OVM-sIgE level can be easily obtained by blood tests in most general hospitals and clinics. Moreover, the study outcome is "severe reactions" and not "positive results", thus this does not restrict OFCs to only mild symptoms.

Limitations

This study was conducted only in a single municipal hospital (i.e., Chiba Kaihin Municipal Hospital) and is therefore a single-center study. All OFCs were conducted using two dosages of the suspected food at an interval of one hour. Thus, the results may vary if the OFC is performed in a different manner. Also, the present study was limited to hen's eggs, thus it cannot be applied to other antigens. In addition, the small sample size without a validation study may affect the reliability of the study. An external validation study in several facilities is preferred to increase reliability as well as generalizability. The variables analyzed in the present study were limited to sex, age, total IgE, EW-sIgE, and OVM-sIgE. Some other factors are known to be associated with severe allergic reactions such as a past history of other allergic diseases (e.g., bronchial asthma, allergic rhinitis, and atopic dermatitis) and underlying cardiac or respiratory diseases (Ebisawa et al., 2017). These factors may become confounders in the present study.

Conclusion

Our study showed that OVM-sIgE may be useful for predicting severe reactions in OFCs, particularly in children who have never eaten hen's eggs. This finding could avoid conducting high-risk OFCs as well as increase the number of OFCs for children with a low risk and thus reduce unnecessary food elimination.

References

DunnGalvin, A., Daly D., Cullinane, C., Stenke, E., Keeton, D., Erlewyn-Lajeunesse, M., Roberts, G.C., Lucas, J. & Hourihane, J.O'B. (2011). Highly accurate prediction of food challenge outcome using routinely available clinical data. *Journal of Allergy and Clinical Immunology 127*(3), 633-639. https://doi.org/10.1016/j.jaci.2010.12.004

Ebisawa, M., Ito, K., Fujisawa, T., on behalf of Committee for Japanese Pediatric Guideline for Food Allergy, The Japanese Society of Pediatric Allergy and Clinical Immunology, The Japanese Society of Allergology. (2017). Japanese guidelines for food allergy 2017. *Allergology International*, *66*, 246-264. http://dx.doi.org/10.1016/j.alit.2017.02.001

Hino, A., Maeda, T., Haneda, Y., Kobayashi, T., Yasui, M., Kando, N. & Ito, K. (2013). Establishment of "Anaphylaxis Scoring Aichi (ASCA)", a new scoring system to be used in an oral food challenge (OFC). *Arerugi*, *62*: 968-979 (in Japanese).

Kansen, H. M., Le, T-M., Meijer, Y., Flokstra-de Blok, B.M.J., Welsing, P.M.J., K. van der Ent, C., Knulst, A.C. & C. van der Erp, F. (2018). The impact of oral food challenges for food allergy on quality of life: A systematic review. *Pediatric Allergy Immunology 29*, 527-537. https://doi.org/10.1111/pai.12905

Nomura, T., Kanda, Y., Kato, T., Sobajima, T., Morishita, T., Sugiura, S. & Suda Y. (2014).

Probability curves focusing on symptom severity during an oral food challenge. *Annals of Allergy, Asthma & Immunology 112*, 556-557. https://doi.org/10.1016/j.anai.2014.04.001

Okada, Y., Yanagida, N., Sato, S. & Ebisawa, M. (2015). Acceleration of tolerance induction effect by avoiding complete elimination. *JJACI*, *29*, 41-47 (in Japanese).

Sicherer, S. H. & Sampson, H. A. (2017). Food allergy: A review and update on epidemiology, pathogenesis, diagnosis, prevention, and management. *Journal of Allergy and Clinical Immunology 141*(1), 41-58. https://doi.org/10.1016/j.jaci.2017.11.003

Sugiura, S., Matsui, T., Nakagawa, T., Sasaki, K., Nakata, J., Kando, N. & Ito, K. (2016). Development of a prediction model of severe reaction in boiled egg challenges. *Allergology International 65*, 293-299. http://dx.doi.org/10.1016/j.alit.2016.01.005

Walkner, M., Warren, C. & Gupta, R. S. (2015). Quality of life in food allergy patients and their families. *Pediatric Clinics of North America*, *6*, 1453-1461. http://dx.doi.org/10.1016/j.pcl.2015.07.003

Table 1

Characteristics of the study population

Variables	**N**		**Results**
Age (years)	156	median (range)	1 (0 – 12)
Sex (male)	156	number (%)	87 (55.8)
Egg protein (g)	156	median (range)	0.15 (0.05 – 1.3)
TS/Pro	156	median (range)	0 (0 – 600)
TS/Pro ≥ 31	156	number (%)	46 (29.5)
Negative result	156	number (%)	106 (67.9)
Adrenaline	156	number (%)	10 (6.4)
IgE (IU/ml)	154	median (range)	134 (2 – 16203)
EW-sIgE (class)	156		
0		number (%)	4 (2.6)
1		number (%)	8 (5.1)

2		number (%)	22 (14.1)
3		number (%)	67 (43.0)
4		number (%)	39 (25.0)
5		number (%)	10 (6.4)
6		number (%)	6 (3.9)
OVM-sIgE (class)	145		
0		number (%)	50 (34.5)
1		number (%)	5 (3.5)
2		number (%)	23 (15.9)
3		number (%)	39 (26.9)
4		number (%)	22 (15.2)
5		number (%)	4 (2.8)
6		number (%)	2 (1.4)

Note. This table shows the characteristics of the 156 cases. Egg protein is the total amount of egg protein challenged in one OFC.

TS: Total Score; Pro: Egg protein; TS/Pro: TS/Pro $\geq$ 31 indicates the OFCs with a severe reaction. Adrenaline refers to the OFC cases that needed treatment with adrenaline injection. EW-sIgE: Egg white-specific IgE, OVM-sIgE: Ovomucoid-specific IgE.

Classes 0-1 are grouped as 1, classes 2-3 are grouped as 2, and classes 4-6 are grouped as 3 for statistical analysis.

Table 2

Results of univariate analysis

Variables		TS/Pro < 31 (non-severe)	TS/Pro ≥ 31 (severe)	p-value
Age	Years	1.63	1.93	.28
	(n)	(110)	(46)	
Sex				
Male	%	52.7	63	
	(n)	(58)	(29)	.24
Female	%	47.3	37	
	(n)	(52)	(17)	
IgE	IU/ml	283.5	825.6	.03
	(n)	(110)	(44)	
EW-sIgE (group)				< .01

1	%	10	2.2	
	(n)	(11)	(1)	
2	%	64.5	39.1	
	(n)	(71)	(18)	
3	%	25.5	58.7	
	(n)	(28)	(27)	
OVM-sIgE (group)				
1	%	51.5	6.8	
	(n)	(52)	(3)	
2	%	39.6	50	< .01
	(n)	(40)	(22)	
3	%	8.9	43.2	
	(n)	(9)	(19)	

EW-sIgE: Egg white-specific IgE, OVM-sIgE: Ovomucoid-specific IgE

Table 3

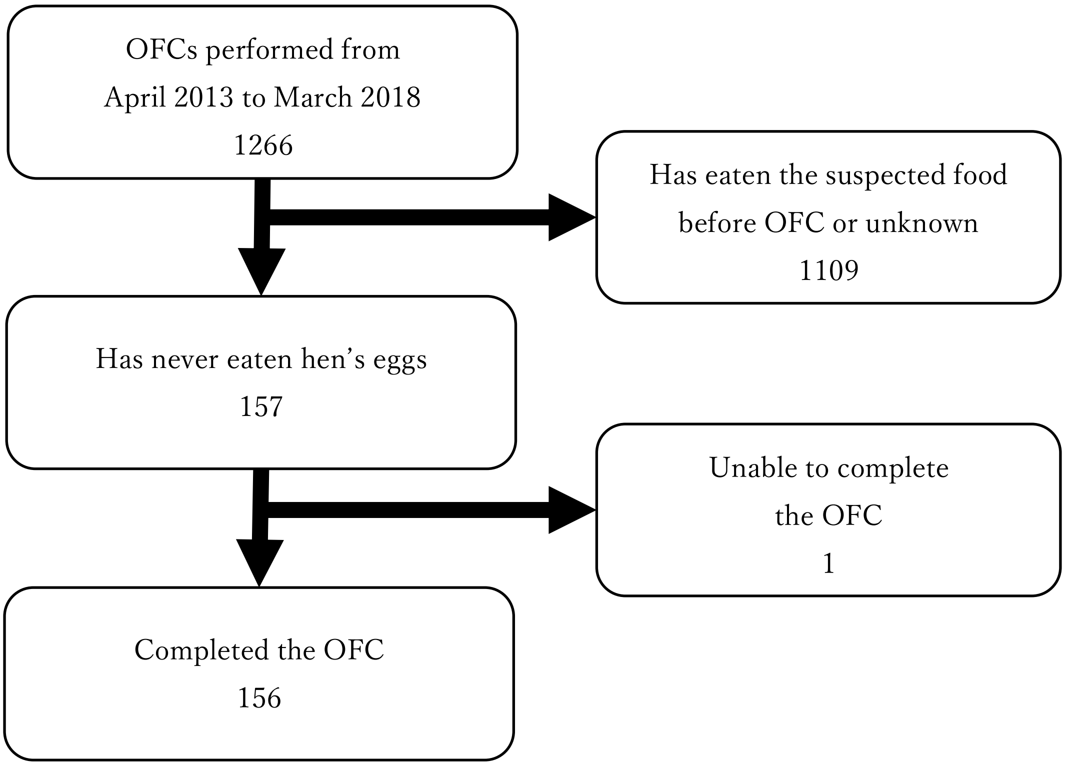
Results of the logistic regression analysis

Variables	Odds Ratio	P-value	95%CI	
Age	0.86	.315	0.64	1.16
Sex（male）	1.36	.472	0.58	3.28
IgE	1.00	.576	1.00	1.00
EW-sIgE				
2	0.26	.312	0.02	3.55
3	0.80	.862	0.06	10.30
OVM-sIgE				
2	19.00	< .01	3.75	96.36
3	26.18	< .01	4.59	149.42

EW-sIgE: Egg white-specific IgE, OVM-sIgE: Ovomucoid-specific IgE

Figure 1

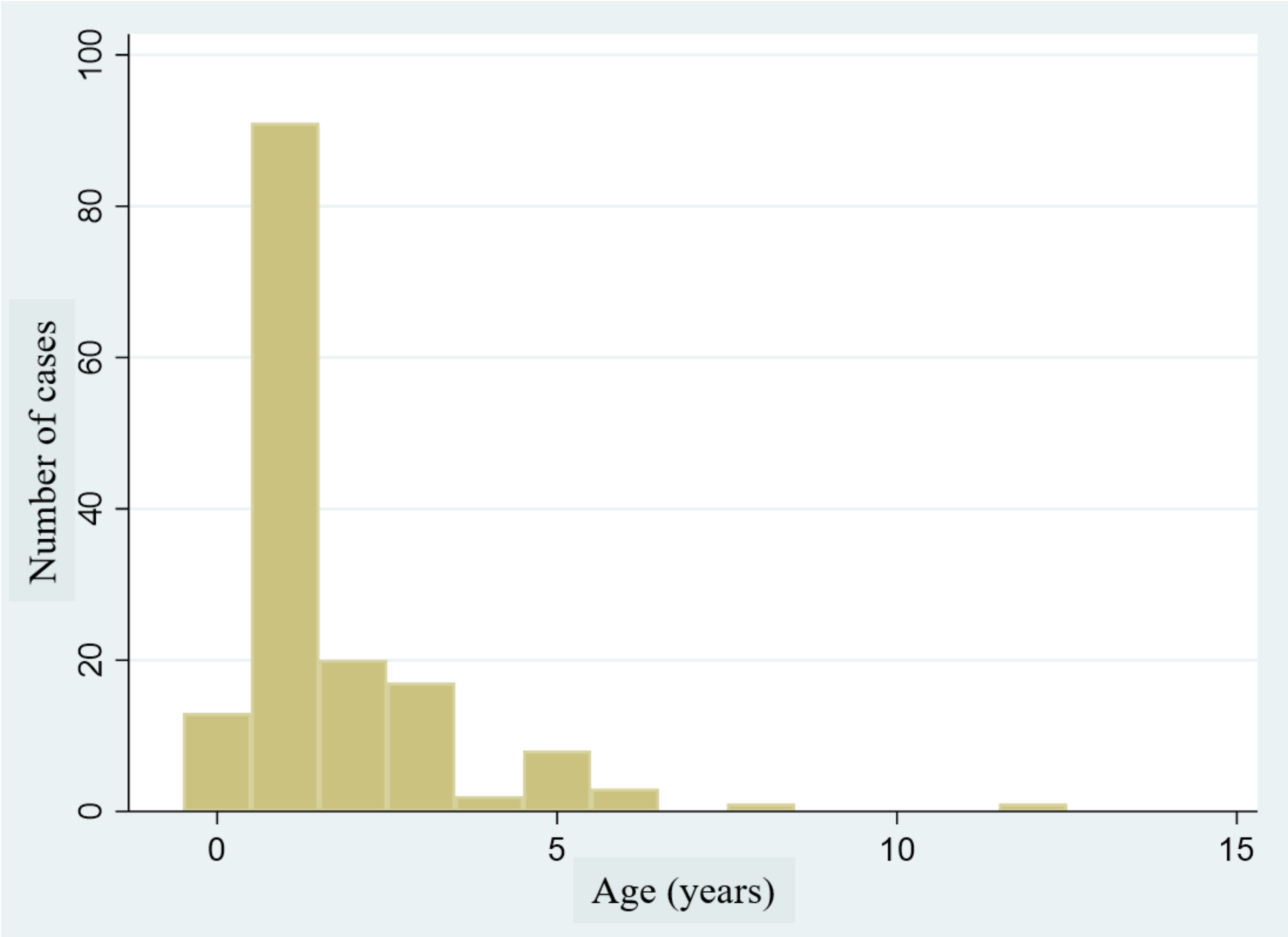
Flowchart of the study



OFC: Oral food challenge

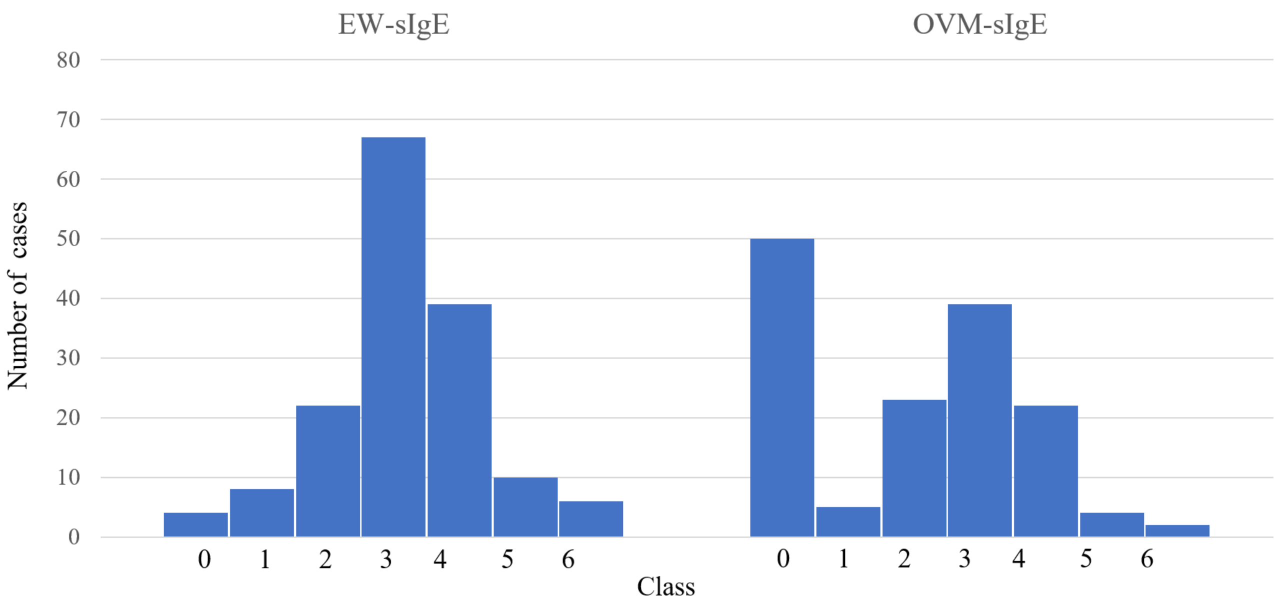
Graph 1

Distribution of ages of the study population



Graph 2

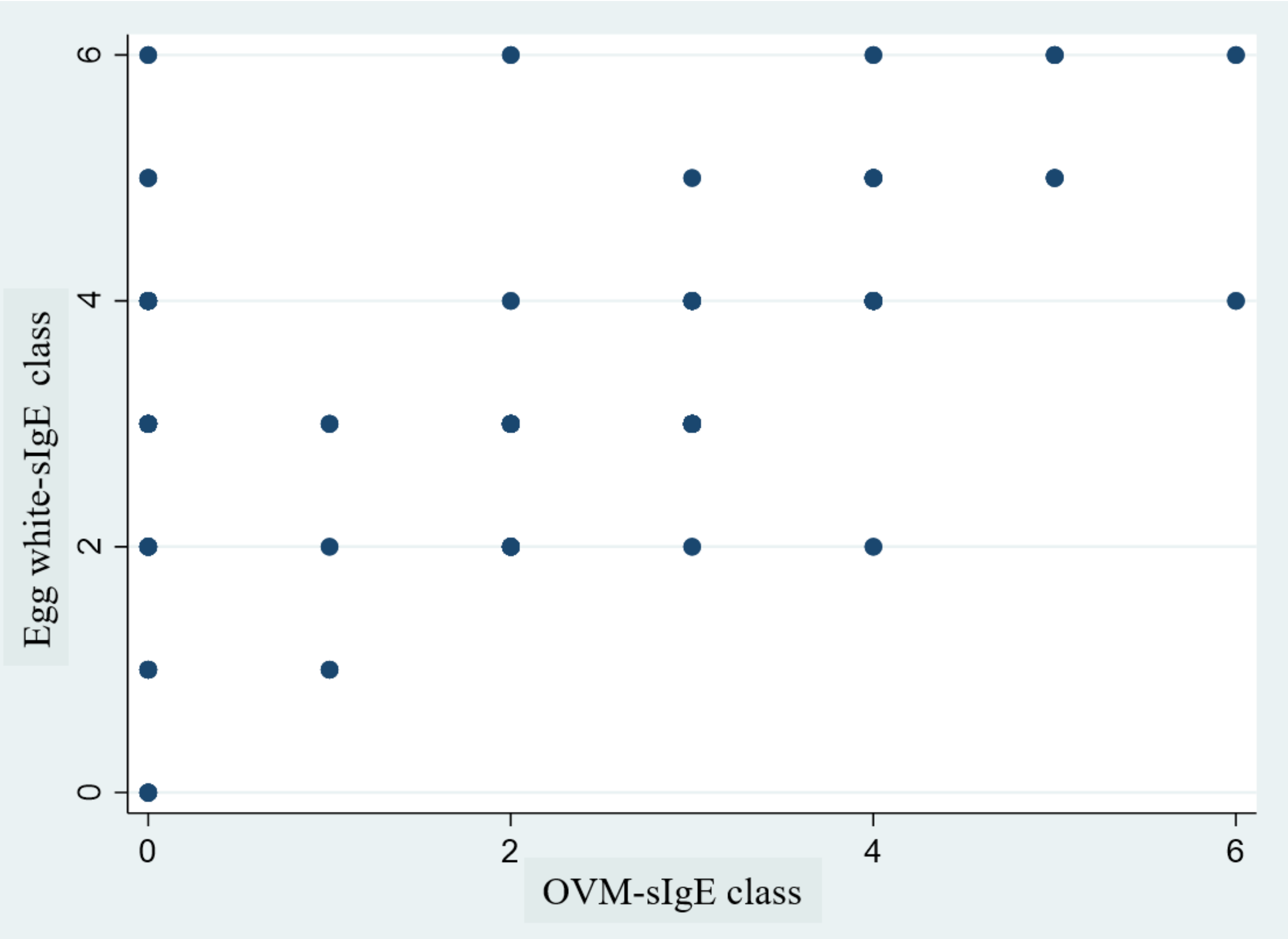
Distributions of EW-sIgE and OVM-sIgE



EW-sIgE: Egg white-specific IgE; OVM-sIgE: Ovomucoid-specific IgE

Graph 3

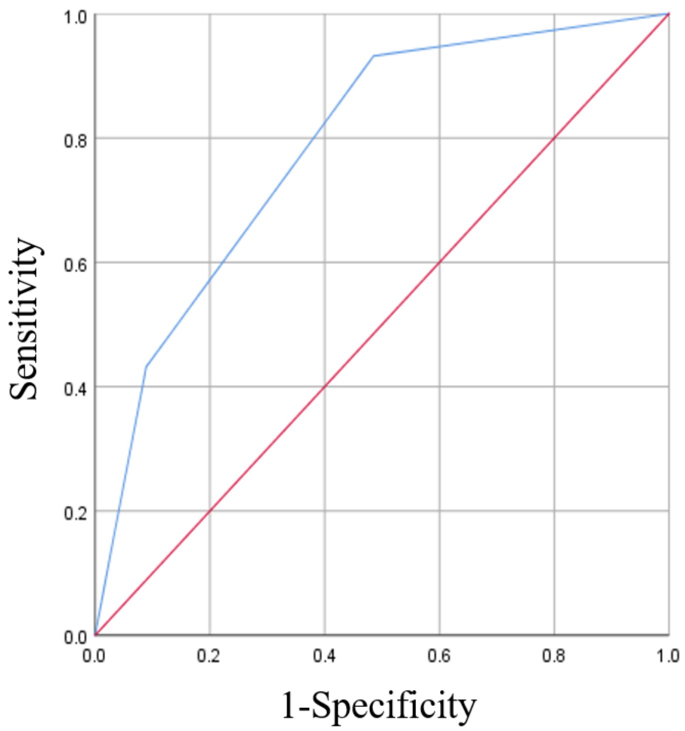
Correlation between EW-sIgE and OVM-sIgE



OVM: Ovomucoid

Graph 4

ROC curve for OVM-sIgE



The AUC is 0.787.

ROC: Receiver operating characteristics; AUC: Area under the curve; OVM-sIgE: Ovomucoid-specific IgE