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# Oral food challenge test results of patients with food allergy with specific IgE levels >100 UA/ml

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**Abstract.** Specific IgE level (sIgE) is an important factor indicating sensitization status in children with food allergies (FAs). The present study aimed to clarify oral food challenge test (OFC) results in children with FAs with sIgE levels ≥100 UA/ml compared with those in children with sIgE <100. The retrospective study analyzed patients who underwent OFC with egg white, cow milk and wheat at Gifu Prefectural general medical center, Gifu, Japan between July 2017 and March 2023. Clinical history, total IgE (tIgE), sIgE and correlation between sIgE, sIgE/tIgE and eliciting dose as the amount of intake protein were examined. In the <100 group, positive OFC showed significantly higher sIgE for egg white, ovomucoid and casein than negative OFC (P<0.05); however, there was no significant difference between positive and negative OFC in the ≥100 group. In the <100 group, positive OFC showed significantly higher sIgE/tIgE for ovomucoid, milk and casein than negative OFC (P<0.05); however, there was no significant difference in sIgE/tIgE between positive and negative OFC in the ≥100 group. There was a significant negative correlation between eliciting dose and sIgE for egg white and wheat (P<0.05). For milk and wheat, there was no significant difference between ≥100 group and the <100 group with regard to positive rates in the OFC. Therefore, OFC may be safely performed by decreasing total challenge dose for the ≥100 group.

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*Abbreviations:* s, specific; t, total; FA, food allergy; OFC, oral food challenge

*Key words:* food allergy, tolerance, threshold, anaphylaxis, oral, challenge test

## Introduction

In recent years, the prevalence of food allergies (FA) in children has been increasing. Food allergy prevalence increased from 3.5% in 1999 to 7.7% in 2009 among Chinese infants (1). A more than threefold increase in the prevalence of peanut and tree nut allergy between 1997 and 2008 has been documented (2). The most reliable diagnostic method for FA is oral food challenge (OFC). Predictors of symptoms that may appear by OFC include history of anaphylaxis, type of food allergy, high levels of specific (s)IgE antibody titer and asthma (3,4). As sIgE is a numerical value, it is easy to observe changes over time. sIgE is associated with food tolerance up to 3 years of age, making it useful in evaluating the course of FA in clinical practice (5-7). Furthermore, probability curve may be used as a reference to predict the results of OFC. However, it is difficult to conclude whether probability curves have external validity if the patient population and dose differ from those in clinical practice. In addition, each probability curve has its own 95% confidence interval and it is challenging to predict the outcome of OFC based on the probability curve alone, even if it is well-adapted to the patient population from which the curve was generated and the clinical situation. In patients with sIgE >100 UA/ml (≥100 group), the positive rate of OFC is ~100%; however, reports indicate that the positive predictive value does not reach 90% in ≥100 group (5,8-10).

There are conflicting reports regarding whether sIgE levels are associated with anaphylaxis and severity of FA (11-13). Patients may continue unnecessary food elimination based solely on sIgE levels, leading to overestimation of high-risk cases. Delays in OFC lead to prolonged and unnecessary elimination of food and contribute to adverse effects such as decreased bone density, as in the case of eliminating milk (14). The more the food type is removed, the more it affects growth (15). Furthermore, unbalanced diet may be a risk factor for obesity (16).

sIgE assayed by Immuno CAP® (Thermo Fisher Scientific, Inc.) is classified into seven levels ranging from class 0 to 6 (≥100 group) (17). The association between sIgE levels and clinical characteristics of children with FAs is unclear. Therefore, the present study aimed to clarify the characteristics of children with FAs and sIgE ≥100 compared with patients with sIgE <100 UA/ml, with a focus on clinical characteristics and OFC results.

## Materials and methods

*Study design*. The present retrospective study was performed at Gifu Prefectural General Medical Center, Gifu, Japan from July 2017 to March 2023. The study was approved (approval no. 773-2) by the Ethics Committee. The study was based on chart review of OFC results eliciting objective reactions to wheat, egg and milk (18). Participants (n=572) with egg white (n=299), milk allergy (n=201) and wheat allergy (n=72) were recruited. A total of 69% of participants were male. Participants were patients aged 0-16 years who were clinically reactive to eggs, milk and wheat with sIgE >0.35 UA/ml. OFC was performed for diagnosis of food allergies, confirmation of tolerance and increase of intake of allergic food at home. The age and the clinical history of each patient were analyzed. Children who had experienced anaphylaxis within the past 6 months and those for whom data such as total (t)IgE levels and egg white, wheat, milk, ovomucoid, ω5 gliadin and casein sIgE allergy were not available were excluded from the study. Probability curves for predicting OFC outcomes were taken from reference (10).

*IgE test*. tIgE and sIgE serum levels in response to egg white, cow milk, wheat, ovomucoid, casein and ω5 gliadin were assessed using sandwich assays (ImmunoCAP®, Thermo Fisher Scientific, Inc.), according to the manufacturer's instructions (Cat. nos. UF1, UF2, UF4, UF233, UF78 and UF416 for egg white, cow milk, wheat, ovomucoid, casein and ω5 gliadin respectively. Within 1 year of the OFC, serum samples were taken by venipuncture. In the ≥100 group, samples were diluted 10-fold or 100-fold and then assayed by ImmunoCap®.

*OFC*. Written consent was obtained from parents or guardians of participants prior to OFC. Following IgE tests, OFC was performed within 1 year. The open OFC test was performed in accordance with the Japanese Guideline for Food Allergy 2020 (19). Anaphylaxis was defined in accordance with National Institute of Allergy and Infectious Disease (20). The total challenge dose depended on the dose of egg white, cow milk and wheat ingested daily before the OFC test. OFC was performed under medical supervision with access to emergency support. Patients underwent physical examination by a doctor prior to feeding initiation to ensure that patients are healthy enough to undergo OFC. Vital signs and observations for lung and skin were recorded on clinical charts. Any signs or symptoms during the OFC were recorded. Eggs were boiled at 100˚C for 20 min and separated into egg white and yolk immediately after cooking, of which only egg whites were used for the test. Udon noodles were used as the wheat source. The number of load was one to five times.

The interval between each load was 15 to 60 min. After 2 h from the last load, the patient was allowed to go home if no symptoms were induced. Eliciting dose was defined as the lowest dose of egg white, cow milk or wheat eliciting an objective allergic reaction as described in the allergy guidelines (19). The eliciting dose was converted to protein mass as follows: 45 g boiled egg = 4.5 g egg white protein; 10 g cow milk = 0.33 g protein and 10 g udon = 0.26 g wheat protein.

*Response to symptom induction*. Depending on the severity of symptoms, oral antihistamines, inhaled β-stimulants and intramuscular adrenaline injection were administered according to the Japanese Guideline for Food Allergy 2020 (19).

*Statistical analysis*. The data are presented as median and inter quartile range. Mann-Whitney U test was used for continuous variables. Fisher's exact test was used to analyze categorical variables. Spearman's rank correlation coefficient was used to determine correlation of eliciting dose and sIgE that did not follow a normal distribution. All tests were two-sided. All analyses were performed using EZR ver 1.61 (jichi.ac.jp/saitama-sct/SaitamaHP.files/statmed.html). P<0.05 was considered to indicate a statistically significant difference.

## Results

*Characteristic of participants*. A total of 299 patients with egg, 201 with cow milk and 72 with wheat allergy were recruited; patients with incomplete data were excluded from the study. A total of 17 patients with egg, 24 with cow milk and 17 with wheat allergy were included in the ≥100 group (Fig. 1). A total 237 patients with egg, 137 with cow milk and 48 with wheat allergy were included in the <100 group.

The median age in the ≥100 group was older than that in the <100 group. In patients with egg white allergy, ≥100 group had significantly more previous anaphylaxis than the <100 group. In the ≥100 group, positive rates were 100, 64 and 67% for egg white, milk and wheat allergies, respectively In the <100 group, positive rates were 17, 40 and 28% for egg white, milk and wheat allergies, respectively (Table I). Other allergic complications such as asthma, allergic rhinitis and atopic dermatitis tended to be more common in the ≥100 group. tIgE in ≥100 was higher than in the <100 group. Median sIgE levels in the ≥100 group were 170, 248, 197, 144 and 285 UA/ml for egg white, cow milk, wheat, ovomucoid and casein, respectively (Table II). Median sIgE levels in the <100 group were 6.1, 6.4, 11.6, 2.8, 5.5 and 1.0 for egg white, cow milk, wheat, ovomucoid, casein and ω-5 gliadin allergies, respectively.

*OFC and eliciting dose*. The ≥100 group had significantly lower total loading dose than the <100 group. (Table III). In the ≥100 group of patients with milk and wheat allergy, there was no significant difference in the loading dose regardless of whether the test result was positive or negative. In the <100 group, the egg loadings were significantly lower for positive compared with negative OFC; however, no significant differences were found for milk and wheat. The minimum amount of loading protein that did not induce symptoms was 0.0033 and 0.0026 g for milk and wheat, respectively.

sIgE predicts the probability of positive outcomes in OFC (3,5). Therefore, correlation between positive OFC and sIgE were analyzed. In the ≥100 group, a significant difference in sIgE between positive and negative OFC was not observed (Fig. 2A). In the <100 group, positive OFC showed higher sIgE

Table I. Patient characteristics.

| Characteristic | Egg white ≥100 | Egg white <100 | Milk ≥100 | Milk <100 | Wheat ≥100 | Wheat <100 |
|---|---|---|---|---|---|---|
| Male (%) | 11 (65) | 155 (63) | 15 (63) | 106 (71) | 9 (53) | 37 (65) |
| Age, years (IQR) | 7 (5-8)[a] | 4 (2-7) | 7 (6-8)[a] | 6 (3-8) | 9 (8-11)[a] | 6 (3-8) |
| History of anaphylaxis (%) | 6 (35)[a] | 34 (14) | 9 (36) | 29 (19) | 3 (18) | 11 (19) |
| Asthma (%) | 5 (29) | 45 (18) | 7 (29) | 25 (17) | 9 (53) | 16 (28) |
| Allergic rhinitis (%) | 0 (0) | 36 (15) | 2 (8) | 12 (8) | 1 (7) | 11 (19) |
| Atopic dermatitis (%) | 5 (29) | 84 (34) | 8 (3) | 43 (29) | 4 (24) | 28 (49) |
| sIgE, UA/ml (IQR) | 170 (151-212) | 6.07 (3-17) | 248 (161-332) | 6 (3-25) | 197 (133-354) | 13.4 (4-42) |
| tIgE, UA/ml (IQR) | 1154 (1,028-2,297)[a] | 361.5 (96-1,055) | 2,542 (1,560-5,008)[a] | 463 (151-1,304) | 627 (423-1,128) | 824 (272-1,883) |
| Number of OFC tests (%) | 7 (41) | 247 (100) | 11 (46) | 150 (100) | 9 (53) | 57 (100) |
| Positive OFC rate, % | 100[a] | 17 | 64 | 40 | 67 | 28 |

[a]P<0.05 vs. <100. s, specific; t, total; OFC, oral food challenge; IQR, interquartile range.

Table II. Median specific IgE levels.

| Group | Egg white | Cow milk | Wheat | Ovomucoid | Casein | ω5 gliadin |
|---|---|---|---|---|---|---|
| ≥100 UA/ml | 170 | 248 | 197 | 144 | 285 | Not detected |
| <100 UA/ml | 6 | 6 | 12 | 3 | 6 | 1 |

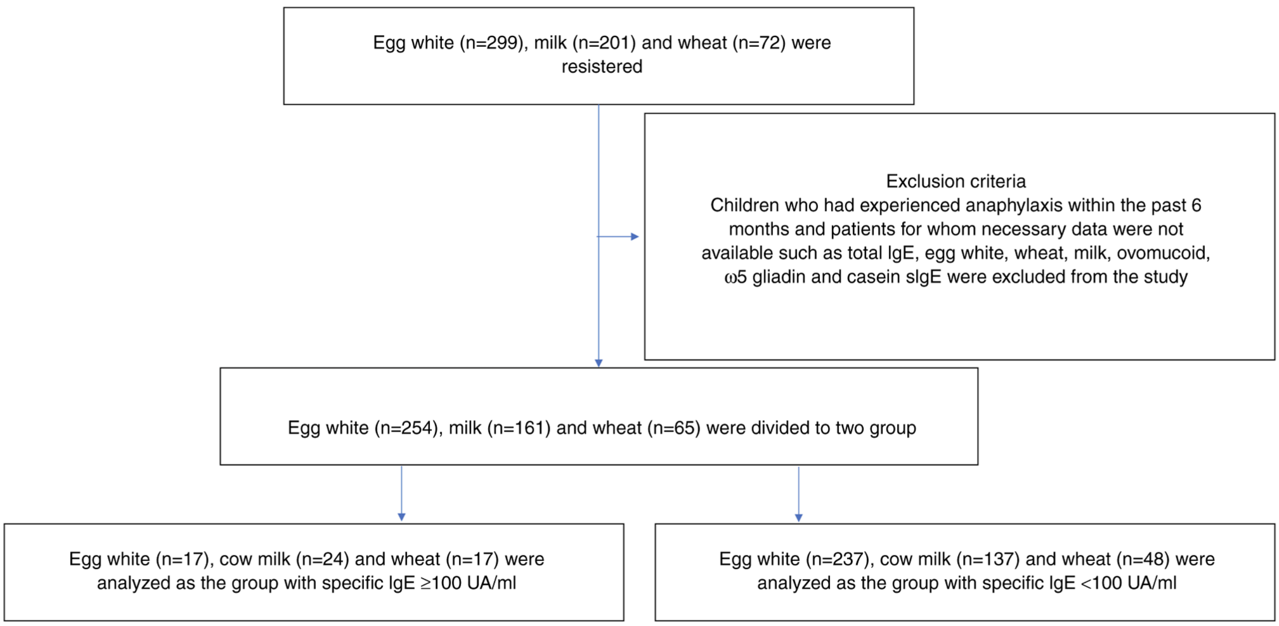


Figure 1. Study enrollment, screening and participants.

for egg white, ovomucoid and casein allergies compared with those shown by the negative OFC (Fig. 2B).

Total IgE in the ≥100 group was higher than in the <100 group. Therefore, correlation between positive OFC and sIgE/tIgE was analyzed. In the ≥100 group, a significant difference in sIgE/tIgE between positive and negative OFC was not observed (Fig. 2C). In the <100 group, positive OFC showed higher sIgE/tIgE for ovomucoid, cow milk and casein allergies compared with those shown by the negative OFC (Fig. 2D).

Finally, eliciting dose in OFC was analyzed (Fig. 3). The eliciting dose of egg white and udon noodles was correlated with sIgE for egg white and wheat allergy, respectively; however, there was no correlation between eliciting dose and sIgE for cow milk allergy.

Table III. Median total protein load.

| Group | Egg white ≥100, g (IQR) | Egg white <100, g (IQR) | Milk ≥100, g (IQR) | Milk <100, g (IQR) | Wheat ≥100, g (IQR) | Wheat <100, g (IQR) |
|---|---|---|---|---|---|---|
| Overall | 2 (1-4)[a] | 29 (7-40) | 1.0 (0.3-2.2)[a] | 14.0 (3.0-68.0) | 1.00 (1.00-3.00)[a] | 50.0 (10.0-200.0) |
| Positive | 2 (1-4)[a] | 3 (1-4) | 0.03 (0.01-0.08)[a] | 0.5 (0.1-2.2) | 0.04 (0.03-0.07)[a] | 1.3 (0.3-5.2) |
| Negative | Not detected | 3 (1-3) | 0.09 (0.01-0.29)[a] | 1.7 (0.3-2.2) | 0.003 (0.003-0.070)[a] | 1.3 (0.3-5.2) |

Note that the amount (g) for egg white is expressed as total load, not protein load. [a]P<0.05 vs. <100. IQR, interquartile range.

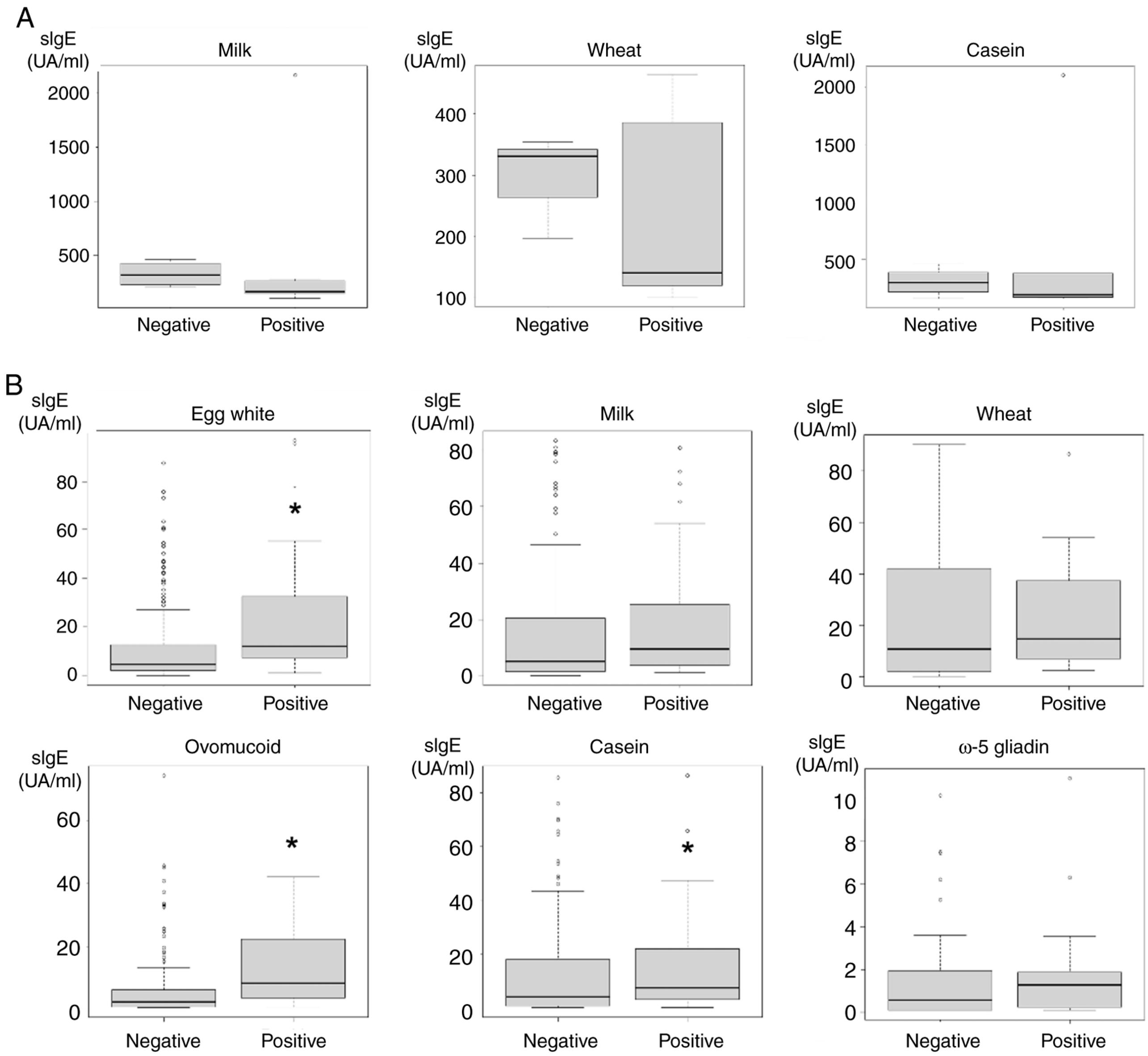


Figure 2. Continued.

## Discussion

The present assessed clinical characteristics and OFC results in the ≥100 group. To the best of our knowledge, no previous studies investigated sIgE ≥100. Previous studies on peanuts showed that the higher the sIgE value, the lower the

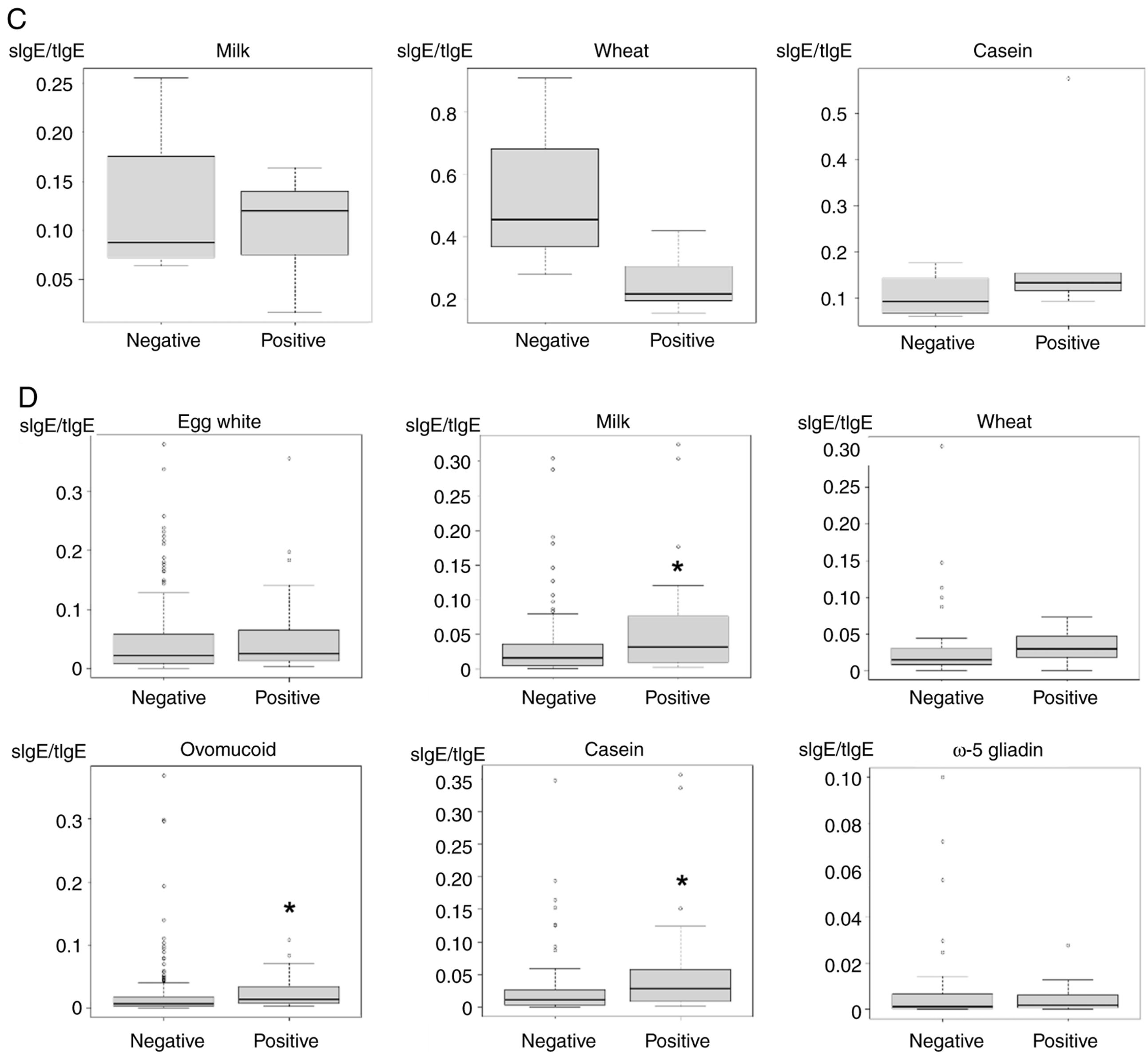


Figure 2. Association between OFC, sIgE and sIgE/tIgE. (A) In the ≥100 group, significant difference of sIgE between positive and negative OFC was not observed. (B) In the <100 group, the positive OFC showed higher sIgE for egg white, ovomucoid and casein compared with negative OFC. (C) In the ≥100 group, a significant difference in sIgE/tIgE between positive and negative OFC was not observed. (D) Positive OFC showed a higher sIgE/tIgE for ovomucoid, cow milk and casein compared with negative OFC. All OFC result of egg white was positive. There was no patient whose sIgE of ω-5 gliadin was over 100. *P<0.05 vs. negative. OFC, oral food challenge; s, specific; t, total.

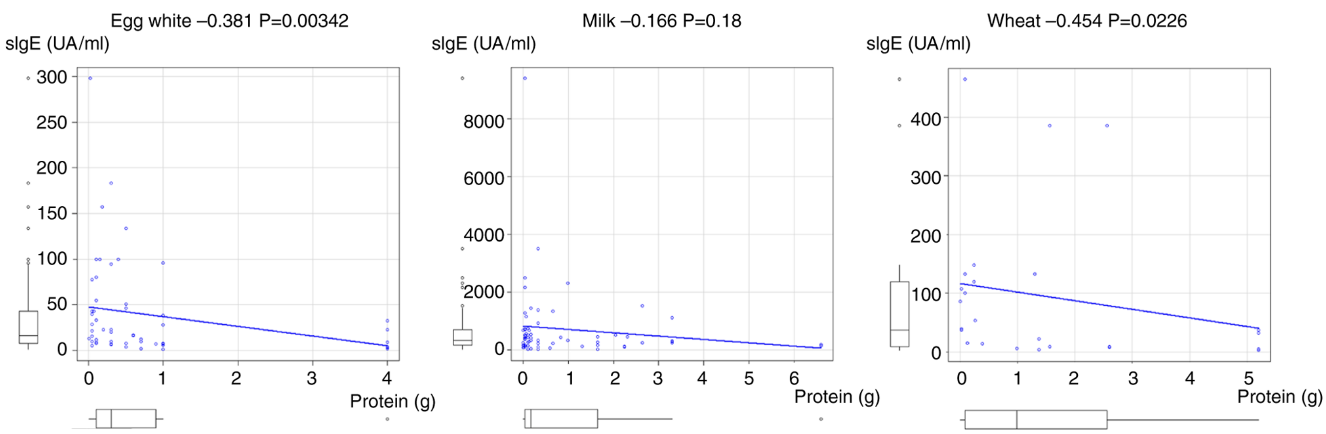


Figure 3. Spearman's rank correlation coefficient. Correlation of eliciting dose of egg white and udon noodles with sigE for egg white and wheat. The box-and-whisker diagram shows the interquartile range of sIgE and protein.

eliciting dose in OFC (21,22). For other foods, the higher the sIgE value, the lower the eliciting dose. The results of the present study may be useful in determining the loading levels for OFC. For egg white, the prevalence of anaphylaxis was significantly higher in the ≥100 compared with that in the <100 group. In the ≥100 group, positive rates were 100, 64 and 67% for egg white, milk and wheat allergies, respectively, which differed from those expected by the probability curve except for egg white allergy (10). In addition, there was a significant difference in the positive rate of egg white allergy in the ≥100 compared with <100 group, whereas there was no significant difference in positive rates of milk and wheat allergies in the ≥100 group compared with those in the <100 group. Because the positive rate of OFC was 100%, avoiding OFC for egg white allergy with 0.02 g loading protein in the ≥100 group may be recommended; however, OFC may be safely performed for milk and wheat allergies in the ≥100 group by setting the amount of intake appropriately. In the present study, the minimum amount of loading protein that did not induce symptoms upon wheat intake was 0.0026 g, hence this amount could be used as a guide for loading tests. In milk intake, a loading protein level <0.0033 g may not induce symptoms. For egg white intake, all OFCs of the ≥100 group were positive, and it was not known what loading level might safely be used in OFC; however, it was considered necessary to at least decrease the loading level to <0.02 g protein, which was the minimum loading level in the present study. With regard to the interval between loading, 60 min interval is associated with significantly lower symptom severity than 30 and 40 min intervals (23). Although single doses were mostly used in the present study due to the minute amounts, it may be possible to perform loading tests more safely by using smaller doses at 60-min intervals.

The ≥100 group for egg white allergy exhibited significantly more anaphylaxis than the <100 group; however, prediction of the onset of anaphylaxis is challenging based on sIgE (24). To the best of our knowledge, no study which have analyzed ≥100 group; however, the results should be verified in the future with a larger number of patients

sIgE/tIgE ratio is useful in predicting outcome of OFC to distinguish it from false-positive sIgE in patients with atopic dermatitis (24). However, significant correlations have been observed only for peanut allergy and no correlations have been shown for egg white, milk and wheat allergy. In the <100 group, the correlation among egg white, wheat, ovomucoid and casein allergies for both sIgE and sIgE/total IgE ratio between positive and negative groups, was consistent with that of a previously reported study (25). By contrast, in the ≥100 group, there was no significant difference for sIgE and sIgE/tIgE ratio between the positive and negative groups. The values of sIgE above 100 and sIgE/tIgE levels may be not useful for predicting OFC result in the ≥100 group.

Further investigation is needed to determine whether sIgE and sIgE/tIgE correlate with the results of the OFC, especially in the ≥100 group.

Previous studies have suggested a significant negative correlation between sIgE and the threshold of OFC loading (22,26). In the present study, the ≥100 group had a significantly lower threshold than the <100 group, indicating a negative association between sIgE and threshold. This does not mean that OFC cannot be performed in patients with high sIgE; however, it is necessary to decrease the loading amount to the maximum extent for safety. Eliciting dose in OFC gradually increases as the patient continues to eat small amounts of food (27); hence, exploring the dose which does not induce the allergic symptoms by performing OFC with very small quantities of food is meaningful. Continuing to eat that amount may raise the eliciting dose.

Moreover, if the threshold can be raised, induction of allergic symptoms by accidental ingestion of small amounts of food may be decreased.

The present study has certain limitations. First, it was a single-center, retrospective study with a small number of patients and lack of age-matching. These effects may have caused selection bias. To resolve this, the sample size should be increased and the population should be age-matched. Second, the amounts of food loaded were not matched. The loading dose was determined at the discretion of the physician in charge of the loading test. Since the amount of food loaded has a notable impact on the results of the loading test (19), it is necessary to conduct the test with the same amount of food loaded in the future.

In peanut allergy, patient characteristics associated with symptom thresholds are sex and atopic dermatitis (28,29). For the present study, significant difference was not found in either of these in the ≥100 group; however, if the number of patients was increased, a change may be observed. The ages of patients in the ≥100 group were significantly higher than in the <100 group. There are reports that older age is associated with symptom severity and adrenaline administration in OFC (30,31). Therefore, in the present study, age may have influenced the results. This suggests that acquiring tolerance takes a long period for the ≥100 group. However, increasing the amount of food that can be eaten can decrease the burden on patients and their families. Additionally, decreasing the opportunity to perform OFC based solely on sIgE may be disadvantageous to patients and their families. Food allergies not only affect individuals with allergic reactions but also cause psychological stress for both patients and their families due to the limitations that come with avoiding certain foods (32,33). Basophil activation test is associated with symptom severity and threshold in OFC in peanut allergy (34). Basophil activation test, which were not investigated in this study, may predicts OFC positivity in the patients with food allergy.

For milk and wheat allergy, there was no significant difference in positive OFC in the ≥100 compared with that in the <100 group, Therefore OFC may be safely performed by adjusting the amount of intake for the ≥100 group. When performing OFC for the ≥100 group for egg white allergy, the timing and the amount of intake must be considered.

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## Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

## Authors' contributions

SY and KH wrote the manuscript and analyzed data. ME and IA contributed to the conception and design of the study and revised the manuscript. SY and KH confirm the authenticity of all the raw data. MK and HK analyzed and interpreted and revised the manuscript. All authors have read and approved the final manuscript.

## Ethics approval and consent to participate

The requirement for informed consent was waived due to the retrospective nature of the study. The study was approved by the Ethical Review Committee of Gifu Prefectural General Medical Center, Gifu, Japan (approval no. 773-2).

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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