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Treatment difficulties in wheat oral immunotherapy and the predictive value of wheat-specific IgE

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Abstract

Background: Factors associated with wheat oral immunotherapy (OIT) difficulties in patients with IgE-mediated wheat allergy have not been well studied.

Objective: We aimed to assess factors associated with difficulties in wheat OIT.

Methods: We retrospectively collected data from children under 18 years of age with history of IgE-mediated wheat allergy who underwent wheat OIT. The initial specific IgE (sIgE) of wheat and omega-5-gliadin, wheat skin prick test (SPT) sizes, eliciting doses, and adverse reactions during the OIT were evaluated.

Results: A total of 81 children were enrolled, with a mean age of 7.0 ± 2.7 years at the initiation of wheat OIT. The median follow-up duration was 2 years (IQR 1.2–3.0 years). Difficulties in wheat OIT included patients who experienced frequent reactions (at least grade 2 or exercise-induced reactions) or deviated from the up-dosing protocol, which we defined as 'Complicated cases.' Twenty-six patients (32.1%) were complicated cases. Initial wheat-sIgEs were significantly higher in complicated cases than in noncomplicated cases (median of 192.3 kUA/L (IQR 30.4–590.0) vs 6.9 kUA/L (IQR 1.9–100.0) (p = 0.001)). Initial omega-5-gliadin-sIgEs in the complicated group were also significantly higher, with a median of 15.0 kUA/L (IQR 6.3–69.8) vs 1.6 kUA/L (IQR 0.2–11.4) (p < 0.001). The risk factors for complicated cases include higher omega-5-gliadin-sIgEs and anaphylaxis during the oral food challenge test (aOR 1.035 and 5.684, respectively).

Conclusion: The initial wheat and omega-5-gliadin-sIgEs were significant risk factors for complicated OIT patients and could be used to monitor these patients carefully during the OIT period.

Key words: Oral immunotherapy, Food allergy, IgE-mediated, Anaphylaxis, Wheat

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Introduction

Wheat is one of the leading causes of severe immediate allergic reactions to food in children. Typically, children with IgE-mediated wheat allergy tend to outgrow the allergy by 6 years of age.[1,2] However, remission is uncommon in highly-sensitized patients.[1,2] While strict avoidance is the standard treatment for food allergies, wheat is difficult to avoid as it is a common ingredient used to prepare a wide range of foodstuffs. As a result, these patients have impaired quality of life compared to those with allergies to other foods.[3] In recent decades, oral immunotherapy (OIT) has emerged as an alternative treatment for food allergies. To date, several studies on wheat oral immunotherapy have reported positive outcomes. The rates of short-term unresponsiveness were 41–61.1%.[4-6] However, OIT protocols, wheat sources, and amount of wheat maintenance dose have shown variations across studies. Vital wheat gluten (VWG), a concentrated form of wheat, was used in a randomized, double-blind, placebo-controlled trial.[7] After 2 years, the investigator observed that 30% of participants using a low-dose VWG (1445 mg of wheat protein) achieved desensitization, while 13% reached sustained unresponsiveness. In addition, they found that 11 (24%) participants discontinued from the study. The reasons for discontinuation were the dosing symptoms, non-adherence, and participant decision. In Thailand, a three-step wheat OIT protocol was successfully applied in children with severe wheat allergies.[8] We retrospectively reviewed the medical records of 26 patients who underwent wheat OIT. Although 13 patients (50%) experienced adverse reactions during the build-up phase, most of them continued the OIT. The retention rate was as high as 88%, suggesting factors beyond the frequency of reactions may influence protocol adherence.[8]

Adverse events during wheat OIT are common and could occur in any phase of the OIT. Reactions that required epinephrine injection occurred in approximately 11–20% of subjects[7,9] The amount of wheat consumed, the degree of wheat sensitization, and certain cofactors could aggravate symptoms that may influence the frequency and severity of reactions. A study from Japan evaluated the long-term prognosis of patients receiving wheat OIT and divided the patients into symptomatic and asymptomatic groups.[10] They could not find any predictive factors for developing adverse reactions, including the level of wheat and omega-5-gliadin-sIgE. Interestingly, 7 out of 8 patients in the symptomatic group had exercise as a trigger. The lower maintenance dose of wheat OIT had fewer adverse events than the conventional approach. During the 1-year maintenance period with a daily intake of 53 mg of wheat protein, OIT reactions were only 4.1%, and anaphylaxis occurred at 0.1% at home.[11] Interestingly, using the lower maintenance dose, none of the patients dropped out of the protocol in both 1-year[11] and 3-year follow-ups.[6] However, the efficacy of using the lower maintenance dose is doubtful. The 3-year follow-ups showed the rate of short-term unresponsiveness was 41%, but the rate of sustained unresponsiveness was not evaluated. In another study comparing 100% to 25% of the maintenance dose, 12 patients with wheat allergy were recruited. They found 7 participants (58%) in the 25% dose achieved short-term unresponsiveness. However, 2 participants (16.6%) discontinued the OIT due to adverse events.[5] Compared to the low-dose OIT, this option provided patients with more food choices in their daily lives but might increase the risk of adverse events and lead to discontinuing the OIT.

The successful OIT treatment depends on the efficacy and feasibility of adhering to the protocol. Our centers tried to identify patients who cannot adhere to the protocol due to frequent or severe adverse events affecting their quality of life. Our previous study showed wheat-sIgE was a predictor for anaphylaxis.[12] Therefore, this study aimed to investigate whether the level of wheat-sIgEs is related to the difficulties in wheat OIT. Furthermore, we sought to identify other factors associated with difficulties in wheat OIT, including adverse events and compliance.

Methods

Study population

This retrospective study was conducted at Siriraj Hospital and the Samitivej Allergy Institute (SAI), Bangkok, Thailand. All children under 18 years of age with IgE-mediated wheat allergy confirmed by positive oral food challenge (OFC) test who underwent wheat OIT between 2012 and 2020 were included in the study. The clinical history, the results of the investigations, and the details of the OIT were reviewed. Patients who had incomplete medical records were excluded. The SAI and the Siriraj Institutional Review Board (SIRB) approved the study protocol (COA no. Si 887/2020).

Wheat-sIgE, ω5G-sIgE, and skin prick test

Wheat-sIgE, omega-5-gliadin (ω5G)-sIgE, and skin prick test (SPT) were performed before OFC. Wheat-sIgE and ω5G-sIgE levels were measured with ImmunoCAP® (Phadia, Uppsala, Sweden). As previously described, SPT was performed using an in-house wheat extract (1:10).[13,14]

OFC and OIT protocol

Prior to starting wheat OIT, all patients underwent OFC with wheat, either a double-blind placebo control or an open food challenge. The OFC was performed in the hospital setting to confirm the diagnosis of wheat allergy and to find out the lowest amount of wheat that induces allergic symptoms (eliciting dose-ED). The protocol followed the PRACTALL recommendation with some modifications regarding step dosing.[15] The starting dose was 1 mg of wheat flour (Kite flour®, containing 13 % wheat protein), followed by 3 mg, 10 mg, 30 mg, 50 mg, 100 mg, 300 mg, 1 gm, 3 gm. Patients may switch from wheat flour to white bread (Farm house®, Bangkok, Thailand, containing 62% wheat) after reaching 1 or 3 gm of wheat flour. The starting dose of bread was 10 gm and 30 gm of wheat (approximately 3.9 gm of wheat protein or 2 slices of bread). An increasing amount of wheat flour or bread was administered every 30 minutes until allergic symptoms occurred.

Wheat OIT was initiated on the day following OFC with the maximum tolerated quantity of wheat that was identified during the OFC. During the dose escalation phase, patients were instructed to consume wheat once daily and take a second-generation antihistamine 30 to 60 minutes before the dose as a premedication. They were also advised to refrain from exercising for 1 hour before or 2 hours after wheat ingestion. The daily dose could be skipped in the presence of augmentation factors such as fever, infection, diarrhea, or menstruation. If adverse reactions occurred during OIT, patients were instructed to record their symptoms and dosage. In all instances, prescriptions of prefilled syringes or auto-injectors containing epinephrine were provided, along with the appropriate training on their administration. Participants return to the hospital every 2-4 weeks for further dose escalation for 20-40% of the previous dose. The up-dosing might be postponed if they had grade 1 reactions in a previous week, during menstruation, or had any infection on that particular day. Once maintenance doses were achieved, patients were instructed to follow the protocol. The maintenance dose consisted of 30 grams of wheat, which is approximately equivalent to 3.9 grams of wheat protein or 2 slices of bread, and it was recommended to consume at least 3 days a week. The maintenance lower than the targeted dose was implemented when patients experienced at least a grade 2 reaction, and parents consented to modify the protocol.

Classification of complicated vs. uncomplicated cases

Depending on the difficulty during the wheat OIT, the patients were classified into complicated or noncomplicated groups. The 'complicated case' was defined if the patients had one of the following criteria: (i) patients who experienced 2 times of at least grade 2 reactions[16] during the up-dosing phase; or (ii) patients who experienced 2 times of exercise-induced reactions during the up-dosing phase; or (iii) patients who deviated from the up-dosing protocol at least 2 times (not able to tolerate an increment of 20-40% of wheat during build-up). The "uncomplicated cases" were defined as patients with none of the above criteria. The severity of allergic reactions was classified into grade 1 to 5 according to the World Allergy Organization (WAO) grading systems.[16] Severe reactions were defined if patients developed at least grade 2 reactions. Anaphylaxis was diagnosed using the NIAID/FAAN criteria.[17]

Statistical analysis

Descriptive statistics are used for baseline characteristics data. i.e., categorical data as frequency (percentages), continuous data as mean ± standard deviation (SD), and median (interquartile range). Differences between groups were compared by unpaired t-test for continuous data with normal distributions, Mann-Whitney U test for continuous data for nonnormal distributions, and chi-square test for categorical data. The Mann-Whitney U test and the Kruskal-Wallis test with Dunn's for multiple post hoc analyses were used to compare differences of specific IgE antibodies to wheat and ω5G. The performance of ImmunoCAP tests to predict complicated cases was evaluated using receiver operating characteristics curve (ROC) analysis to derive an area under the curve (AUC). A *p*-value less than 0.05 was considered statistically significant. Univariate and multivariate logistic regressions were used to identify risk factors that predicted complicated group from uncomplicated group. Parameters with a *p*-value less than 0.2 in univariate logistic regression were included in the multivariate analysis. All data analysis was performed with PASW Statistics (SPSS) 18.0 (SPSS Inc., Chicago, IL, USA).

Results

Subject characteristics

A total of eighty-one subjects were enrolled in the study. **Table 1** presents the baseline characteristics of the participants. The characteristics of the subjects between 2 study sites are shown in **Table S1**. The mean age at the time of OIT initiation was 7.0 ± 2.7 years. Approximately half of the subjects were male (51.9%). The median age of onset of wheat allergy was 9 months (IQR 6–12). The median duration of follow-up was 2 (IQR of 1.2–3.0) years.

Table 1. Baseline characteristics of the study subjects. (N = 81)

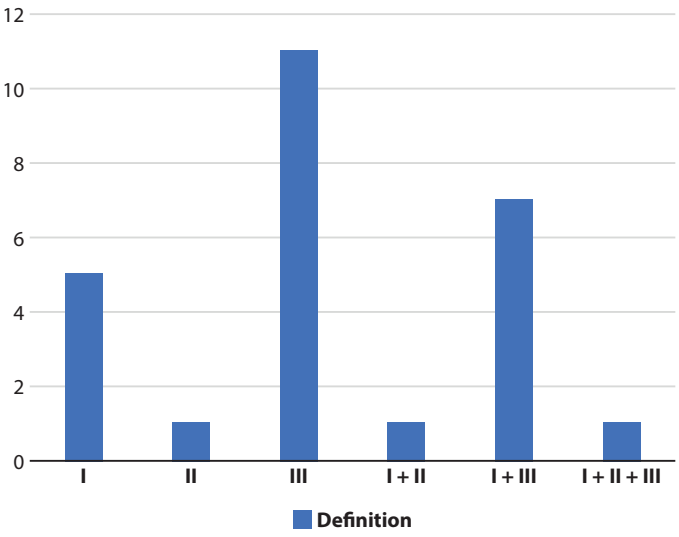
	Total (n = 81)	Complicated (n = 26)	Uncomplicated (n = 55)	*p*-value
Age onset, month, median (IQR)	9 (6-12)	8 (6-12)	10 (6-12)	0.45
Age when start OIT, year, mean ± SD	7.0 ± 2.7	7.1 ± 3.1	7.0 ± 2.5	0.87
Male, n (%)	42 (51.9)	13 (50.0)	29 (52.7)	0.82
History of anaphylaxis, n (%)	59 (72.8)	21 (80.8)	38 (69.1)	0.27
Frequency of accidental reaction before OIT				**0.04**
< 3 time/year	71 (87.7)	20 (76.9)	51 (92.7)	
≥ 3 time/year	10 (12.3)	6 (23.1)	4 (7.3)	
Asthma	11 (13.6)	3 (11.5)	8 (14.5)	0.71
Allergic rhinitis	53 (65.4)	18 (69.2)	35 (63.6)	0.62

Table 1. (Continued)

	Total (n = 81)	Complicated (n = 26)	Uncomplicated (n = 55)	*p*-value
Atopic dermatitis	26 (32.1)	7 (26.9)	19 (34.5)	0.49
Food allergy other than wheat	44 (54.3)	13 (50.0)	31 (56.4)	0.59
Wheat-sIgE, kUA/L, median (IQR)				
Before OIT	22.8 (2.9-344.5)	192.3 (30.4-590.0)	6.9 (1.9-100.0)	0.001
Peak level	46.5 (11.2-363.5)	241.8 (42.1-590.0)	24.7 (4.2-228.0)	0.002
Omega-5-gliadin-sIgE, kUA/L, median (IQR)				
Before OIT	5.8 (0.3-24.2)	15.0 (6.3-69.8)	1.6 (0.2-11.4)	< 0.001
Peak level	6.4 (0.9-28.3)	21.3 (7.8-69.8)	4.0 (0.3-15.3)	< 0.001
Wheat SPT MWD before OIT, mm, median (IQR)†	8.5 (5.0-15.0)	13.0 (5.9-17.6)	7.8 (4.5-13.5)	0.07
Mean up dose, time/month, mean ± SD	1.53 ± 0.62	1.33 ± 0.57	1.62 ± 0.63	0.05

†Data available in 48 patients (14 from complicated and 34 from uncomplicated cases)
IQR, interquartile range; OIT, oral immunotherapy; SD, standard deviation; sIgE, specific IgE; SPT, skin prick test; MWD, mean wheal diameter

Of the recruited subjects, 32.1% (26 out of 81) were classified as "complicated cases" according to our criteria. The remaining subjects were categorized as "uncomplicated cases." **Figure 1** presents the causes of these complicated cases. The most common type of complicated case was a deviation from the protocol on at least 2 occasions and/or frequent reactions during wheat OIT. The reasons for deviating from protocol included having grade 1 reactions, infections, menstruation, or a busy schedule.



Definition I: Frequent allergic reaction during OIT (≥ 2 times of at least grade 2 reaction (WAO))
Definition II: Frequent exercise-induced reaction during OIT (≥ 2 times/course)
Definition III: Deviation from OIT protocol ≥ 2 times/course

Figure 1. Complicated patients were classified according to the three definition criteria (N = 26).

When comparing uncomplicated and complicated groups, we observed a significant difference in the initial levels of wheat-sIgE ($p = 0.001$), ω5G-sIgE ($p < 0.001$), and the frequency of accidental reaction before OIT ($p = 0.04$) (**Table 1**, **Figure 2A** and **Figure 2B**). No significant differences were observed for age of onset, age at OIT initiation, gender, type, and frequency of reactions prior to OIT, initial SPT mean wheal diameter (MWD) for wheat, coexisting atopic diseases, family history of atopic diseases, nor socioeconomic status.

Furthermore, when comparing the uncomplicated and complicated groups, the OFC results before OIT showed that the patients in the complicated group had significantly a higher rate of anaphylaxis during OFC (88.5% vs 61.8%, $p = 0.018$) and injection of epinephrine (80.8% vs 56.4%, $p = 0.03$) than in the uncomplicated group (**Table 2**). The eliciting dose in the uncomplicated group was higher than in the complicated group. However, the difference did not reach a statistical difference (300 mg vs 100 mg, $p = 0.05$).

Adverse events during wheat OIT

Of the 81 recruited subjects, 46 (56.8%) had adverse events during OIT. Anaphylaxis was reported in 25 (30.9%) subjects. The characteristics of those who had experienced at least one allergic reaction during the OIT were cutaneous symptoms in 36 (44.4%) subjects, respiratory symptoms in 27 (34.6%), gastrointestinal symptoms in 19 (23.5%), and cardiovascular symptoms in 1 (1.2%). There were 22 (27.2%) subjects who required at least one experience of epinephrine injection during OIT. The triggers for developing reactions are shown in **Figure S1**. The most common trigger identified was exercise.

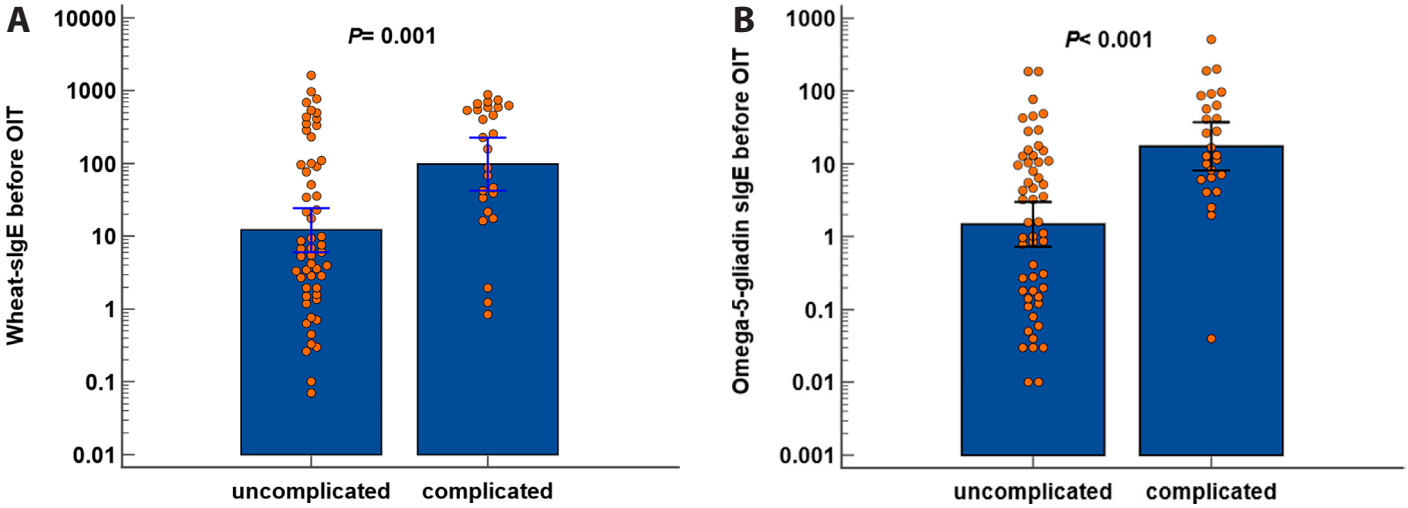


Figure 2. The log10 values of serum-specific IgE (sIgE) levels before wheat oral immunotherapy (OIT) to wheat (A) and omega-5-gliadin (ω5G) (B) compared between complicated and uncomplicated cases.

Table 2. Result of wheat oral food challenge test.

	Total (n = 81)	Complicated (n = 26)	Uncomplicated (n = 55)	*p*-value
OFC reactions				0.018
Anaphylaxis	57 (70.4)	23 (88.5)	34 (61.8)	
Non-anaphylaxis	24 (29.6)	3 (11.5)	21 (38.2)	
Severity grading during OFC,† n (%)				0.07
1	23 (28.4)	3 (11.5)	20 (36.4)	
2	25 (30.9)	10 (38.5)	15 (27.3)	
3	33 (40.7)	13 (50.0)	20 (36.4)	
Required epinephrine injection during OFC, n (%)	52 (64.2)	21 (80.8)	31 (56.4)	0.03
Eliciting dose, mg of wheat, median (IQR)	300 (100-1000)	100 (37.5-300)	300 (100-1860)	0.05

†Severity grading according to WAO criteria 2020
IQR, interquartile range; OFC, oral food challenge

Characteristics of patients with exercise-induced reaction

Of the 81 patients, 14/81 (17.3%) had exercise-induced reactions. Five out of 14 (35.7%) had an exercise-induced reaction alone. We found that patients with a higher level of wheat-sIgE or ω5G-sIgE before OIT had a significantly higher risk of exercise-induced reactions (p = 0.005 and p = 0.013, respectively). However, there were no significant differences in age-onset, sex, the coexistence of atopic diseases, initial wheat SPT MWD, the eliciting dose of wheat, and the frequency of the up-dosing protocol (**Table S2**).

Final disposition at the endpoint of the study

Of the 81 subjects who underwent wheat OIT, we classified them into subgroups by final disposition at the end point of the study into 4 groups: maintenance targeted dose (MT), maintenance less than the target dose (LT), during the build-up phase, and dropout group. Thirty-nine subjects completed the build-up phase, and 32/39 patients can maintain the targeted dose (≥ 2 slices of bread per day or approximately 30 gm of wheat). However, 7 patients could not reach the targeted dose. These patients were classified into the maintenance less than targeted dose group (LT). The median dose of wheat in this group was 7440 mg (IQR 2232-22320 mg) of wheat (967 mg of wheat protein). Thirty-six subjects were still in the build-up phase. These patients can continue updosing regularly. Six subjects dropped out of wheat OIT due to poor compliance or frequent reactions (**Table S3**).

When we compared the MT group and the LT group, we found a significantly higher initial ω5G-sIgE 40.90 kUA/L (IQR 15.20–186.00) in the LT group vs 0.98 kUA/L (IQR 0.14–11.40) in the MT group (**Table S3**, **Figure S2B**). Although there was no significant difference in the initial wheat-sIgE between the MT group and the LT group (**Table S3**, **Figure S2A**)

Table 3. Logistic regression analysis to identify risk factors that predicted complicated wheat oral immunotherapy.

Risk factors	Univariate analysis			Multivariate analysis		
	OR	95%CI	*p*-value	Adjusted OR	95%CI	p-value
Wheat-sIgE before OIT	1.002	1.000-1.003	0.04	1.000	0.995-1.002	0.40
Omega-5-gliadin -sIgE before OIT	1.013	1.001-1.024	0.03	1.035	1.004-1.067	0.03
Frequency of reaction	1.528	1.005-2.323	0.05	1.425	0.797-2.546	0.23
Up dosing frequency	0.469	0.212-1.038	0.06	0.181	0.058-0.566	0.003
Anaphylaxis during OFC	4.735	1.264-17.733	0.02	5.684	1.112-29.050	0.04

CI, confidence interval; OFC, oral food challenge; OIT, oral immunotherapy; OR, odd ratio; sIgE, specific IgE

Predictors of the complicated case in wheat OIT

The initial wheat-sIgE, ω5G-sIgE, and anaphylaxis reactions during OFC were significant predictors of complicated cases. After adjusting for sex, age, coexisting atopic disease, and frequency of the up-dosing protocol, the multivariate analysis showed that ω5G-sIgE (aOR 1.035, 95%CI 1.004–1.067) and anaphylaxis reactions during OFC (aOR 5.684, 95%CI 1.112–29.05) were identified as risk factors for the complicated case. On the other hand, more frequent up-dosing was a protective factor for complicated cases (aOR 0.181, 95%CI 0.058–0.566). (**Table 3**)

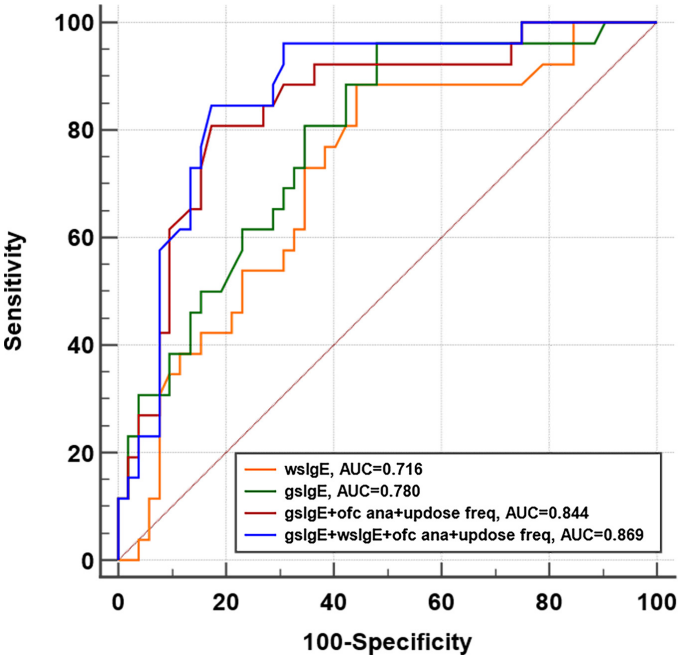


Figure 3. Receiver Operating Characteristic (ROC) Curve analysis for predicting the performance of the diagnostic model to predict "complicated case" for wheat oral immunotherapy.

wsIgE, wheat sIgE before OIT; gsIgE, omega-5-gliadin-sIgE before OIT; ofc ana, anaphylaxis during oral food challenge test; up dosing freq, up dosing frequency

Figure 3 shows the ROC curves illustrating the predictive performance of various factors to identify complicated cases of wheat OIT. The results indicate that the initial wheat-sIgE and ω5G-sIgE are effective in predicting complicated cases (AUC 0.716 and 0.780), respectively. Furthermore, our findings demonstrated that combining the history of anaphylaxis during OFC, frequency of up-dosing, and initial levels of wheat-sIgE and ω5G-sIgE enhances the diagnostic capacity, producing an AUC of 0.869.

The optimal cut-off points for wheat-sIgE and ω5G-sIgE to predict the 'complicated case' were 9.9 kUA/L and 3.6 kUA/L, respectively (**Table S4**). In addition, the ω5G-sIgE > 1.6 kUA/L gave 96.6% NPV. This finding means that if a patient's ω5G-sIgE level is below or equal to 1.6 kUA/L, there is a 96.6% probability that it would be an uncomplicated case.

Discussion

This retrospective review identified the difficulties in wheat OIT and classified them into complicated and uncomplicated groups. We found that the initial ω5G-sIgE and the history of anaphylaxis during OFC were significant predictors for complicated cases of wheat-OIT.

The most common reasons for discontinuing OIT treatment were occurrences of adverse events that patients could not tolerate, or they could not comply with the protocol.[7,8] A study by Makita et al. could not find significant parameter differences between symptomatic and asymptomatic wheat OIT cases.[10] Among 19 patients, 8 (42.1%) were identified as symptomatic. Our study used a different definition, describing patients who failed wheat OIT either due to frequent adverse events or could not adhere to the protocol as complicated cases. We found that only 32% of our patients were defined as complicated cases, which is lower than the rate found in previous studies.[7,15] The slower up-dosing protocol and the switch to LT could explain the lower rate of complicated cases in our study.

Previous studies could not identify factors that predicted the unsuccessful wheat OIT.[10,18] Baseline wheat-sIgE between the symptomatic and asymptomatic group in Makita's study were 90.5 kUA/L (69.57->100) vs 60.9 kUA/L (23.75->100), respectively (p = 0.407). The difference was not statistically significant.[10] A study by Kulmala et al[18] identified factors related to unsuccessful therapy as those who discontinued therapy at some point during the study. They found no significant factors to differentiate between the unsuccessful and successful therapy groups. Our study found that the ω5G-sIgE before OIT and a history of anaphylaxis during OFC were predictors of complicated cases. In contrast, the up-dosing frequency was a protective factor. The ω5G-sIgE was previously reported to be a predictor of wheat anaphylaxis and a lower threshold dose of wheat OFC.[19,20] We demonstrate that it also predicted complicated wheat OIT cases.

Interestingly, we found the frequency of up-dosing as a protective factor for complicated cases. The reason behind this could potentially be attributed to the retrospective approach we employed in our study. We hypothesized that patients who typically do not experience adverse reactions displayed a higher frequency of clinic visits for up-dosing than those who did experience reactions. The cut-off points for predicting complicated cases of wheat OIT have never been reported. Our study showed that the optimal cut-off point was 9.9 kUA/L for wheat-sIgE and 3.6 kUA/L for ω5G-sIgE. The negative decision point was 9.92 kUA/L for wheat-sIgE and 1.6 kUA/L for ω5G-sIgE. The negative predictive values (NPV) were 91.4% and 96.6%, respectively (**Table S3**). Therefore, patients with sIgE levels less than these cut-off levels might have a lower risk of being a complicated case. However, positive decision points yielded a positive predictive value (PPV) of only 66.7% for wheat-sIgE and 75% for ω5G-sIgE.

The direct comparison of safety in wheat OIT among studies and protocols varied across studies. Our study reported adverse reactions by using WAO classification[16] (grades 1–5). It differed from the classification used in previous studies.[4,7,18] Twenty-five out of 81 patients (30.9%) experienced anaphylaxis (defined by the involvement of two or more organs).[17] Although our study showed a higher rate of anaphylaxis, no patient experienced more than a grade III WAO reaction. Most of them had only a grade I WAO. The most common symptoms were cutaneous reactions. Out of 81 patients, 21 (25.9%) required at least one epinephrine injection during OIT (22.2% during the build-up phase and 3.7% during the maintenance phase). This data corresponds to the study by Nowak et al.,[7] which showed that 21.74% (5/23 patients) used epinephrine injections during the build-up and/or maintenance phase over 52 weeks of wheat OIT. Furthermore, our study also found that the factors that induced allergic reactions were similar to those in previous studies such as exercise, infection, and others.[10,21]

The median achievable dose in LT patients was 967 mg of wheat protein (equivalent to about ½ slice of bread). This amount was higher than in previous studies of the low-dose wheat OIT. Nagakura et al.[11] defined "low-dose desensitization" as when a patient could ingest 53 mg without symptoms. For this reason, we compared our data with the study by Kulmala et al.[18] The initial ω5G of their study was lower than ours (median 6.02 kUA/L vs. 40.9 kUA/L), but the median achievable dose in that study was also lower than ours (445 mg of wheat protein). However, they had a higher dropout rate than our study (43% vs 7.4%). The differences could be attributed to a longer build-up period in our study (13 months in MT and 19 months in LT), while the study from Kulmala et al. had a build-up period of only 4 months.

When comparing the dropout rate with other previous studies,[4,7,18] we had fewer dropout rates (6/81,7.4%). Due to our study protocol, patients were allowed to switch to the LT group. In addition, our protocol had a low incremental rate (20–40%) and good patient adherence. As a result, we had a lower dropout rate than the other studies.

The limitations of our study include that it was a retrospective study and that we had a variation in the follow-up period (median 24 months, IQR14-36 months). However, our results closely mirror real-world conditions, in contrast to the controlled perspective of a blinded prospective study.

In summary, this is the first study to identify complicated cases in wheat OIT. We found that the initial wheat-sIgE, the initial ω5G-sIgE, and a history of anaphylaxis during OFC were significant predictors of patients with complicated OIT. Furthermore, the initial ω5G-sIgE was also an associated factor in patients who could not reach the target dose during wheat OIT. We suggested that in patients who have predictors for complicated wheat OIT, the lower maintenance dose should be considered to keep patients in the OIT protocol.

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Author's Contribution

- PP and PV conceptualized this study.
- NR, CW, PT, AS, SW contributed to subject recruitment and sample collection.
- WS contributed to data analysis.
- SW and PP participated in writing the original draft.
- All authors have read and approved the manuscript.

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Supplementary Figure

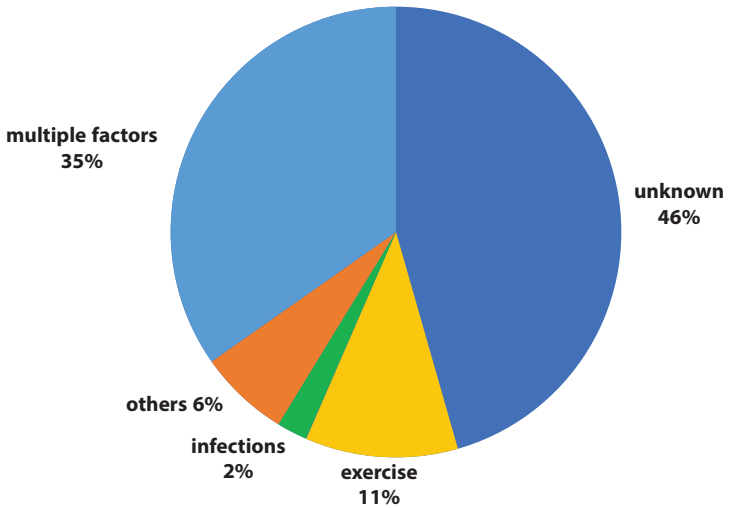

Figure S1. The percentage of trigger factors that induced allergic reactions during wheat oral immunotherapy period in this study.

Multiple factors = more than one triggers, others = other specific cause such as menstruation, empty stomach

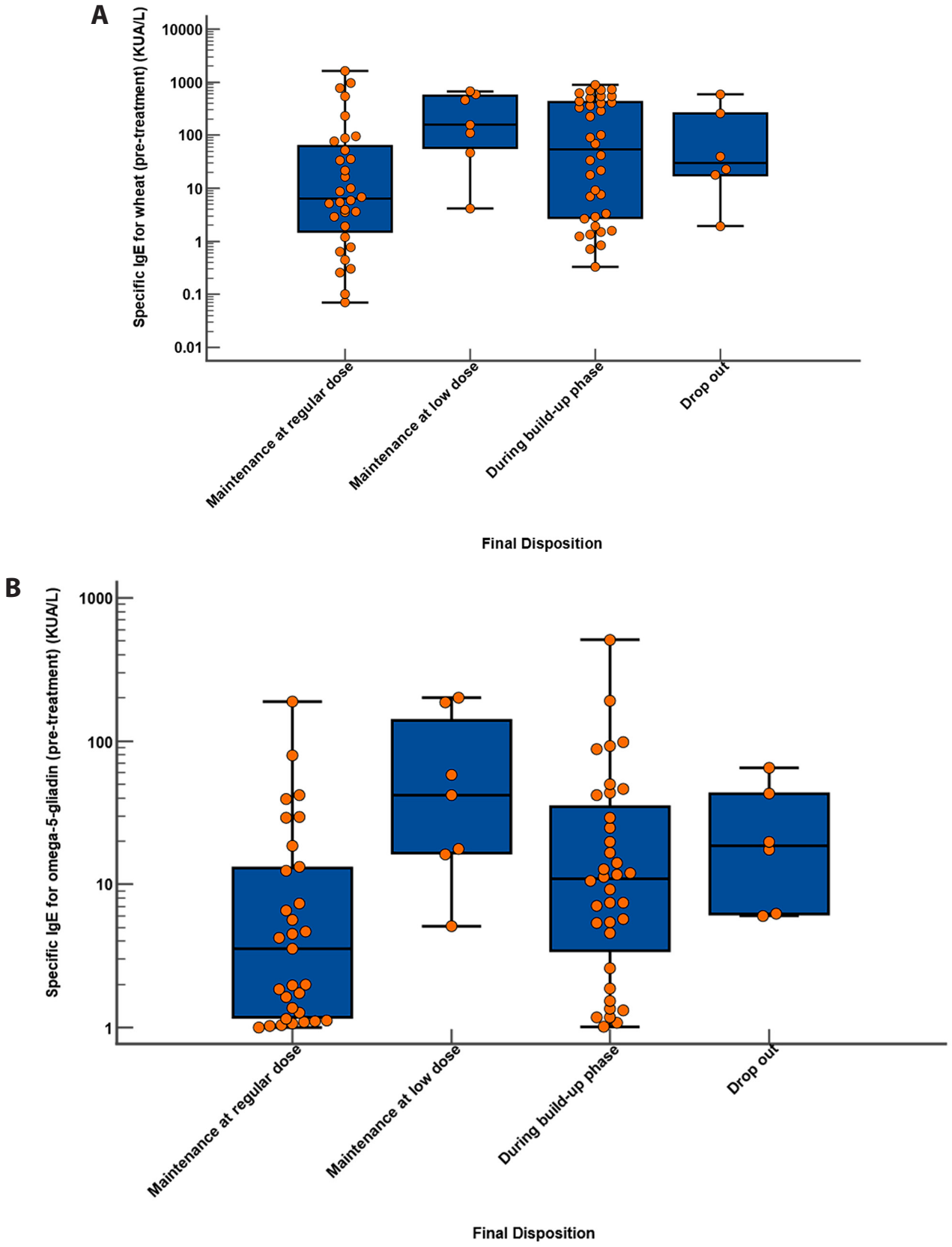

Figure S2. Serum-specific IgE (sIgE) levels before wheat oral immunotherapy (OIT) to wheat (A) and omega-5-gliadin (ω5G) (B) compared between final disposition of the study subjects (N = 81).