Allergy Asthma Immunol Res. 2024 Sep;16(5):555-561
https://doi.org/10.4168/aair.2024.16.5.555
pISSN 2092-7355·eISSN 2092-7363

Allergy, Asthma & Immunology Research AAIR

Brief Communication



# Diagnostic Decision Point for IgE-Mediated Wheat Allergy in Children

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**Received:** Mar 20, 2024
**Revised:** Jun 13, 2024
**Accepted:** Jun 19, 2024
**Published online:** Aug 13, 2024

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## ABSTRACT

The diagnostic decision point can help diagnose food allergies while reducing the need for oral food challenge (OFC) tests. We performed a multicenter survey of children aged 0–7 years from January 1, 2018 to March 31, 2022. A total of 231 children were recruited from 18 institutions. Wheat allergy (WA) or non-wheat allergy (NWA) was determined on the basis of OFC results and symptoms. There were no differences in age, sex, family history of allergy or allergic comorbidities between the WA and NWA groups. According to receiver operating characteristic analysis for wheat-specific immunoglobulin E (IgE), the optimal cutoff value, positive decision point, and negative decision point were 10.2, 33.5, and 0.41 kU/L, respectively. For the ω-5 gliadin-specific IgE, their values were 0.69, 3.88, and 0.01 kU/L, respectively. This new diagnostic decision point may be used to diagnose WA in Korean children.

**Keywords:** Demographic; diagnosis; food allergy; ingestion; wheat; specific IgE

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**Disclosure**
There are no financial or other issues that might lead to conflict of interest.

## INTRODUCTION

Wheat allergy (WA) is a common cause of food allergies in children. WAs have been reported in 0.2%-1.3% of children in Korea.[1-3] Accurate diagnostic criteria are needed to decrease burdens on patients and families. Currently, oral food challenge (OFC) is the gold standard for diagnosing food allergies. However, OFC is laborious and can cause adverse reactions.[4] The diagnostic decision point (DDP), a numerical standard for measuring food-specific immunoglobulin E(sIgE) levels through blood or skin tests,[5] is a potential alternative for diagnosing WA. Since Sampson first reported the usefulness of DDP of serum-sIgE to food allergens,[6] it has been applied clinically worldwide,[5] especially when OFC is difficult to perform in children.[7] In this multicenter study, we established the DDP of wheat and ω-5 gliadin-sIgE in Korean children.

## MATERIALS AND METHODS

We retrospectively analyzed data from children aged 0 to 7 years diagnosed with WA (the WA group) compared to those without wheat allergy (the nonwheat [NWA] group) across 18 institutions from January 1, 2018 to March 31, 2022 (**Supplementary Table S1**). WA was defined as a positive OFC result or an immediate allergic reaction within 2 hours of consuming a wheat-containing food, whereas NWA was defined as a negative OFC result or no symptoms after consuming wheat-containing food. OFC was performed and assessed according to Korean guidelines.[4] We recorded demographic characteristics, including sex, age, allergic comorbidities, family history of allergies (bronchial asthma, allergic rhinitis, food allergies, chronic urticaria, and drug allergies), and clinical symptoms. Wheat and ω-5 gliadin sIgE values were measured using ImmunoCAP (Thermo Fisher Scientific, Waltham, MA, USA). The DDP was obtained in 3 ways. The optimal cutoff value is the point at which the sum of sensitivity and specificity was the highest. The positive decision point (DP) was a value with a specificity of 95%, and the negative DP was a value with a sensitivity of 95% in the receiver operating characteristic (ROC) curve. In this study, positive DP was selected as DDP, which is the criterion for food avoidance.

Statistical analysis was performed using MedCalc (MedCalc Software, Ostend, Belgium) and SPSS version 12.0 (SPSS inc., Chicago, IL, USA). For comparisons, the Mann-Whitney test and $\chi^2$ test were used. Since it was not a normal distribution, the median and interquartile range (IQR) were obtained.

This multicenter study was approved by each hospital's Institutional Review Board (CNUSJ 2021-05-008-005, CHUNCHEON 2021-04-010, HKS 2022-01-016, AJOUIRB-MDB-2021-119, SCHBC 2019-12-010-001, ISPAIK 2022-05-018, KUGH-2021-11-026, INHAUH 2022-06-005, NHIMC 2021-04-006, HDT 2021-04-003, SCHUH 2021-04-011-002, YSH 9-2021-0135, BSM 2021-07, 2021-3180-001, and SMC 2021-03-045-002).

## RESULTS

### Characteristics of the subjects

A total of 231 children were researched retrospectively and divided into 2 groups, the WA (n = 133) and NWA (n = 98) groups. There were no differences in sex, age, allergic comorbidities, or family history of allergy between the 2 groups (**Table**).


https://doi.org/10.4168/aair.2024.16.5.555

**Table.** Demographic and clinical characteristics of the study subjects (n = 231)

| Characteristics | WA (n = 133) | NWA (n = 98) | *P* value |
|---|---|---|---|
| Male | 91 (68.4) | 56 (57.1) | 0.097 |
| Age groups | 19.0 (6–84) | 24.0 (5–84) | 0.120 |
| ≤ 12 months | 10.0 (6–12) | 10.0 (5–12) | 0.827 |
| 13–24 months | 17.0 (13–24) | 18.0 (13–24) | 0.562 |
| 25–48 months | 34.0 (25–47) | 34.0 (25–47) | 0.843 |
| > 48 months | 66.0 (59–84) | 62.0 (52–84) | 0.796 |
| Symptoms of wheat allergy | | | |
| Skin | 118 (88.7) | | |
| Respiratory | 42 (31.6) | | |
| Cardiovascular | 4 (3.0) | | |
| Gastrointestinal | 10 (7.5) | | |
| Neurologic | 4 (3.0) | | |
| Anaphylaxis | 54 (40.6) | | |
| History of familial allergy | 77 (57.9) | 59 (60.2) | 0.724 |
| Comorbid allergic diseases | | | |
| AD | 92 (69.2) | 69 (70.4) | 0.840 |
| BA | 9 (8.1) | 5 (5.9) | 0.600 |
| ARC | 29 (21.8) | 21 (21.4) | 0.945 |

Values are presented as number (%) or median (range).
WA, wheat allergy; NWA, non-wheat allergy; AD, atopic dermatitis; BA, bronchial asthma; ARC, allergic rhinoconjunctivitis.

## Differences in wheat and ω-5 gliadin sIgE levels between the WA and NWA groups

The median and IQR of wheat-sIgE were 12.35 (3.89–39.0) kU/L and 2.02 (0.50–7.41) kU/L in the WA (n = 132) and NWA (n = 98) groups, respectively, and were significantly different ($P < 0.0001$). The median ω-5 gliadin-sIgE the values and IQR in the WA (n = 88) and NWA (n = 34) groups were 1.68 (0.36–5.78) kU/L and 0.34 (0.06–0.73) kU/L, respectively, and were significantly different ($P < 0.001$) (**Fig. 1**).

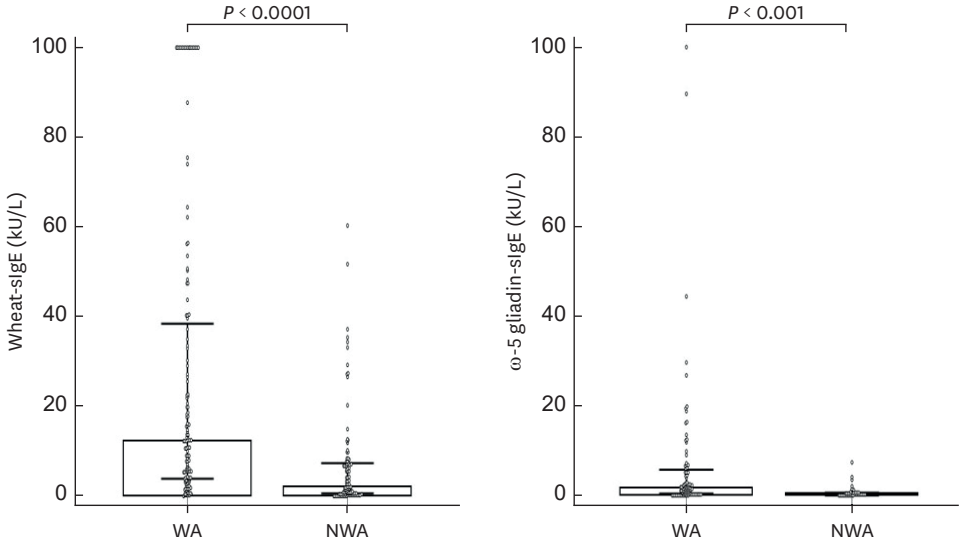
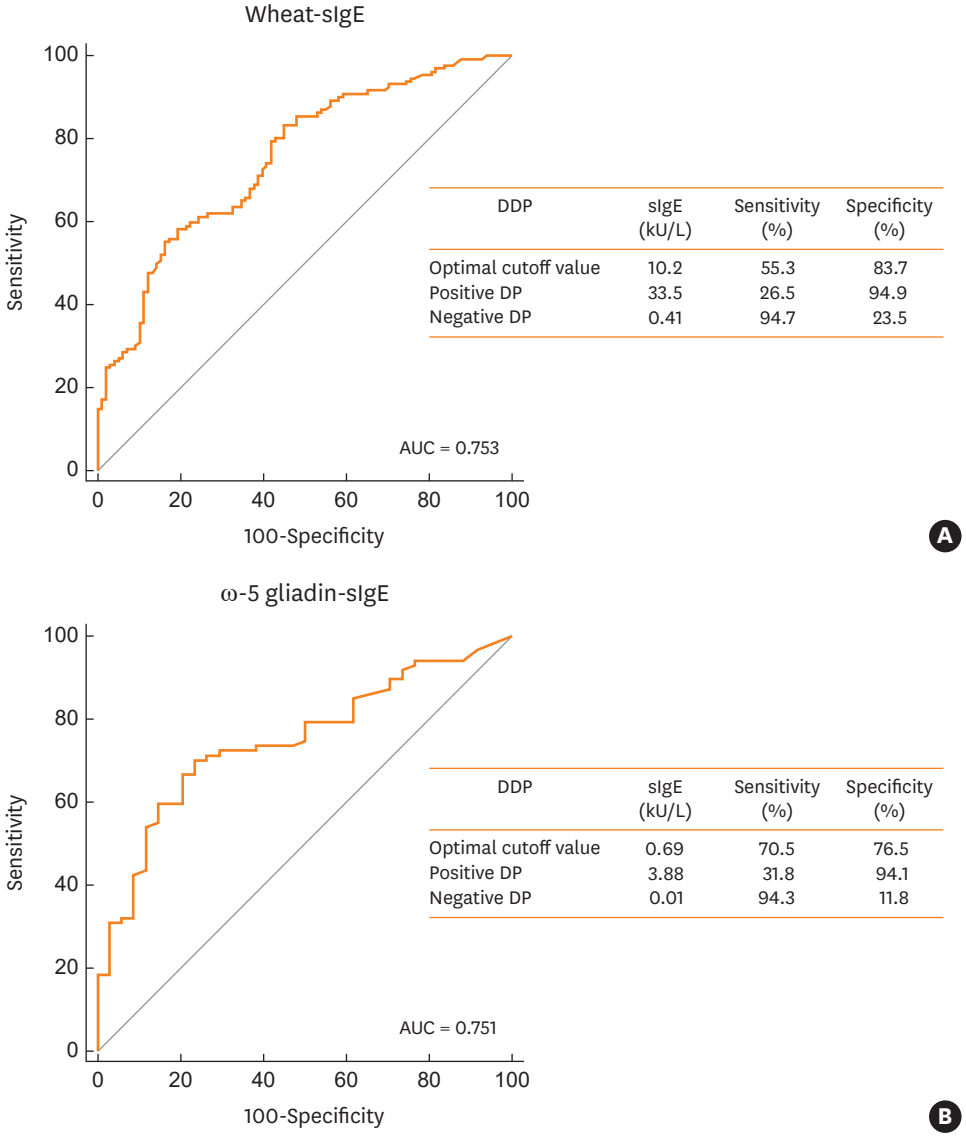



**Fig. 1.** Comparison of wheat and ω-5 gliadin sIgE levels between the WA and NWA groups. The median wheat sIgE levels were 12.35 and 2.02 kU/L for the WA and NWA groups, respectively, and the median ω-5 gliadin sIgE levels were 1.68 and 0.34 kU/L, respectively. All data showed statistically significant differences ($P < 0.001$).
sIgE, specific immunoglobulin E; WA, wheat allergy; NWA, non-wheat allergy.


https://doi.org/10.4168/aair.2024.16.5.555




| DDP | sIgE (kU/L) | Sensitivity (%) | Specificity (%) |
|---|---|---|---|
| Optimal cutoff value | 10.2 | 55.3 | 83.7 |
| Positive DP | 33.5 | 26.5 | 94.9 |
| Negative DP | 0.41 | 94.7 | 23.5 |

| DDP | sIgE (kU/L) | Sensitivity (%) | Specificity (%) |
|---|---|---|---|
| Optimal cutoff value | 0.69 | 70.5 | 76.5 |
| Positive DP | 3.88 | 31.8 | 94.1 |
| Negative DP | 0.01 | 94.3 | 11.8 |

**Fig. 2.** ROC curve. (A) ROC curve for wheat-sIgE and DDPs. (B) ROC curve for ω-5 gliadin-sIgE and DDPs.
ROC, receiver operating characteristic; sIgE, specific immunoglobulin E; DDP, diagnostic decision point; DP, decision point; AUC, areas under the curve.

## ROC analysis

The areas under the ROC curve (AUC) for wheat and ω-5 gliadin-sIgE were 0.753 and 0.751, respectively (**Fig. 2**). The optimal cutoff value for wheat-sIgE was 10.2 kU/L (sensitivity, 55.3%; specificity, 83.7%), with 33.5 kU/L for positive DP (sensitivity, 26.5%; specificity, 94.9%) and 0.41 kU/L for negative DP (sensitivity, 94.7%; specificity, 23.5%). The optimal cutoff value, positive DP, and negative DP for ω-5 gliadin-sIgE were 0.69 kU/L (sensitivity, 70.5%; specificity, 76.5%), 3.88 kU/L (sensitivity, 31.8%; specificity, 94.1%), and 0.01 kU/L (sensitivity, 94.3%; specificity, 11.8%), respectively.

## DDPs for infants

We measured DDPs in children under 1 year of age. Statistical analysis was possible only for wheat- sIgE (n = 37). The AUC was 0.893 ($P < 0.0001$). The optimal cutoff values, positive DP


https://doi.org/10.4168/aair.2024.16.5.555

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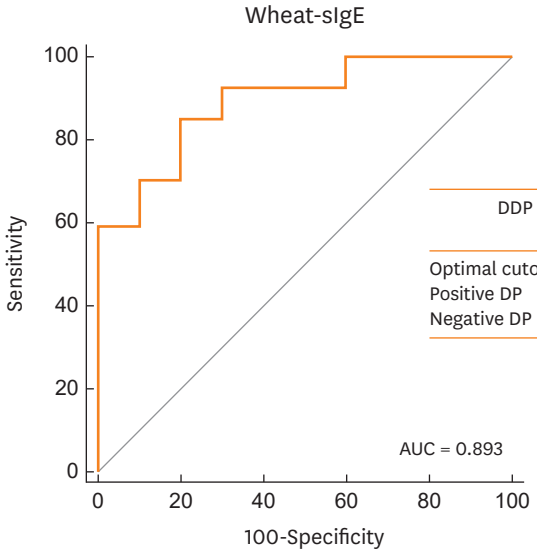


| DDP | sIgE (kU/L) | Sensitivity (%) | Specificity (%) |
|---|---|---|---|
| Optimal cutoff value | 1.63 | 85.2 | 80.0 |
| Positive DP | 4.03 | 70.4 | 90.0 |
| Negative DP | 0.58 | 92.6 | 70.0 |

**Fig. 3.** ROC curve for wheat-sIgE and diagnostic decision points under the age of 1.
ROC, receiver operating characteristic; sIgE, specific immunoglobulin E; AUC, areas under the curve; DDP, diagnostic decision point; DP, decision point.

and negative DP were 1.63 kU/L (sensitivity, 85.2%; specificity, 80.0%), 4.03 kU/L (sensitivity, 70.4%; specificity, 90%), and 0.58 kU/L (sensitivity, 92.6%; specificity, 70.0%), respectively (**Fig. 3**).

## DISCUSSION

The DDP value of wheat varies across ages and countries. In a retrospective study with American children, the DDP for wheat-sIgE was 26 kU/L (sensitivity, 61%; specificity, 90%).[6] In a study with Swedish children aged 1–17 years, the DDPs were 70 kU/L for wheat and 1.3 kU/L for ω-5 gliadin.[8] However, a single-center study on Korean children measured an optimal cutoff point for wheat-sIgE to be 0.90 kU/L (sensitivity, 97%; specificity, 89%), a positive DP of 3.12 kU/L (sensitivity, 77%), and a negative DP of 0.90 kU/L (specificity, 89%).[9] We included 18 institutions as well as data from a narrower age range (< 7 years old). Compared to the Korean study, this study measured a higher optimal cutoff point (10.2 vs. 0.90 kU/L) and positive DP (33.5 vs. 3.12 kU/L). However, the negative DP for wheat-sIgE was lower compared to the previous Korean study (0.41 vs. 0.90 kU/L). The DDP was relatively lower for those under 1 year of age, and wheat restriction may be considered if the wheat-sIgE is 4.03 kU/L or higher (positive DP).

A component-resolved diagnosis helps to identify clinically meaningful sensitization.[10] The ω-5 gliadin is a commercially available wheat component, and its association with wheat-dependent exercise-induced anaphylaxis is generally well known.[8,11,15] However, whether ω-5 gliadin-sIgE has a diagnostic value for WA is debatable.[12,16,17] In this study, compared to wheat (33.5 kU/L), ω-5 gliadin has a DDP as low as 3.88 kU/L, which may be another criteria for food restriction.

This study has some strengths: This is a multicenter study conducted by food allergy specialists using the same criteria. In addition, the DDP was measured in infants. Patients under the age of 1 have many barriers to OFC testing, so using DDP will help determine


https://doi.org/10.4168/aair.2024.16.5.555

whether to avoid wheat. This study also has some limitations. Food allergy was diagnosed based on OFC results and symptoms. In addition, the number of subjects tested for ω-5 gliadin-sIgE was small, limiting statistical power.

In conclusion, this multicenter study measured the DDP for wheat- and ω-5 gliadin-sIgE, which were 33.5 and 3.88 kU/L, respectively, and the DDP for those under the age of 1 for wheat was 4.03 kU/L. These values can be used to diagnose WA in children.

## SUPPLEMENTARY MATERIAL

### Supplementary Table S1

Hospitals and registrants in the wheat diagnostic decision point study

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