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RESEARCH ARTICLE

Usefulness of Gly m 4-specific IgE test in the diagnosis of Rosaceae fruit-oral allergy syndrome caused by Betulaceae pollen sensitization

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Abstract

Background: Pollen-food allergy syndrome (PFAS) is caused by the cross-reaction of the specific IgE to pollen allergens with similar allergens contained in fruits, vegetable, and nuts. The representative allergen responsible for this cross-reaction is pathogenesis-related protein (PR)-10. Specific IgE test using Gly m 4, soybean PR-10, is widely used to diagnose soy allergy. We aimed to investigate whether the Gly m 4-specific IgE test is useful for predicting oral allergy symptoms (OAS) to Rosaceae fruits in PFAS caused by Betulaceae pollen sensitization.

Methods: Forty-one patients with suspected PFAS were enrolled. Specific IgE levels were measured against alder pollen, apple, peach, pear, and Gly m 4, and correlation between test results and allergic symptoms was assessed to compare the accuracy of these allergen-specific IgE tests.

Results: Of the 41 patients, 32 were positive for alder pollen-specific IgE. Of those, 16 showed OAS to at least one of apple, peach, and pear (OAS (+) group), and the rest 16 cases showed no symptoms (OAS (–) group). The Gly m 4-specific IgE value was significantly higher in the OAS (+) group ($p = .014$), and the highest in area under the receiver operating characteristics curve. The cut-off value for detection of the OAS (+) group was 2.65 UA/ml, with a sensitivity of 62.5% and a specificity of 81.3%. Other allergen-specific IgE values were not significantly different between the two groups.

Conclusions: In the subjects sensitized to Betulaceae pollen allergens, the Gly m 4-specific IgE test is useful for predicting OAS of Rosaceae fruits.

KEYWORDS

Betulaceae pollen, cross-reactivity, Gly m 4-specific IgE test, pollen-food allergy syndrome (PFAS), Rosaceae fruits

1 | INTRODUCTION

Pollen-food allergy syndrome (PFAS) is an IgE-mediated immediate-type food allergy that occurs in subjects sensitized to specific pollen allergens such as Betulaceae.[1,2] The symptoms are irritation and/or edema of the oropharyngeal mucosa due to ingestion of food containing allergens having a structure similar to that of the sensitized pollen allergen. The worldwide prevalence of PFAS is estimated at 10%–35%,[2] with a wide variety of foods being responsible for this, including fruits, vegetables, and nuts. A typical symptom is the oral allergy syndrome, in which specific IgE against pathogenesis-related protein (PR)-10 in birch or alder pollen cross-reacts with PR-10 in Rosaceae fruits.[2] Apples, peaches, pears, and other Rosaceae fruits are the major culprits. Specific IgE tests using crude extracts of these fruits have been developed for diagnosis of fruits allergy. However, the main allergens, PR-10 and profilin, are unstable and easily denatured during fruit storage and processing, making these tests less sensitive. In addition, one of the major issues is the difficulty in distinguishing asymptomatic sensitization (false positive) from symptomatic sensitization. A prick-to-prick test using actual fruits is another diagnostic tool. The prick test requires fresh fruits and vegetables, so that it would not be convenient as a daily test in clinical practice. In addition, it is known that there are differences in the allergen content depending on the type of fruit and the storage condition, with the results not being consistent.[3–5] Recently, allergen-specific IgE tests using purified allergens or recombinant allergens have been developed. These tests have become widely used because of their high accuracy in diagnosing IgE-mediated food allergies, and are now called "component resolved diagnosis" or "component resolved diagnostics".[6,7] The Gly m 4-specific IgE test, which is established using soybean PR-10, is useful to diagnose soybean allergy related to birch pollen allergy with a sensitivity close to 100%.[8,9] In 2016, the test was registered into the clinical examination covered by national health insurance system in Japan. The aim of this study was to investigate whether the Gly m 4-specific IgE test is useful for predicting oral allergy symptoms against Rosaceae fruits possessing PR-10 in the subjects sensitized to alder pollen.

2 | SUBJECTS AND METHODS

2.1 | Subjects

Of the 41 patients who visited the dermatology department of Shimane University Hospital for suspected PFAS from June 2009 to December 2020, 32 patients who tested positive for alder-specific IgE and suspected of having PFAS were enrolled. The mean age of the enrolled patients was 37.2 years old (range 11–70), with 15 and 17 being men and women, respectively. At the time-point of consultation, none of the patients were undergoing immunotherapy. The study was approved by the Medical Research Ethics Committee, Shimane University Faculty of Medicine (approval number: 1570 and 5407).

2.2 | Evaluation of allergic symptom

Each patient was asked whether they had shown symptoms of oral allergy when they ingested three any of the three Rosaceae fruits (apple, peach, and pear). Those who had oral allergy symptoms (OAS) following the consumption of at least one of it were grouped into the OAS (+) group and those who had no clinical symptoms into the OAS (−) group. The patient was also asked whether he had shown allergic symptoms when he ingested soy or soy products, including soymilk.

2.3 | Allergen-specific IgE test

Specific IgE of alder pollen, Gly m 4, apple, peach, and pear were measured using ImmunoCAP® (ThermoFisher Diagnostics). The results are expressed as units of allergen per milliliter (UA/ml). In this study, allergen-specific IgE values ≥0.7 UA/ml were defined as a positive result.

2.4 | Statistical analysis

Differences in allergen-specific IgE test values between the OAS (+) and OAS (−) groups were analyzed using the Mann–Whitney *U* test. Receiver operating characteristics (ROC) curve analysis was carried out on the diagnostic accuracy of the allergen-specific IgE tests. Mann–Whitney *U* test was performed using GraphPad Prism version 7.03 for Windows, GraphPad Software, La Jolla California USA, www.graphpad.com. The ROC curve analysis was performed using SPSS Statistics ver. 25 (IBM Corporation). The level of significance was set at 0.05 ($p = .05$).

3 | RESULTS

Of the 32 patients with suspected PFAS in whom the alder pollen-specific IgE test was positive, 16 patients were categorized into the OAS (+) group, and the rest 16 patients were categorized into the OAS (−) group. The mean age of the subjects of the OAS (+) group was 39.1 ± 22.8, and with 7 and 9 being men and women, respectively. The mean age of the subjects of the OAS (−) group was 35.3 ± 20.9, with equal numbers representing women ($n = 8$) and men ($n = 8$). Allergen-specific IgE levels in the OAS (+) and OAS (−) groups are shown in Tables S1 and S2, respectively. These allergen-specific IgE values were compared between the OAS (+) and OAS (−) groups (Figure 1, Table S3). The mean value of alder pollen-specific IgE was not significantly different between the two groups ($p = .051$). The mean value of Gly m 4-specific IgE was significantly higher in the OAS (+) group ($p = .014$). The mean value of apple-, peach-, and pear-specific IgE was not significantly different between the two groups.

In ROC curve analysis of the allergen-specific IgE levels, the area under the ROC curve (AUC) was the highest at 0.703, 0.754, 0.516, 0.563, and 0.479 for alder pollen-, Gly m 4-, apple-, peach-,

and pear-specific IgE, respectively (Figure 2). The cutoff value for alder pollen-specific IgE in the detection of the OAS (+) group was 5.63 UA/ml, with a sensitivity of 81.3% and a specificity of 62.5%. The cutoff value for Gly m 4-specific IgE was 2.65 UA/mL, with a sensitivity of 62, 5%, and a specificity of 81.3%.

Next, the OAS (+) and OAS (−) groups were further divided according to soy allergy (Table 1). A total of 10 patients (nine patients allergic to soy milk and one patient allergic to soybean sprouts) were included in the 32 patients studied. All the 10 patients had positive Gly m 4-specific IgE. Of these, four patients were included in the OAS (+) group (25% of 16 patients) and the remaining six patients were included in the OAS (−) group (37.5% of 16 patients). The mean value of Gly m 4-specific IgE in the soy allergy (+) and OAS (+) group was 12.7 ± 13.1 UA/mL, whereas that of Gly m 4-specific IgE in the soy allergy (+) and OAS (−) group was 5.2 ± 4.6 UA/ml.

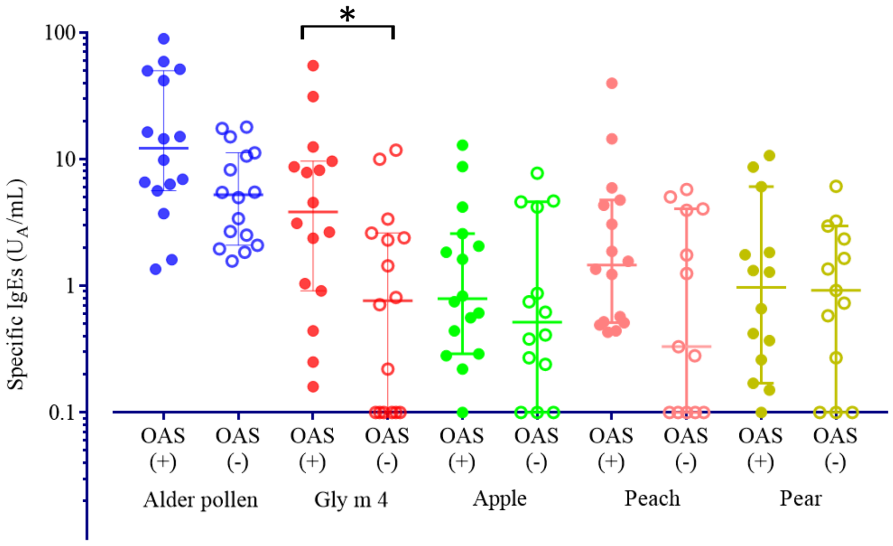

FIGURE 1 Allergen-specific IgE levels of the OAS (+) and OAS (−) groups. Alder pollen-, Gly m 4-, apple-, peach-, and pear-specific IgE levels were compared between OAS (+) group and OAS (−) group. *Difference was statistically significant ($p < .05$).

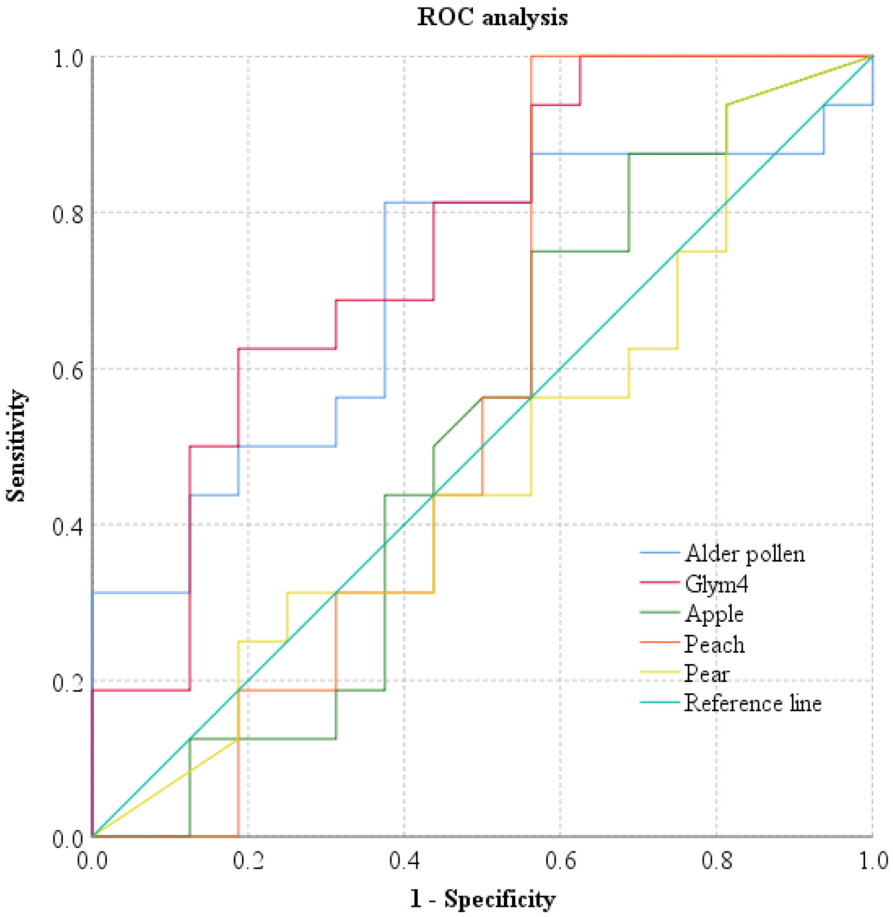

FIGURE 2 ROC curve analysis of the allergen-specific IgE tests. ROC curve analysis was performed for alder pollen-, Gly m 4-, apple-, peach-, and pear-specific IgE levels in the 32 subjects sensitized to alder pollen

TABLE 1 Gly m 4-specific IgE values associated with or without soy allergy

Group	OAS (+)		OAS (−)	
Soy allergy	+	−	+	−
No. of patients	4	12	6	10
[a]Gly m 4-specific IgE level (mean ± SD)	12.7 ± 13.1	8.1 ± 15.1	5.2 ± 4.6	0.5 ± 0.8

[a]Gly m 4-specific IgE was measured using ImmunoCAP®.

4 | DISCUSSION

In the present study, apple-, peach-, pear-, and Gly m 4-specific IgE levels were compared between the OAS (+) and OAS (−) groups. Only Gly m 4-specific IgE levels were significantly higher in the OAS (+) group. The AUC was the highest for Gly m 4-specific IgE, and the cut-off value for Gly m 4-specific IgE in the detection of the OAS (+) group was 2.65 UA/mL, with a sensitivity of 62.5% and a specificity of 81.3%. These results indicate that, in the subjects sensitized to alder pollen, the Gly m 4-specific IgE test is useful for predicting clinical allergy symptoms caused by Rosaceae fruits, although Gly m 4 is PR-10 of Fabaceae soybean.

When sensitized to Bet v 1 or Aln g 1, Bet v 1- or Aln g 1-specific IgE cross-react with the PR-10 protein family contained in fruits, vegetables, and nuts, resulting in oral allergy syndrome. However, not all fruits, vegetables, and nuts harboring the PR-10 protein family exhibit clinical symptoms. This may be due to the variation in the homology and similarity between the PR-10 protein family in fruits, vegetables, and nuts and Bet v 1 or Aln g 1. In Japan, white birch grows in some northern areas such as Hokkaido, while alder grows in most of Japan except Hokkaido. Since alder grows wild in Shimane Prefecture where Shimane University is located, the amino acid sequence of Aln g 1 was compared with those of PR-10 family proteins in 13 foodstuffs (hazelnut Cor a 1 of the Betulaceae family, soybean Gly m 4 and peanut Ara h 8 of the Fabaceae family, almond Pru du 1, apple Mal d 1, peach Pru p 1, pear Pyr c 1, cherry Pru av 1, and strawberry Fra a 1 of the Rosaceae family, celery Api g 1 and carrot Dau c 1 of the Apiaceae family, gold kiwi Act c 8 of the Actinidaceae family, and tomato Sola l 4 of the Solanaceae family). PR-10 of alder pollen and the 13 foodstuffs were searched using http://www.allergen.org, and homology and similarity among these PR-10 sequences were calculated. The homology and similarity results are shown in Tables 2 and 3, respectively. There was a high correlation between homology and similarity among these 14 PR-10 family proteins. Homology at >50% with alder pollen Aln g 1 was found in Cor a 1 of Betulaceae family, Pru p 1, Pru av 1, Mal d 1, Pyr c 1, Pru du 1, and Fra a 1 of Rosaceae family, and Act c 8 of Actinidaceae family. In cases sensitized to alder pollen Aln g 1, it is presumed that these fruits, nuts and vegetables cause allergic symptoms. The species showing >50% homology with Gly m 4 were Ara h 8 of Fabaceae family, Pru av 1, Pru p 1, Mal d 1, Fra a 1, Pyr c 1, and Pru du 1 of Rosaceae family. The sensitization to PR-10 of these foodstuffs is likely to be detected by the Gly m 4-specific IgE test. Based on the above, it is inferred that in the patients sensitized to alder pollen who have positive Gly m 4-specific IgE test, clinical allergy symptoms are likely to occur after ingestion of Rosaceae family fruits (peach, apple, pear, cherry, and strawberry) and almond possessing PR-10 that are highly homologous to both Aln g 1 and Gly m 4. However, tests for almond sensitization have been reported to have very low predictive value when evaluated with oral food challenge.[10–12] In particular, almond is generally consumed toasted in Japan; therefore, the results of Gly m 4-specific IgE test should be carefully interpreted for clinical allergy symptoms against almond.

When soy allergy is considered in the OAS (+) and OAS (−) groups, high Gly m 4-specific IgE level is associated with soy allergy in addition to oral allergy to Rosaceae fruits. On the other hand, there exist cases which are allergic to soy products even with low level of the Gly m 4-specific IgE but not allergic to Rosaceae fruits. This suggests that higher values of Gly m 4-specific IgE are associated with allergic reaction to a wide range of foodstuff in the cases sensitized to alder pollen. We have previously highlighted the possibility that the basophil activation test using soymilk is useful for the diagnosis of soymilk allergy in combination to Gly m 4-specific IgE test in alder pollen-sensitized cases.[13] The usefulness of the basophil activation test in the diagnosis of PFAS for Rosaceae fruits remains to be investigated.

Notably, there were no significant differences between the OAS (+) and OAS (−) groups in the apple-, peach-, and pear-specific IgE tests (Table 1 and Figure 1). This is possibly because these tests are constructed using crude extracts of apple, peach, and pears, respectively, of which content of causative allergens is low, since PR-10 is unstable and easily denatured during the process for constructing these tests.[3–5,9] In addition, although profilin of alder pollen has not been identified, additional allergens such as profilin, are possibly contained in these extracts of apple, peach, and pear, apart from RP-10. These allergens might be related to the results that specific IgE antibodies against these allergens were not significantly different between the two groups.[2]

In the present study, the cutoff value of 2.65 UA/mL in the Gly m 4-specific IgE test by ImmunoCAP® had 62.5% sensitivity and 81.3% specificity to identify allergy symptoms against Rosaceae fruits. To date, there have been no clinical studies in the literature investigating the relationship between Gly m 4-specific IgE testing and allergic symptoms to Rosaceae fruits. So far there have been several studies on the accuracy of allergen-specific IgE test using RP-10 protein family. Positive rate of Ara h 8-specific IgE test was reported to be 80% in the diagnosis of peanut allergy complicated by Birch pollen allergy.[14] In a study of 20 patients with apple allergy associated with white birch pollinosis, the positive rate of the Mal d 1-specific IgE test (sensitivity 100%) was higher than that of the apple-specific IgE test (sensitivity 95.2%).[15] Recently, Kiguchi et al. found that 24 out of 59 PFAS cases (40.7%) were Gly m 4-specific

TABLE 2 Amino acid homology among the PR-10 protein family contained in the fruits, vegetables, and nuts

Family	Generic	Allergen	Aln g1	Cor a1	Gly m4	Ara h8	Pru du1	Mal d1	Pru p1	Pyr c1	Pru av1	Fra a1	Api g1	Dau c1	Act c8	Sola l4
Betulaceae	Alnus	Aln g1	100													
Betulaceae	Corylus	Cor a1	76.1	100												
Fabaceae	Glycine	Gly m4	49.1	47.8	100											
Fabaceae	Arachis	Ara h8	43.4	42.1	70.3	100										
Rosaceae	Prunus	Pru du1	54.1	52.8	52.2	48.4	100									
Rosaceae	Malus	Mal d1	54.7	54.7	53.5	47.8	67.9	100								
Rosaceae	Prunus	Pru p1	57.2	58.5	54.1	49.1	73.6	82.4	100							
Rosaceae	Pyrus	Pyr c1	54.7	54.7	52.2	47.8	69.8	94.3	83.0	100						
Rosaceae	Prunus	Pru av1	56.6	57.9	54.1	49.7	73.0	84.3	98.1	83.6	100					
Rosaceae	Fragaria	Fra a1	54.1	55.3	52.8	49.7	71.7	76.7	82.4	76.1	80.5	100				
Apiaceae	Apium	Api g1	40.3	37.1	37.3	36.1	40.3	37.1	40.3	36.5	39.6	42.1	100			
Apiaceae	Daucus	Dau c1	37.1	39.0	36.1	36.2	39.0	36.6	39.8	35.8	39.1	26.2	81.0	100		
Actinidiaceae	Actinidia	Act c8	50.3	51.6	46.2	44.0	52.2	51.6	56.0	50.9	55.3	52.8	43.7	43.0	100	
Solanaceas	Solanum	Sola l4	40.9	40.3	42.1	39.6	50.3	43.4	49.7	42.1	49.1	49.1	37.7	33.3	47.8	100

TABLE 3 Amino acid similarity among the PR-10 protein family contained in the fruits, vegetables, and nuts

Family	Generic	Allergen	Aln g1	Cor a1	Gly m4	Ara h8	Pru du1	Mal d1	Pru p1	Pyr c1	Pru av1	Fra a1	Api g1	Dau c1	Act c8	Sola l4
Betulaceae	Alnus	Aln g1	100													
Betulaceae	Corylus	Cor a1	88.1	100												
Fabaceae	Glycine	Gly m4	67.3	63.5	100											
Fabaceae	Arachis	Ara h8	64.8	61.6	82.9	100										
Rosaceae	Prunus	Pru du1	76.1	73.0	67.9	67.9	100									
Rosaceae	Malus	Mal d1	72.3	70.4	69.2	70.4	83.6	100								
Rosaceae	Prunus	Pru p1	74.2	72.3	68.6	68.6	85.5	91.2	100							
Rosaceae	Pyrus	Pyr c1	71.7	70.4	68.6	68.6	84.9	96.8	93.1	100						
Rosaceae	Prunus	Pru av1	74.8	73.0	69.2	69.2	86.2	91.8	99.4	93.7	100					
Rosaceae	Fragaria	Fra a1	71.7	72.3	67.3	68.6	83.6	86.8	92.5	88.1	91.8	100				
Apiaceae	Apium	Api g1	59.7	59.1	56.3	55.7	64.8	57.9	60.4	58.5	60.4	60.4	100			
Apiaceae	Daucus	Dau c1	56.0	55.3	54.4	55.6	62.9	54.7	58.4	55.3	58.4	57.8	92.2	100		
Actinidiaceae	Actinidia	Act c8	69.8	71.7	66.5	63.5	74.2	72.3	73.0	71.1	73.0	72.3	63.9	61.4	100	
Solanaceas	Solanum	Sola l4	64.2	62.9	61.0	60.4	69.2	63.5	66.0	63.5	66.0	64.2	57.9	55.3	64.2	100

IgE-positive, whereas in 199 pollen allergy cases without PFAS only 32 (16.1%) were Gly m 4-specific IgE-positive in a survey of adolescents.[16] More recently, molecular multiplex IgE test methods have been evaluated for the diagnosis of pollen-associated food allergy, and revealed that the Mal d 1-, Gly m 4-, and Cor a 1-specific IgE test showed significant correlations to apple, soy, and hazelnut allergies, respectively, associated with pollen sensitization. In contrast, Api g 1-, and Ara h 8-specifc IgE tests showed only a weak correlation with clinical symptoms against celery and peanut, respectively.[17] These results support the usefulness of the specific IgE test using PR-10 family proteins in the diagnosis of Rosaceae fruits and nuts in birch or alder pollen sensitization cases. By comparing the diagnostic accuracy between Pru av 1-, Pru p 1-, Mal d 1-, Fra a 1-, or Pyr c 1-specific IgE test and Gly m 4-specific IgE test for oral allergy symptoms with Rosaceae fruits, more accurate tests may be obtained, and further verification is needed.

In the 32 patients studied, the *p*-value (.051) of the alder pollen-specific IgE test was slightly above significance level for the identification of the OAS (+) group. If more patients could be recruited, there would become a significant difference in the test. The limitation of this study was a relatively small number of patients in the OAS (+) ($n = 16$) and OAS (−) ($n = 16$) groups included; therefore, it is necessary to verify these findings in a larger group of patients. Another limitation was that diagnosis of food allergy was obtained from retrospective clinical information, meaning that the diagnosis of food allergy had to be validated by oral food challenge.[9,18,19]

In conclusion, the Gly m 4-specific IgE test was shown to be useful in predicting the occurrence of OAS against Rosaceae fruits with a cutoff value of 2.65 UA/ml, where the sensitivity and specificity were 62.5% and 81.3%, respectively. Subjects with high Gly m 4-specific IgE levels need to pay attention in ingesting Rosaceae fruits, such as peach, apple, pear, cherry, and strawberry.

AUTHOR CONTRIBUTIONS

All the authors contributed to the study. T.Y., Y.C., and E.M. designed the study. T.Y. performed the research and analyzed the data. O.Y. supervised the experiments. K.K. performed statistical analysis. T.Y. and E.M. wrote and edited the manuscript. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST

There are no conflicts of interest to be disclosed in connection with this report.

ETHICS STATEMENT

The study was approved by the Medical Research Ethics Committee, Shimane University Faculty of Medicine (approval number: 1570 and 5407).

Approval of the research protocol: The study was approved by the Medical Research Ethics Committee, Shimane University Faculty of Medicine (approval number: 1570 and 5407).

Informed consent: We obtained written informed consent from the participants at the time of enrollment.

Registry and the Registration No.: N/A.

Animal Studies: N/A.

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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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