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ORIGINAL ARTICLE

Risk prediction of severe reaction to oral challenge test of cow's milk

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Abstract

Cow's milk is one of the most common food allergens among children. Oral food challenge tests determine the threshold dose of allergens, but have not been standardized. To reduce the severe reactions, we developed a practical model of the test. We studied 111 high-risk patients who underwent a first milk oral food challenge on the risk-stratified dose between 2011 and 2017 for predicting the severe reaction risk. Severe reactions were defined as showing ≥ 3 of Sampson's classification grade. Twenty-eight patients (25%) showed severe reactions without death. Prior to oral food challenge, severe reaction patients experienced milk avoidance (71% vs. 45%, $p = 0.02$) or bronchial asthma (61% vs. 28%, $p = 0.003$) more frequently and showed higher milk-specific IgE levels (median 28.3 vs. 7.7 U_A/mL, $p < 0.0001$) than non-severe reaction patients. Multivariate logistic regression analyses established a formula including severe reaction-associated factors; increased levels of milk-specific IgE (odds ratio 11.61, $p = 0.001$), milk avoidance (odds ratio 3.88, $p = 0.02$), and bronchial asthma (odds ratio 3.75, $p = 0.02$). This model had 86% sensitivity and 56% specificity (cut-off 0.25) for risk. Five patients with < 25% probability developed severe reactions, which started in ≥ 3 grade dyspnea up to 20 mL of challenge.

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Conclusion: This model could effectively reduce the severe reaction development on the first milk oral food challenge test according to the individual needs.

What is Known:
- *Higher levels of milk-specific IgE values, bronchial asthma, and complete milk avoidance are independent risk factors of severe reactions during the cow's milk oral food challenge.*

What is New:
- *Statistical analyses of our milk oral food challenge records for 111 patients helped us develop a model formula predicting severe reactions at the first test with high specificity and sensitivity.*
- *This simple risk-stratified protocol is useful for minimizing the adverse events in the first milk challenge.*

Keywords Anaphylaxis · Food allergy · Multivariate logistic regression · Oral food challenge · Prediction model

Abbreviations

AUC	Area under the curve
CM	Cow's milk
IgE	Immunoglobulin E
OFC	Oral food challenge
OR	Odds ratio
ROC	Receiver operating characteristics

Introduction

A food allergy is defined as an adverse reaction to food mediated by an immunologic mechanism, involving specific IgE (IgE-mediated), cell-mediated mechanisms (non-IgE-mediated), or both IgE- and cell-mediated mechanisms (mixed IgE- or non-IgE-mediated) [17, 24]. The oral food challenge (OFC) is the most essential measure to make a definite diagnosis of food allergy and determine the threshold dose of allergens in individuals [29]. The prevalence of childhood food allergy is increasing worldwide, not only in the United States (US) and Western Europe but also in Asia [2, 19, 23]. It has been estimated 8% of US children, in which 2.4% have multiple food allergies, and 3% experience severe reactions [9]. With the increasing number of patients, the demand for better management through OFCs has greatly increased in the last decade. However, the OFC method remains to be standardized, as differences in patients' conditions, including the severity of allergy, the magnitude of sensitization dose, and the selective need of avoidance or immunotolerance, affect the results. Nevertheless, challenge tests have continued to be performed at each institution with the empirical efforts on reducing severe adverse events [30].

The OFC can induce the life-threatening anaphylaxis that requires an urgent admission to the intensive care units unless managed appropriately [18]. The patients at high risk for anaphylaxis are thus recommended to receive the OFC test in expert hospitals. Careful protocols including a series of precise small increment in the challenging dose do not always warrant the safety. Probability curves predicting OFC results based on food-specific-IgE values are widely used to prevent serious allergic reactions [15, 21]. However, the proposed probability for the risk of severe OFC reactions does not have sufficient reproducibility. Although many confounding factors affect the risk probability, including the history of asthma, an older age, skin prick test levels, and a history of multiorgan system reactions [3, 8, 11, 20, 26], the most critical predictors for OFC outcomes remain unclear. There are few published models to predict the risk of severe adverse events in OFC for milk allergy. Sugiura et al. [28] have recently proposed the predictive models for severe reactions in the challenges of cow's milk, although times of OFC were not considered in individuals. The first OFC for high-risk children is challenging for themselves, their parents, and pediatricians. The simple, safe, and highly effective methods are required for the first milk OFC in ambulatory practice.

In the present study, we explored a model predicting the risk for developing severe reactions during the first OFC test. The clinical utility and issues associated with this equation model consisting of effective variables are also discussed.

Methods

Study population

The milk OFC test was consecutively performed 221 times by allergists at the tertiary institutions for food allergy, Fukuoka Higashi Medical Center and Fukuoka Children's Hospital in Japan, from September 2011 to July 2017. Among the total cases, the 111 patients who underwent the test for the first time to determine the tolerable dose of milk in their daily life were enrolled for the study. Cow's milk allergy was diagnosed based on the evidence of repeated allergic symptoms after milk ingestion and positive milk-specific IgE according to the Japanese Guideline for Food Allergy 2014 [29]. All tests were completed in hospital after the informed consent and assent were obtained from patients and their guardians, respectively. This observational study was approved by the Institutional Review Board at the institutions (H29-clini2).

Selection of variables associated with severe adverse reaction

Clinical variables were collected from the medical records of patients who underwent a unified protocol of OFC, including their age, sex, date, and severity of the first onset of milk allergy, duration of complete avoidance of milk, and consumed amount of milk until the first OFC, serum levels of milk-specific and total IgE antibodies, presence or absence of anaphylaxis episode, bronchial asthma, atopic dermatitis, and family history of bronchial asthma, atopic dermatitis, and food allergy, as reported previously [3, 8, 11, 15, 20, 21, 26]. A history of bronchial asthma was defined as having more than three episodes of wheezing illness according to the Japanese Pediatric Guidelines for the Treatment and Management of Asthma 2012 [10]. A diagnosis of atopic dermatitis was made based on the criteria of ICD-9 [14]. The serum concentrations of total IgE and milk-specific IgE were measured within 6 months before the OFC using a fluorescent enzyme immunoassay and ImmunoCAP (Phadia AB; Uppsala, Sweden), respectively. A milk-specific IgE value of >100 U_A/mL was regarded as 100 U_A/mL. In this study, "severe reaction" was defined as a severe adverse event with a Sampson's classification grade of ≥ 3 [22].

Milk OFC protocol

The unified protocol of the open-labeled OFC was modified according to the Japanese Guideline for Food Allergy 2014 [29]. All subjects had restricted ingestion of cow's milk due to apparent reactions of immediate hypersensitivity or had class 2 or more milk-specific IgE (>0.7) with unexperienced ingestion or complete avoidance of milk for the previous 6 months. The following types of food were prepared as doses for the milk challenge: STEP 1 (1–19 mL) with cookie (1 sheet corresponding to 1 mL baked milk), STEP 2 (20–49 mL) with stew (1 mL corresponding to 1 mL boiled milk), STEP 3 (50–99 mL) with yogurt (1 mL corresponding to 1 mL raw milk), and STEP4 (100–200 mL) with raw cow's milk. The starting dose was set at STEP 1–4 according to each patient's condition: STEP 1 for patients who had unexperienced ingestion or complete avoidance of milk but were positive for milk-specific IgE, STEP 2 for patients who had <20 mL of milk ingestion or who had unexperienced ingestion or complete avoidance of milk with class ≤ 3 milk-specific IgE (<17.5), STEP 3 for patients who had <50 mL of milk ingestion, or who had the unexperienced ingestion or complete avoidance with class ≤ 2 milk-specific IgE (<3.5), and STEP 4 for patients who had <100 mL of milk ingestion, or who had the unexperienced ingestion or complete avoidance with class ≤ 1 milk-specific IgE (<0.7).

The challenging dose was escalated every 15 min in a doubling fashion from 16th to 4th of the target amount, and the remaining food was given finally; the target was determined according to the STEP allocated. During the 2-h scheduled observation period, clinical signs and symptoms were carefully monitored. The test was stopped if the subject showed any gastrointestinal manifestations, respiratory symptoms, non-contact cutaneous reactions, or multisystem reactions. The results of the OFC were evaluated according to the Sampson's classification.

Statistical analysis

Mann-Whitney *U* test was used to compare the continuous variables, and a Fisher's exact test was used to compare the proportion of each of the clinical characteristics between patients who developed severe reactions and those who did not. To identify the independent predictors for the anaphylaxis, multivariable logistic regression models were constructed using the backward stepwise selection; $p<0.05$ was required for entry into the model. The discriminatory capacity of the model was assessed using the area under the receiver-operating characteristics (ROC) curve. A cut-off point for ROC curve was calculated by the Youden index. The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written. All the analyses were carried out using the JMP Pro® 13 (SAS Institute Inc., Cary, NC, USA). For all analyses, a two-sided probability value below 0.05 was considered to indicate statistical significance.

Results

Characteristics and OFC outcomes of patients

The demographics, baseline profiles, and allocated STEPs of patients are shown in Table 1. The baseline data were compared between patients who developed severe reactions (Sampson's classification grade ≥ 3) and those who did not. Severe reaction-developed patients had experienced complete milk avoidance (71% vs. 45%, $p=0.02$) or bronchial asthma (61% vs. 28%, $p=0.003$) more frequently and showed higher levels of milk-specific IgE (median 28.3 vs. 7.7 U_A/mL, $p<0.0001$) than non-severe reaction patients. The total consumed dose and the starting dose in patients with severe reactions were significantly lower than seen in those with non-severe reactions (Table 1). Milk-specific IgE value was not correlated with total IgE value ($r=0.47$).

Clinical features on the reactions during OFC

The major manifestations were immediate allergic reactions. Treatment was performed according to the severity grading based on the most severe symptoms observed for each

Table 1 Clinical and laboratory profiles prior to the OFC test of patients showing any reactions during the test

	Total	Severe reactions[a]	Non-severe reactions	*p* value
Number of patients, male: female	111, 77:34	28, 20:8	83, 57:26	1.00
Age, month[b]	40, 9–144	43, 17–118	39, 9–144	0.42
Clinical findings				
History of anaphylaxis	68 (61%)	21 (75%)	47 (57%)	0.12
Complete milk avoidance	57 (51%)	20 (71%)	37 (45%)	0.02
Bronchial asthma	40 (36%)	17 (61%)	23 (28%)	0.003
Atopic dermatitis	58 (52%)	17 (61%)	41 (49%)	0.38
Family history of bronchial asthma	46 (41%)	15 (54%)	31 (37%)	0.18
Family history of atopic dermatitis	48 (43%)	10 (36%)	38 (46%)	0.39
Family history of food allergy	38 (34%)	11 (39%)	27 (33%)	0.65
Laboratory findings				
Total IgE, U_A/mL[b]	657, 17–19,400	756, 59.5–5250	557, 17–19,400	0.18
Milk-specific IgE, U_A/mL[b]	13.4, 0.11–100	28.3, 4.54–100	7.7, 0.11–100	< 0.0001
Sampson's classification				
Grade 1/2/3/4/5	15/14/15/13/0	0/0/15/13/0	15/14/0/0/0	
STEP of the milk OFC				
STEP 1/2/3/4	56 /24 /11 /20	20 /4 /4 /0	36 /20 /7 /20	0.009
Loaded dose of milk in the OFC				
Total consumed dose, mL[b]	9, 1–200	4, 1–50	20, 1–200	0.0002
Starting dose, mL[b]	1.25, 0.0625–12.5	0.375, 0.125–3.0	1.25, 0.0625–12.5	0.002

[a] Severe reactions were defined to show grade 3 or more according to Sampson's classification

[b] Each number represents the median and ranges

OFC oral food challenge

affected organ. Epinephrine was intramuscularly given to patients with over grade 4 symptoms or those with grade 3 symptoms who had a history of severe anaphylaxis, rapidly progressive symptoms, circulatory failure, or uncontrollable respiratory symptoms after inhalation of bronchodilators. Severe reactions in 28 patients were 13 grade 4 and 15 grade 3 by Sampson's classification. All 13 grade 4 patients showed respiratory symptom. Twelve and three grade 3 patients had respiratory and gastrointestinal symptoms, respectively. Intramuscular injections of epinephrine controlled all severe reactions in 14 patients (13%).

Risk factors for the development of severe reactions

A multivariate analysis identified milk-specific IgE value as the single risk factor for the development of severe reactions (odds ratio [OR] 11.61, $p = 0.001$, Table 2). The median ratio of milk-specific IgE values to total IgE values was higher in severe reaction-developing patients than seen in non-severe reaction-developing patients ($p = 0.001$, Fig. 1), but the distribution overlapped substantially. In the multivariate logistic regression analysis, a high value of milk-specific IgE (odds ratio [OR] 6.43, $p = 0.0007$), history of bronchial asthma (OR 3.86, $p = 0.012$), and complete milk avoidance (OR 4.09, $p = 0.013$) were selected as independent factors to differentiate patients who developed severe reactions from those who did not (Table 3). A predictive formula for severe reactions was given as follows: Logit (P) = − 3.38 + 1.86 × log (milk-specific IgE value) + 0.70 × (complete milk avoidance; yes 1, no 0) + 0.67 × (bronchial asthma; yes 1, no 0). The probability discriminated severe reaction group from non-severe reaction group (median 0.43 vs. 0.10, $p < 0.0001$, Fig. 2a). The area under the ROC curve was 0.83, although the Hosmer-Lemeshow statistics showed no significance (Fig. 2b). For the optimal cut-off, the sensitivity and specificity in the discrimination between severe reactions and non-severe reaction groups were 86% and 56%, respectively.

Severe reaction-developed patients with < 25% of risk probability

No patients developed severe reactions in response to the starting dose in the risk-stratified protocol. The clinical profiles of five severe reaction-developing patients with a probability of < 25% (cut-off point for ROC curve) are shown in Supplementary Table S1. Four patients (all STEP2 OFC)

Table 2 Multivariate analysis for variables associated with severe reactions

Variables	Odds ratio	95% confidence interval	*p* value
Milk-specific IgE value (log)	11.61	3.07–60.54	0.001
Complete milk avoidance	3.88	1.22–14.06	0.02
Bronchial asthma	3.75	1.18–13.06	0.02
Atopic dermatitis	3.12	0.92–12.41	0.07
Family history of bronchial asthma	1.42	0.44–4.56	0.55
Age, month	1.01	0.98–1.03	0.60
Family history of food allergy	0.89	0.27–2.79	0.85
Previous history of anaphylaxis	0.75	0.21–2.62	0.65
Total IgE value (log)	0.44	0.10–1.79	0.26
Family history of atopic dermatitis	0.43	0.11–1.56	0.20

Continuous variables were log-transformed in the analyses. AUC = 0.85

developed severe reactions in response to 20-mL loaded dose, while the remaining one patient (STEP1 OFC) developed severe reactions in response to 1 mL after a starting dose of 250 μL milk. All five patients firstly showed respiratory symptoms, and three patients showed skin eruption. However, two patients did not show any other clinical symptoms (Supplementary Table S1). There was no significant association between the total consumed dose of milk and age at the first onset of allergic symptom or age at the time of the test among severe reaction and non-severe reaction patients (Supplementary Figure S1). The interval from the onset of allergic symptoms to the OFC test did not differ markedly between the five patients with < 25% of risk probability and the 23 those with ≥ 25% risk.

Discussion

We have established a model for predicting a severe reaction at the first milk OFC test with a risk-stratified protocol. It has an advantage on the safety of OFC for high-risk patients having less information. For children with > 25% of probability, in-hospital or reduced dose OFC may be recommended in practice. On the other hand, for children with < 25%, it is necessary to perform OFC in early childhood and finish the complete milk avoidance. Low-dose oral immunotherapy suggests the efficacy of ingesting a small amount of antigen to increase the threshold dose [1]. Although the effects depend on the kind of foods and the mode of tolerance induction, our OFC model may allow the early tolerance induction for infants with severe milk allergy.

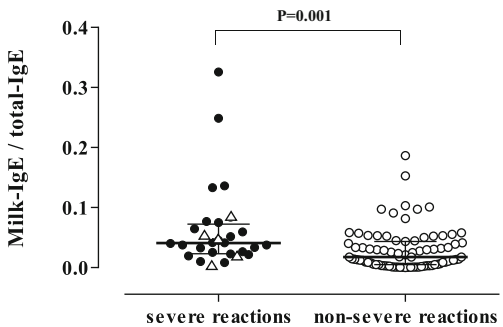

Fig. 1 The ratio of milk-specific IgE levels to total-IgE levels in patients who did or did not develop severe reactions. Bars indicate the medians with interquartile ranges. The median ratio of milk-specific IgE value to total IgE value was higher in patients with severe reactions (●) than seen in those without severe reactions (○) ($p = 0.001$), although the distribution overlapped substantially. △: patients with a probability of developing severe reactions ≤ 25%

No single variable or calculated parameters discriminated the group of patients who developed severe reactions from those without severe reaction development with high specificity and sensitivity. The formula consisting of three variables had good sensitivity (86%, cut-off 0.25) but not high specificity. The sensitivity in our study was higher than that of a previous study that showed that the prediction scores of 8 to 10 had a sensitivity of 38.4% for discriminating severe reaction cases [28]. Because the severity in OFC test in their study [28] was not assessed by the Sampson's classification, the comparison might not be effectively made. Severe reaction development was not predicted in 5 of 111 patients (5%), even when using our risk-stratified protocol. These results underscored a small subgroup of high-risk patients with milk allergy, whose predisposition might be difficult to characterize by the combination of known clinical variables.

The OFC is a critical tool for determining the tolerable dose of allergens. Infants have the greatest need for accurate food allergy assessments, given the nutritional problems, high incidence, severity, and a rare complete resolution after oral immunotolerance therapy [5, 12]. The first milk OFC test provides useful information for the management of complete avoidance or tolerable ingestion in daily life. Therefore, safe methods of performing this test have long been explored. Even in our careful risk stratification

Table 3 Multivariate logistic regression analysis for the prediction of severe reactions in the milk OFC

	Logistic coefficient (β)	Standard error	Odds ratio	95% CI	*p* value
Intercept	− 3.38				
Milk-specific IgE value (log)	1.86	0.79	6.43	2.41–20.96	0.0007
Complete milk avoidance	0.70	0.28	4.09	1.42–13.30	0.013
Bronchial asthma	0.67	0.27	3.86	1.38–11.48	0.012

OFC oral food challenge, *CI* confidence interval

The severe reaction predictive formula is given as follows:

Logit (P) = − 3.38 + 1.86 × log (milk-specific IgE value) + 0.70 × (milk avoidance; yes 1, no 0) + 0.67 × (bronchial asthma; yes 1, no 0)

protocol, severe reactions occurred in more than 20% of patients. Although the definition of severe reactions was varied among reports, the incidence in our study was similar to that of Yanagida's report [32] or lower than Sugiura's one [28]. Approximately 90% of them required no epinephrine control. These indicate that high-risk OFC was safely completed in our tertiary center for food allergy. Of three distinctive variables (complete milk avoidance, bronchial asthma, and milk-specific IgE) between the severe reactions and non-severe reaction groups, only milk-specific IgE was selected as a marker by the multivariate analyses. High milk-specific and low total IgE values were reportedly identified as an independent risk factors for the development of a severe reaction in the milk OFC [3]. Non-specific or low-affinity IgE suppresses the specific IgE-mediated activation of basophils in vitro [7]. The total serum IgE levels are associated with the clinical severity or reactivity of patients with a milk [13], β-lactam [31], or hymenoptera venom allergy [27]. In the present study, milk-specific IgE levels and the ratio of those to the total IgE levels were determined to be the significant markers for severe reactions, but both values mostly overlapped substantially between the two groups. Horimukai et al. [13] reported that the ratio of specific IgE to total IgE offered no advantage for diagnosing symptomatic food allergies, as the total IgE levels showed a lognormal distribution, but specific IgE levels did not. The discrepant results between their report [13] and ours might be due to the non-linear correlations between specific IgE and total IgE levels. Total IgE but not milk-specific IgE values increase with age. The study subjects in our study were younger than those of Horimukai' report [13]; median months of age were 40 and 52, respectively. As shown in Fig. 1, significant differences in the median values with poor separation might also represent the distinct distribution between total and specific IgE levels.

The presence of only three variables in the formula represents a limitation of our equation. The present model did not reconcile the specificity and sensitivity on the probability for severe reactions (Fig. 2). The three selected variables in the formula showed significant differences between severe reaction and non-severe reaction group patients. However, the multivariate analysis indicated that these variables were confounding with respect to the risk of severe reactions. Bronchial

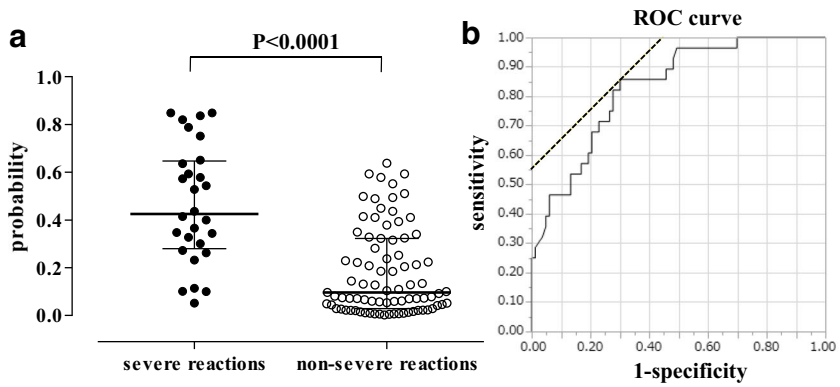

Fig. 2 **a** Calculated probability of the risk of developing severe reactions between the severe reaction and non-severe reaction groups. ○: 28 patients who developed severe reactions. ●: 83 patients who did not develop severe reactions. Logit (P) = − 3.38 + 1.86 × log (milk-specific IgE value) + 0.70 × (complete milk avoidance; yes 1, no 0) + 0.67 × (bronchial asthma; yes 1, no 0). Logit (p) = log(p/1-p). Each bar indicates the median and inter-quartile range of probability. The probability was significantly higher in the severe reaction group than in the non-severe reaction group ($p < 0.0001$). **b** The area under the ROC curve was 0.83. For cut-off point $p = 0.25$/sensitivity 86% and specificity 56%

asthma of patients has been recognized as a risk factor for a severe reaction in the OFC test [4]. The modified Asthma Prediction Index (mAPI) [6] is a clinical index for defining asthma risk for children ≥ 2 years of age and includes the parental history of asthma as the major criterion. The diagnosis of bronchial asthma is practically difficult in infancy, due to occasional experiences of one or more wheezing episodes before the age of 3 years in association with respiratory virus infections [16, 25]. For the two categorical variables selected in the equation, transforming to any continuous variables and establishing cut-off levels are required to improve both the sensitivity and specificity for discriminating severe reaction and non-severe reaction patients. However, the poor separation rate (Fig. 2) in the probability might be ascribed to the limitation in statistical analysis without the consideration of genetic predisposition in individuals (supplementary Table S1). Further studies should explore the characterization of the immunological profile in ultra-high-risk patients whose manifestations start at the neonatal stage or in early infancy.

The present study has several limitations. First, the sample was small in number and an unrecognized selection bias might be introduced, even though all tests were performed at two hospitals specializing in diagnosing and treating food allergy. Second, there might have been modulating effects from materials other than the milk protein in the challenging foods that influenced the sensitization. Third, there might have been additional effects of medications, as corticosteroids and immunosuppressants but not anti-allergic drugs were washed out at least 3 months before the study.

In conclusion, the risk-stratified protocol and a formula for predicting the risk of developing severe reactions may have a clinical utility for minimizing the rate of adverse events in the first milk challenge. However, the difficult reconciliation between the sensitivity and specificity in the model suggested a certain predisposition in the high-risk group patients.

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Authors' contributions Takahiro Kawahara, Junichiro Tezuka, and Shouichi Ohga were the principal investigators taking primary responsibility for the paper. Natsuko Masumoto and Makiko Nanishi completed the survey questionnaires, made the clinical diagnosis, and confirmed the clinical and laboratory data. Takahito Ninomiya and Hideki Nakayama supported the clinical study with helpful discussions. Satoshi Honjo supported the statistical analysis. Takahiro Kawahara and Junichiro Tezuka wrote the first draft of the manuscript.

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Compliance with ethical standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This investigation was approved by the Institutional Review Board at the institutions (Registration code: H29-clini2). This article does not contain any studies with animals performed by any of the authors.

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Informed consent was obtained from all individual participants included in the study.

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