

# Natural resolution of non-anaphylactic shrimp allergy in patients diagnosed 10 years earlier by oral food challenge

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## Abstract

**Background:** Shrimp allergy is considered a lifelong condition. The natural resolution of shrimp allergy is not well studied.

**Objective:** To investigate the natural resolution of shrimp allergy among a cohort of patients diagnosed with shrimp allergy 10 years earlier by oral shrimp challenge.

**Methods:** A prospective study recruited patients diagnosed with shrimp allergy to *Penaeus monodon* (*Pm*), *Macrobrachium rosenbergii* (*Mr*), or both from a study conducted during 2005-2006. The current oral shrimp challenges were conducted during 2015-2016. The negative oral shrimp challenge was designated 'resolved shrimp allergy' (RSA), with a positive challenge designated 'persistent shrimp allergy' (PSA). Skin prick and prick-to-prick testing to shrimp were used to determine sensitization.

**Results:** Sixty patients who had positive shrimp challenge from the previous cohort were contacted. Patients who had previous anaphylactic reaction (8 subjects) or allergic reaction after shrimp ingestion within 6 months (6 subjects), were not included. Nine patients refused to participate and 20 patients could not be contacted. Seventeen patients were included. Three were previously diagnosed with allergy to *Pm*, 3 to *Mr*, and 11 to both species. RSA was observed in 1 patient with isolated *Pm* allergy, and in 3 patients with isolated *Mr* allergy. Three of 9 patients with dual allergy had RSA to both species. RSA patients had significantly smaller size of shrimp skin test than PSA patients at both diagnosis and follow-up.

**Conclusions:** At ten years after diagnosis, 46% of patients had RSA. These patients had significantly smaller size of shrimp skin test than PSA patients.

**Key words:** allergy, food allergy, natural resolution, oral food challenge, shrimp, tolerance

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## Introduction

The prevalence of food allergy was 8% and 5% in children adults, respectively.<sup>1</sup> This prevalence was increasing over the past 10-15 years, especially among infants and preschool children.<sup>1</sup> Common food allergens in infants and young children in Asia are milk, eggs and wheat with the prevalence of 0.83-5%, 3-4% and 0.08% respectively. Adults are more allergic to shellfish, fish and peanut with the prevalence of 7.05%, 1.17% and 0.48% respectively.<sup>1-4</sup>

Shellfish, especially shrimp, was a leading cause of food allergy among adolescents and adults.<sup>3,5-8</sup> In Asia, shellfish allergy was more common than peanut allergy which was in contrast to those in Western countries.<sup>7,9</sup> A study from Singapore reported that sensitization to shellfish (77%) was higher than peanut (45%) among children greater than 4 years of age.<sup>10</sup> Moreover, shellfish was the leading cause of food-induced anaphylaxis, especially in Asian countries.<sup>7,8,11,12</sup>

At least 2 studies reported allergy to specific shrimp species in a subset of shrimp allergic patients.<sup>13,14</sup> During 2005-2006, we studied 68 children who had history of shrimp allergy and positive skin tests to shrimp. Using oral food challenges (OFC) to *Penaeus monodon* (*Pm*; saltwater shrimp) and *Macrobrachium rosenbergii* (*Mr*; freshwater shrimp), we identified specific allergy to *Pm* and *Mr* in 17.65% and 23.53% of children, respectively. Positive and negative OFC to both shrimp species was found in 47.06% and 11.76% of children, respectively.<sup>13</sup> A study from Singapore also confirmed species-specific shrimp allergy in adults who had positive OFC to *Pm* and *Litopenaeus vannamei* (*Lv*).<sup>14</sup> Shrimp allergens such as tropomyosin, arginine kinase, myosin light chain and sarcoplasmic calcium binding protein are well characterized in *Pm* and *Lv*.<sup>15</sup> The protein antigens in *Mr* were not widely studied since this shrimp is not available worldwide. Our group has characterized the cross-reactive tropomyosin and non-cross reactive hemocyanin in *Mr*.<sup>16,17</sup>

Unlike egg, wheat, soy, and cow's milk, peanut and shellfish allergy are regarded as lifelong allergies.<sup>5,18,19</sup> However, Ho, *et al.*, followed children less than 2 years of age who had wheal size from skin prick test (SPT) to peanut  $\geq 95\%$  of positive predictive value (PPV) for up to 8 years. Peanut challenges were performed when SPT responses decreased to less than 95% PPV. They found that 21% of children with peanut allergy developed clinical tolerance by 5 years of age.<sup>20</sup> In addition, recent data from the HealthNuts study revealed that 22% of infants with challenge-proven peanut allergy developed peanut tolerance by 4 years of age.<sup>21</sup>

Despite the findings that natural resolution of peanut allergy can occur, the natural course of shrimp allergy has not been well studied. The aim of this study was to investigate the natural resolution of shrimp allergy among a cohort of patients who were diagnosed as having non-anaphylactic shrimp allergy 10 years earlier by OFC, and to identify factors associated with shrimp tolerance.

## Methods

### Subjects

This prospective cohort included patients who were diagnosed with shrimp allergy to *Pm*, *Mr*, or both from a study that we conducted during 2005-2006.<sup>13</sup> The current study was conducted during 2015-2016. Both studies were conducted at the Division of Allergy and Clinical Immunology, Department of Pediatrics, Siriraj Hospital. This study was approved by the Siriraj Institutional Review Board (SIRB), (COA no. 017/2559, EC1). Written informed consent was obtained from all participants.

Due to the ethical concern, patients who had previous anaphylactic reaction to shrimp or recent allergic reaction after shrimp ingestion within the past 6 months, were not included. Patients with underlying diseases such as cardiovascular, hepatobiliary, and renal diseases; severe systemic infection; and/or pregnancy, were excluded. Patients with allergic diseases, such as asthma, allergic rhinitis, urticaria, and atopic dermatitis, were stable for more than 7 days before OFC. Peak expiratory flow rate was more than 70% of predicted value on the day of OFC. None of the patients were on  $\beta$ -blocking agents or systemic corticosteroid.

In our previous study, 68 children with a history of shrimp allergy and skin tests positive to shrimp were orally challenged with *Pm* and *Mr*.<sup>13</sup> We found 12 patients who had allergy to *Pm* only, 16 patients to *Mr* only, and 32 patients to both shrimp species. Patients who had anaphylaxis, and 8 patients who had negative OFC to shrimp were excluded from the current study. The remaining 52 patients met the inclusion criteria and were invited to participate in this study. The flow of participants throughout the study is shown in **Figure 1**.

### Skin test procedure

Skin tests were performed using the previously described method.<sup>13</sup> In brief, SPT using *Pm* and *Mr* extracts (*Pm*SPT and *Mr*SPT), and prick-to-prick (PTP, pricking the food and then pricking the skin of the patients) method using cooked *Pm* and *Mr* (*Pm*PTP and *Mr*PTP) were performed. The *P. monodon* and *M. rosenbergii* extracts were freshly prepared by making a dilution of 1:10 (wt/volume) of raw lyophilized shrimp in Coca's solution. The sensitivity and specificity for *Pm*SPT, *Pm*PTP *Mr*SPT and *Mr*PTP were 97.73% and 8.33%, 100% and 4.17%, 97.92% and 5%, 100% and 0%, respectively.<sup>13</sup> The glycerinated saline and histamine phosphate 10 mg/mL were negative and positive controls, respectively. Antihistamines were discontinued for at least 7 days prior to skin testing. The mean of the largest and midpoint orthogonal diameters of wheals was recorded as the mean wheal diameter (MWD), and was considered positive if it was 3 mm larger than the negative control.

### Oral food challenge procedure

OFC to *Pm* and/or *Mr* was performed in patients identified in our previous study as having allergy to *Pm*, to *Mr*, or to both shrimp species.<sup>13</sup> The open OFC protocol was modified from our and previous reports.<sup>13,22-24</sup> The protocol comprised challenges in three steps, with multiple doses in two of the steps. Steps were performed 15 minutes apart. The provocation dose (PD) in the first step consisted of raw lyophilized shrimp in capsules which were given as follows: 500 mg, 1, 2, and 4 g given at 15-minute intervals. The cumulative PD was 7.5 g. The second step was to identify oral-mucosal reactions by swabbing 2 g of cooked shrimp onto the inner lips, placing it into the mouth without chewing for 5 minutes, and then removed. Lip itching/swelling and/or throat itching was recorded as a positive oral-mucosal reaction. The third step involved open feeding of cooked shrimp. The PD schedule of cooked shrimp was, as follows: 1, 2, 4, and 8 g at 15-minute intervals. The cumulative PD was 15 g. A positive response to one or more steps of the OFC was considered a positive challenge. Patients who had a positive reaction to both shrimp species were challenged 2-4 weeks later with other shrimp species. If the patient had no reaction to the OFC, a telephone follow-up was conducted 2-3 weeks later to inquire if the patient had any reaction to shrimp consumption. Anaphylaxis was diagnosed according to established criteria.<sup>25</sup> Patient symptoms and signs were recorded every 15 minutes during OFC.

### Outcomes of shrimp OFC

Negative shrimp challenge was designated 'resolved shrimp allergy' (RSA), with a positive challenge designated 'persistent

shrimp allergy' (PSA). The outcome of this study was categorized into 3 outcomes as the following:

Outcome 0: Patients had positive OFC to *Pm* only, *Mr* only, or both species in our previous report,<sup>13</sup> but, had negative shrimp OFC in the current study.

Outcome 1: Patients had positive OFC to *Pm* only or *Mr* only in our previous study, and still had positive OFC in the current study. Patients who had allergy to both shrimp species in the previous report<sup>13</sup> tolerated one shrimp species in the current study.

Outcome 2: Patients had positive OFC to both shrimp species in both the previous and current study.

### Statistical analysis

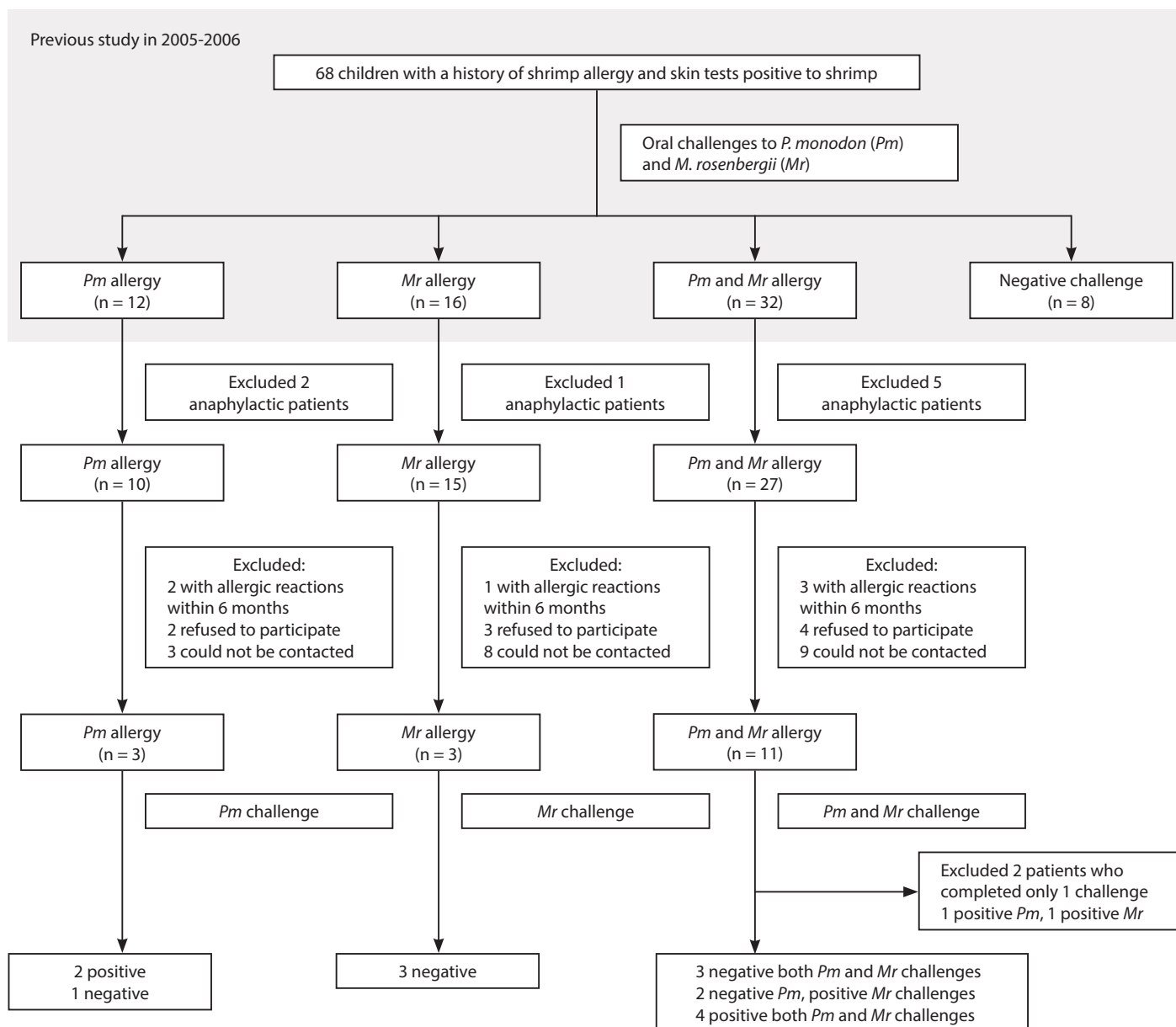
Data are presented as mean ± standard deviation or median and range for continuous data, and as number and percentage

for categorical data. Pearson's chi-square test and Fisher's exact test were used to analyze categorical data. Comparisons between parameters of RSA and PSA groups were done using independent T-test or Mann-Whitney *U* test if the data were not normally distributed. A *p*-value ≤ 0.05 was considered significant.

## Results

### Subjects

Of the 52 patients who met the inclusion criteria, 6 had allergic reaction to shrimp ingestion within the past 6 months, 9 refused to participate and 20 could not be contacted. The remaining 17 patients were recruited. Three patients had isolated allergy to *Pm*, 3 had isolated allergy to *Mr*, and 11 had allergic reaction to both shrimp species (**Figure 1, Tables 1**).



**Figure 1. The flowchart of participants throughout the study and outcome of shrimp challenges. The area in grey zone represents the results from previous study.**

Abbreviations: *Mr*, *M. rosenbergii*; *Pm*, *P. monodon*

**Table 1. Demographic data, skin test response, results of OFC to *M. rosenbergii* and *P. monodon*, cumulative provocation dose, symptoms during OFC, in patients who were previously diagnosed as having allergy to *P. monodon* (P1-3) only, *M. rosenbergii* (M1-3) only or both shrimp species (B1-11).**

No	Sex	Age (year)	MWD from current skin tests (mm)						<i>P. monodon</i> cumulative PD				<i>M. rosenbergii</i> cumulative PD					
			<i>Pm</i> SPT	<i>Pm</i> PTP	<i>Mr</i> SPT	<i>Mr</i> PTP	<i>PmOFC</i> current	Results of current <i>PmOFC</i>	Raw shrimps (g)	Oral-mucosal reaction	Cooked shrimps (g)	Symptoms upon <i>PmOFC</i>	Results of current <i>MrOFC</i>	Raw shrimps (g)	Oral-mucosal reaction	Cooked shrimps (g)	Symptoms upon <i>MrOFC</i>	
P1	M	19	7.5	NP	NP	NP	NP	Negative	7.5	No	15	No	NP	NP	NP	NP	NP	
P2	M	26	8	NP	NP	NP	NP	Positive	7.5	NP	NP	LI	NP	NP	NP	NP	NP	
P3	F	18	16	14	10	9	9	Positive	3	NP	NP	TI	NP	NP	NP	NP	NP	
M1	M	19	3	5	4	3.5	3.5	NP	NP	NP	NP	NP	Negative	7.5	No	15	No	
M2	M	19	7	4.5	3	4	4	NP	NP	NP	NP	NP	Negative	7.5	No	15	No	
M3	F	25	5.5	4	5	3.5	3.5	NP	NP	NP	NP	NP	Negative	7.5	No	15	No	
B1	M	23	4	5.5	6.5	2	2	Negative	7.5	No	15	No	NP	NP	NP	NP	No	
B2	F	24	3	2	3	2	2	Negative	7.5	No	15	No	NP	NP	NP	NP	No	
B3	F	24	10	6	8	9	9	Negative	7.5	No	15	No	NP	NP	NP	NP	No	
B4	F	18	8.5	9	9.5	15.5	15.5	Negative	7.5	No	15	No	NP	NP	NP	NP	TI, LI	
B5	M	24	2.5	2	2	5	5	Negative	7.5	No	15	No	NP	NP	NP	NP	R	
B6	M	23	5	4	3.5	6.5	6.5	Positive	7.5	No	15	TI	NP	NP	NP	NP	TI, LI	
B7	M	18	8	13.5	14.5	14	14	Positive	7.5	Yes	NP	U	NP	NP	NP	NP	U, N/V, AP, A	
B8	M	18	26.5	27.5	33.5	29	29	Positive	7.5	No	15	TI, LI	NP	NP	NP	NP	Flushing	
B9	F	21	11	9	9	7.5	7.5	Positive	7	NP	NP	AG, R, A	NP	NP	NP	NP	TI, U, LSI	
B10	M	20	22	11.5	11.5	11	11	Positive	7	NP	NP	AP	NP	NP	NP	NP	NP	
B11	M	18	13.5	16	11.5	16	16	NP	NP	NP	NP	NP	Positive	7.5	NP	NP	NP	TI, LI, U, N/V, AP, A

**Abbreviations:** A, Anaphylaxis; AG, angioedema; AP, abdominal pain; LI, lips itching; LSI, lips swelling and itching; Mr, *M. rosenbergii*; MWD, mean wheal diameter; NP, not performed; N/V, nausea and/or vomiting; OFC, oral food challenge; PD, provocation dose; Pm, *P. monodon*; PTP, prick-to-prick test; R, rhinitis; SPT, skin prick test; TI, throat itching; U, urticaria

Demographic data, personal and family history of atopy, other food allergy besides shrimp, route of exposure, symptoms and onset of shrimp allergy in the past, are shown in **Table 2**. Underlying allergic diseases, such as asthma, allergic rhinitis, and atopic dermatitis, were found in 76.5% of patients. Allergic reaction to other food, such as crab, mollusks, or fish, was found in 82.4% of patients.

### Results of shrimp OFC

In this study, 1 of the 3 patients (patient's number P1 in **Table 1**) who were previously diagnosed as having isolated allergy to *Pm* had negative challenges to *Pm* (**Figure 1, Table 1**). All of the patients (M1-M3) who were previously diagnosed as having isolated allergy to *Mr* had negative challenges to *Mr* (**Figure 1, Table 1**).

Eleven patients who were allergic to both shrimp species were scheduled for re-challenge to both shrimp species. However, 2 patients (B10, B11) refused to participate in the 2<sup>nd</sup> challenge after having an allergic reaction to the 1<sup>st</sup> challenge (**Figure 1, Table 1**). Therefore, in this group of dual allergy, 10 challenges to *Pm* and 10 to *Mr* were done. Of the 9 patients who had complete OFC to both shrimp species, 3 patients had negative challenges to both species (B1-B3). Two patients had negative challenges to *Pm* but positive challenges to *Mr* (B4-B5). Four patients had positive challenges to both *Pm* and *Mr* (B6-B9).

Therefore, RSA was found in 1/3 of the patients who were previously allergic to *Pm*, and in 3/3 of the patients who were previously allergic to *Mr*. In patients who were previously allergic to both *Pm* and *Mr*, RSA to both shrimp species was found in 3/9 patients.

Overall, there were 26 challenges. Six of 13 (46%) challenges to *Pm* and 6/13 (46%) challenges to *Mr*, were negative. The mean onset of allergic reactions after OFC was 7.50 (range 1-120) minutes. The most common allergic reactions were found on the skin and soft tissue (85.7%), followed by gastrointestinal (21.4%) and respiratory system (14.3%). Anaphylaxis was found in 3 patients who were previously allergic to both shrimp species.

Fifteen patients who completed the challenge protocol, were divided into 3 outcome categories since some patients with dual shrimp allergy had RSA to one shrimp species but PSA to another species. Seven (46.6%) patients (P1, M1-M3, B1-B3 in **Table 1**) had RSA, and were designated as having 'Outcome 0'. Four (26.7%) patients (P2-P3, B4-B5 in **Table 1**) had PSA to one shrimp species, and were designated as having 'Outcome 1'. Four (26.7%) patients (B6-B9 in **Table 1**) had PSA to both shrimp species, and were designated as having 'Outcome 2'. Factors investigated for the association with these outcomes are listed in **Table 2**. No factors were found to significantly associate with RSA. The age at diagnosis of shrimp allergy was not a significant predictor of outcome (data not shown).

**Table 2. Patient characteristics and outcomes of oral food challenges to shrimp**

Characteristics	No. of patients (N = 17) (100%) n (%)	Outcome 0 (N = 7) (46.6%) n (%)	Outcome 1 (N = 4) (26.7%) n (%)	Outcome 2 (N = 4) (26.7%) n (%)	p value
Male gender	10 (58.8%)	4 (57.1%)	2 (50.0%)	2 (50.0%)	1.00
Type of shrimp allergy					0.17
- <i>Penaeus monodon</i> ( <i>Pm</i> )	3 (17.6%)	1 (14.2%)	2 (50.0%)	0 (0.0%)	
- <i>Macrobrachium rosenbergii</i> ( <i>Mr</i> )	3 (17.6%)	3 (42.9%)	0 (0.0%)	0 (0.0%)	
- Both <i>Pm</i> and <i>Mr</i>	11 (64.8%)	3 (42.9%)	2 (50.0%)	4 (100%)	
Current age (years), mean ± SD	21.1 ± 2.9	22.3 ± 2.7	22.1 ± 4.0	20.8 ± 2.5	0.71
Patient history of atopic diseases					0.75
- No	4 (23.5%)	1 (14.3%)	1 (25.0%)	2 (50.0%)	
- Yes	13 (76.5%)	6 (85.7%)	3 (75.0%)	2 (50.0%)	
Family history of atopic diseases					1.00
- No	11 (64.7%)	4 (57.1%)	3 (75.0%)	2 (50.0%)	
- Yes	6 (35.3%)	3 (42.9%)	1 (25.0%)	2 (50.0%)	
Food allergies other than shrimp					0.20
- No	3 (17.6%)	0 (0.0%)	2 (50.0%)	1 (25.0%)	
- Yes	14 (82.4%)	7 (100%)	2 (50.0%)	3 (75.0%)	
Route of exposure to <i>Pm</i> or <i>Mr</i>					NA
- Oral	17 (100%)	7 (100%)	4 (100%)	4 (100%)	
- Touch or vapor inhalation	8 (47.1%)	2 (28.6%)	2 (50.0%)	2 (50.0%)	0.66
Symptoms from the previous shrimp challenge					0.53
- Skin and soft tissue	16 (94.1%)	7 (100%)	3 (75.0%)	4 (100%)	
- Upper respiratory tract	5 (29.4%)	2 (28.6%)	1 (25.0%)	1 (25.0%)	1.00
- Gastrointestinal tract	1 (5.9%)	0 (0.0%)	1 (25.0%)	0 (0.0%)	0.53
Onset of reaction after ingestion of <i>Pm</i> or <i>Mr</i>					0.75
- < 30 minutes	13 (76.5%)	5 (71.4%)	3 (75.0%)	4 (100%)	
- ≥ 30 minutes	4 (23.5%)	2 (28.6%)	1 (25.0%)	0 (0.0%)	



Table 2. (Continued)

Characteristics	No. of patients (N = 17) (100%) n (%)	Outcome 0 (N = 7) (46.6%) n (%)	Outcome 1 (N = 4) (26.7%) n (%)	Outcome 2 (N = 4) (26.7%) n (%)	p value
Route of birth					1.00
- Normal labor	7 (41.2%)	3 (42.9%)	2 (50.0%)	2 (50.0%)	
- Cesarean section	10 (58.8%)	4 (57.1%)	2 (50.0%)	2 (50.0%)	
Duration of breastfeeding (months)					0.81
- < 4 months	10 (58.8%)	5 (71.4%)	3 (75.0%)	2 (50.0%)	
- ≥ 4 months	7 (41.2%)	2 (28.6%)	1 (25.0%)	2 (50.0%)	
Number of siblings					1.00
- < 2	15 (88.2%)	6 (85.7%)	3 (75.0%)	4 (100%)	
- ≥ 2	2 (11.8%)	1 (14.3%)	1 (25.0%)	0 (0.0%)	
Complete avoidance of <i>Pm</i> or <i>Mr</i>					0.06
- No	6 (35.3%)	5 (71.4%)	1 (25.0%)	0 (0.0%)	
- Yes	11 (64.7%)	2 (28.6%)	3 (75.0%)	4 (100%)	

Comparisons between outcomes were done using independent T-test or Mann-Whitney U test if the data were not normally distributed.

Abbreviations: *Mr*, *M. rosenbergii*; *Pm*, *P. monodon*; SD, standard deviation; NA, not available

A telephone follow-up was conducted to inquire if patients with negative challenge developed any allergic reaction upon shrimp consumption. Those follow-up calls revealed no allergic reactions in patients with negative OFC in the current study.

### Results of skin tests

The results of *Pm*SPT, *Pm*PTP, *Mr*SPT, and *Mr*PTP from included patients are shown in Table 1. These skin test results were compared with the results from the previous study in the

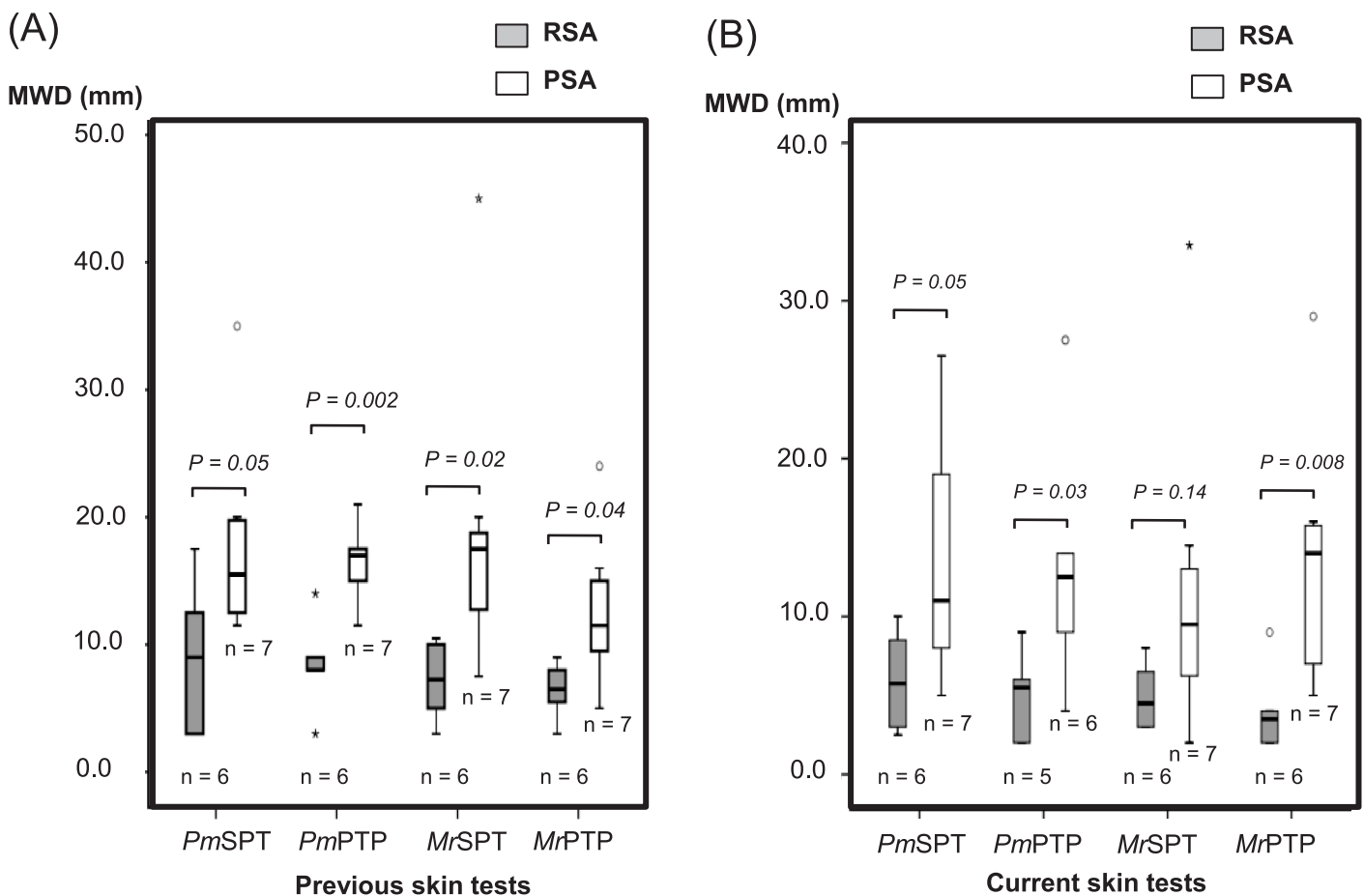


Figure 2. Comparisons of the mean wheal diameter (MWD) of skin tests in patients with 'resolved (RSA)' or 'persistent shrimp allergy (PSA)' from previous (A) and current (B) studies. The numbers under the bars represent number of subjects. Comparisons between groups were done using Mann-Whitney U-test.

Abbreviations: *Mr*, *M. rosenbergii*; MWD, mean wheal diameters; *Pm*, *P. monodon*; PTP, prick-to-prick tests; SPT, skin prick tests.

same patients.<sup>13</sup> The median MWD of *Pm*SPT in the previous and current studies was 12.5 (range 3.0-35.0) mm and 8.0 (range 2.5-26.5) mm, respectively ( $p = 0.11$ ). The median *Pm*PTP in the previous and current studies was 14.0 (range 3.0-21.0) mm and 9.0 (range 2.0-27.5) mm, respectively ( $p = 0.20$ ). The median MWD of *Mr*SPT in the previous and current studies was 10.0 (range 3.0-45.0) mm and 6.5 (range 2.0-33.5) mm, respectively ( $p = 0.02$ ). The median *Mr*PTP in the previous and current studies was 8.5 (range 3.0-24.0) mm and 6.5 (range 2.0-29.0) mm, respectively ( $p = 0.53$ ).

The data of skin tests from our previous study<sup>13</sup> in the same patients included in the current study are shown in **Figure 2A**. The median MWD for *Pm*SPT, *Pm*PTP, *Mr*SPT and *Mr*PTP in patients with RSA were significantly smaller than those in patients with PSA. In the current study, median MWD for *Pm*SPT, *Pm*PTP, *Mr*PTP in patients with RSA were significantly smaller than those in patients with PSA. However, median MWD of *Mr*SPT was not significantly different between RSA and PSA groups. (**Figure 2B**).

In patients with *Pm* allergy, the *Pm*SPT MWD decreased 18.0% (range: -233.3-80.0%) from the data obtained from the previous study in the RSA group, and decreased 29.0% (range: -91.3-63.0%) in the PSA group ( $p = 0.95$ ). The *Pm*PTP MWD decreased 57.1% (range: -83.3-75.0%) from the previous study in the RSA group, and decreased 20.5% (range: -61.8-81.0%) in the PSA group ( $p = 0.79$ ). In patients with *Mr* allergy, the *Mr*SPT MWD decreased 30.0% (range: -116.7-71.4%) from the previous study in the RSA group, and decreased 45.7% (range: -53.3-90.0%) in the PSA group ( $p = 0.95$ ). The *Mr*PTP MWD decreased 37.4% (range: -12.5-69.2%) from the previous study in the RSA group, but increased 20.8% (range: -52.4-69.2) in the PSA group ( $p = 0.10$ ).

## Discussion

Understanding the natural history of shrimp allergy helps physicians to determine whether or not and when rechallenge of shrimp is appropriate. Shrimp allergy has long been considered lifelong, and patients have generally been instructed to strictly avoid shrimp.

Daul, *et al.* investigated the natural history of shrimp hypersensitivity and found that 7 of 11 shrimp hypersensitive patients had positive shrimp challenges.<sup>26</sup> The shrimp-specific IgE (sIgE) of all subjects were stable during the 24-month period and the authors concluded that shrimp hypersensitivity was a persistent condition. In contrast, Ayuso, *et al.* studied IgE-binding to specific epitopes of 4 shrimp allergens in children and adults with immediate allergic reactions to shrimp.<sup>27</sup> Children with shrimp allergy had higher shrimp sIgE, and more intense IgE binding to all shrimp peptides and to more diverse epitopes than adults. These findings suggest a decline in sIgE and the possible waning of shrimp allergy overtime.

The current study followed patients with shrimp allergy 10 years earlier, and re-challenged them to shrimp. We identified RSA in 7/15 (46%) patients who previously had allergy to either *Pm*, *Mr*, or both shrimp species. To our knowledge, this is the first study to demonstrate the resolution of shrimp allergy by performing follow-up challenges in patients who had challenge-proven shrimp allergy.

Skin test size in the current study showed a declining trend compared to the same patients in our previous report.<sup>13</sup> However the decrease was only statistically significant for *Mr*SPT. This finding is in support of Ayuso, *et al.*, who suggested that IgE sensitivity to shrimp decreases over time.<sup>27</sup>

Factors other than specific food antigens that predict persistent food allergy have been reported.<sup>28</sup> These factors include more severe symptoms upon antigen ingestion, lower PD, presence of allergic comorbidities, adult onset, greater SPT MWD, higher food sIgE, and persistent SPT reactivity or food sIgE over time.<sup>1,19-21,28-33</sup> Ho, *et al.* reported that 21% of children with peanut allergy became tolerant by the age of 5 years. Skin prick test to peanut more than 6 mm before the age of 2 years was a predictor of persistent peanut allergy.<sup>20</sup> Peters, *et al.* found that 22% of children with peanut allergy developed tolerance by the age of 4 years. Skin prick test to peanut at 1 and 4 years of age predicted resolved or persistent peanut allergy at 4 years of age.<sup>21</sup> Our present study found smaller skin test sizes in patients with RSA compared to patients with PSA (except for *Mr*SPT) in both the current study and the study we conducted 10 years ago.

The strength of this study is a long-term study and the RSA is proven by OFC. This study has some mentionable limitations. A number of patients were either lost to follow-up or refused to participate since most of them were in adult ages and changed their addresses or would not want to miss their works. Patients with anaphylaxis or recent allergic reaction to shrimp were excluded since they were not allowed to participate by the ethic committee. In general, these patients were not considered shrimp challenge in the real allergy practices.

In conclusion, 46% of shrimp allergic patients had RSA at ten years after diagnosis. Moreover, RSA patients had significantly smaller MWD than PSA patients at both diagnosis and at the ten-year follow-up.

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