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Prevalence and characteristics of adult patients with adult-onset and childhood-onset food allergy

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Abstract

Background: IgE-mediated food allergy (FA) affects health-related quality of life, and may cause life-threatening reactions. Few studies characterizing adult FA patients have been reported, especially first ever reaction (FER) in adult-onset.

Objectives: We describe the characteristics of adult FA patients, especially FER and compare these characteristics between childhood- and adult-onset FA.

Methods: A cross-sectional study of all adult patients visiting the Allergy Clinic, Siriraj Hospital at the outpatient department between January 2009 to December 2019 was conducted. Demographic, clinical data, and first reaction in life data were collected. Adult-onset was defined as ≥ 18 years old.

Results: Of 711 patients visiting the clinic, 174 (24.4%) were FA with a median age of 31.0 years (interquartile range 24.0, 44.0 years); 29.3% were male. FA patients had significantly higher prevalence of sensitization to cockroach compared with non-FA patients (67.4% vs. 56.3%); p = 0.016). The three most common food triggers were shellfish (68.0%), wheat (28.7%), and fruit and vegetables (10.0%). Before diagnosis, 56.7% (97/171) experienced at least 1 food-related anaphylaxis. Of the 166 patients compared on age of onset, 127 (76.5%) were adult-onset. In FER, patients with adult-onset had significantly more reactions to fruit and vegetables, more respiratory system involvement, and more other systems involvement [OR 8.95 (1.13, 1157); p = 0.034; OR 3.15 (95%CI 1.30, 8.25), p = 0.011; OR 10.8 (1.35, 1404), p = 0.019, respectively]. In sensitivity analysis, the cardiovascular system involvement was also significantly more common [OR 2.78 (1.05, 9.15); p = 0.038].

Conclusion: Shellfish was the most common trigger foods in adult FA patients. In FER, anaphylaxis was common for adult-onset. Adult-onset FA patients also had more respiratory, cardiovascular, and other systems involvements than childhood-onset ones. FA awareness, early diagnosis, and proper management are encouraged. Further studies on the adult-onset food allergic patients are required.

Key words: Anaphylaxis, food allergy, shellfish allergy, wheat allergy, fruit allergy, fish allergy, adult-onset, first reaction

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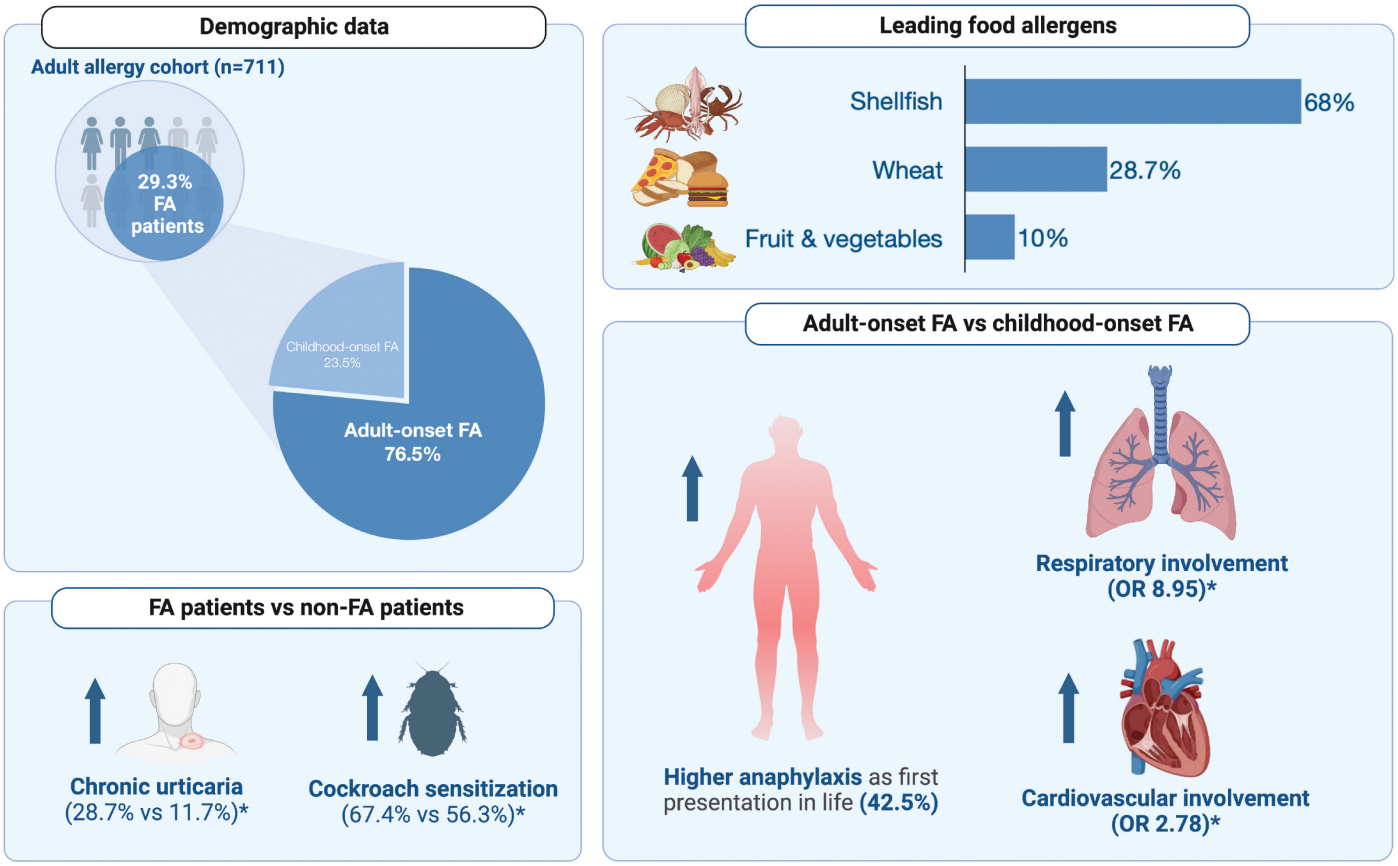
Abbreviations

CI	confidence interval
CU	chronic urticaria
FA	food allergy
FER	first ever reaction
OR	odds ratio
SD	standard deviation
SIgE	specific IgE
SPT	skin prick test
US	The United States of America

Introduction

Food allergy (FA) is defined as a specific immune response to certain food allergens. Various clinical manifestations range from mild to severe life-threatening reactions. Currently, self-reported FA reactions and evidence of sensitization by either skin tests or food-specific IgE (sIgE) evidence are usually accepted as criteria for FA in large epidemiological study.[1] However, the demonstration of IgE sensitization of food allergens, using sIgE or skin tests is not always indicative that a person is allergic to that food because of possible cross-reactivity of food allergens with environmental allergens, possibly confound sIgE or skin tests interpretations.[2] On the other hand, a negative test might result from an insufficient abundance of allergens, irrelevant components/epitopes in the tests, or limited analytical performance of the IgE antibody assay itself. OFC still remains a goal standard for diagnosis of FA despite its invasiveness, and time- and cost-consumption.[3]

The prevalence of FA is on the rise globally, in all age groups, including adults.[2] Data on adult FA is relatively limited compared with FA in children. The adult FA prevalence is varied by region which might depend on geographic variation, food culture, age group, and importantly the definition and diagnostic criteria used in the studies.[4-6] In a recent US population-based study, using a well-structured questionnaire, the prevalence of convincing IgE-mediated self-report FA is 10.8% in adults.[5] The EuroPrevall, the community-based survey, showed that adult FA prevalence across Europe ranges from 2-37%, with a substantial geographical variation in prevalence and causative foods across Europe.[7] In contrast, very little is known about population/community-based adult FA prevalence in Asia.[1] A cross-sectional population-based adult FA prevalence study from Taiwan was estimated at 6.4% in 2004, using convincing history with or without IgE sensitization.[8] In Thailand, there is no available population/community-based or hospital-based prevalence study in adult FA at this moment. Most adult food allergy cases were reported from the retrospective chart review, using the International Classification of Diseases (ICD) code, or data from the emergency department (ED). Food was the most common cause of adult anaphylaxis visiting an emergency department.[9,10]



Graphical abstract: Summary of key important findings of the study

Notes: **p*-value < 0.05; The figure was created by Biorender.
Abbreviation: FA, food allergy

Few studies have reported the characteristics and natural course of adult-onset FA. Kamdar et al. reported 171 adult-onset FA cases using diagnostic codes with chart review, finding that the age of onset peaked in the early 30s, and 49% had at least 1 anaphylaxis. The most common new-onset food allergens were shellfish, tree nut, fish, soy, and peanut.[11] A recent population-based study suggested classical childhood-onset FAs were emerging in adults since the common childhood food allergens were reported by over 20% of adults.[5] After stratification on age of onset, adult-onset food allergic patients were reported to have less physician-diagnosed FA, less epinephrine prescription, and less allergy diagnostic evaluation than other group.[12]

The differences between adult- and childhood-onset, allergist-diagnosed adult FA in Thailand have never been characterized. Therefore, we described the characteristics of patients with IgE-mediated FA, focusing on the clinical characteristics, atopic and non-atopic comorbidities, trigger foods, and first ever reactions (FER), comparing between childhood- and adult-onset.

Methods

Study design, setting, and population

We conducted a cross-sectional study using the data recorded at the clinic of the Division of Allergy and Clinical Immunology, Department of Medicine, Siriraj Hospital, which is a tertiary referral center. All patients evaluated by an allergist between January 2009 to December 2019 were assessed for eligibility. Patients with age 18 years old or more at the time of their first allergy clinic visit, with sufficient data in the medical record were included in the study. Patients who had insufficient detail of clinical history, no diagnosis documentation, significantly unable to provide reliable history during the allergy clinic visit (e.g., severe dementia or critically ill) were excluded from the study. The protocol for this study was approved for ethical considerations by the Siriraj Institutional Review Board, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand [COA no. Si 422/2020, protocol no. 231/2563(IRB3)]. Verbal informed consent was obtained before the phone interview. Patients were told that the research aimed to characterize adult FA patients in Thailand and the nature of the data that we wanted to collect from them, they could refuse to participate at the beginning or any time during the telephone interview, their care would not be affected by refusal to participate, there would be no fees paid or charged for participation, the interview would take 15 minutes, there were risks and benefits of being involved in the study, and they could ask any questions or express any concerns before proceeding further. Next, they were asked verbally whether they consented to join the study.

Data sources and collection

Patients' data were retrospectively reviewed from the Siriraj Information Technology (SiIT), an electronic medical records database maintained by Siriraj Information Technology Department in Siriraj Hospital. We extracted data on demographics, FA history, food-related reaction, age of onset, comorbidities (atopic and non-atopic disease), allergologic tests (skin prick test (SPT), food-sIgE, and oral food challenge), and the allergist's diagnosis.

Next, all FA patients were then approached for an interview by a trained medical personnel telephone interviewer using a standardized questionnaire to gather the missing or additional data for further analyses. The questionnaire included demographic data, atopic diseases and non-atopic comorbidities, family history of food allergy, the age of onset of the food allergy, the frequency, and the trigger foods. We also collected the history of the FER including trigger foods, time to onset after exposure, and clinical manifestations. If a patient did not answer the telephone call, we attempted to call three more times within one week or attempted to identify them at our outpatient clinic before considering them loss of contact.

Study definitions

The diagnosis of FA was based on the allergist's conclusion, using a combination of available data on compatible food-related reaction, food sensitization, and oral food challenge with the allergist's judgement. Subjects without FA diagnosis documentation were categorized as non-FA group. Adult-onset FA was defined as onset at aged 18 years or older. Atopic and non-atopic comorbities were defined as physician-diagnosed ones. For aeroallergen sensitization data from skin prick test, house dust mite sensitization was defined as a positive test result to either *Dermatophagoides pteronyssinus* or *Dermatophagoides farinae*, cockroach to either American or German cockroach, pollen to Bermuda grass, Johnson grass, Careless weed, or Acacia, mammalian epithelium to cat, dog, or mouse. Regarding system involvement, skin/mucosal involvement was defined as any of urticaria, lip angioedema, oral pruritis, tongue swelling, eyelid angioedema, facial swelling, or itching; respiratory system involvement as any of chest tightening, nasal congestion, repetitive cough, trouble breathing or wheezing; gastrointestinal system involvement as any of abdominal pain, diarrhea or nausea/vomiting; cardiovascular system involvement as any of chest pain, palpitations, or fainting/dizziness/feeling light-headed, and others system involvement. Anaphylaxis was classified using the NIAID/FAAN Consensus Criteria 2005.[13]

Statistical analysis

Data were analyzed descriptively. Continuous data are presented as mean (SD) for parametric distribution or median (interquartile range) for non-parametric distribution. Categorical data are presented as frequency (%). Descriptive univariate penalized logistic regression by Firth's logistic regression was performed to compare patients with an adult- or childhood-onset food allergy by complete case analysis and multiple imputation sensitivity analysis of missing data.[14] Firth's logistic regression is a penalized logistic regression method that corrects for small sample size bias and separation in small sample sizes.[15] Confidence intervals were profile likelihood, which may be appropriately asymmetrical at low sample sizes at which the normality assumption may be violated.[16] Some data were missing due to loss of contact by telephone during further data collection by telephone interview. Missing data were assumed to be missing at random, so multiple imputation was performed by multivariate imputation by chained equations by the fully conditional specification method using logistic regression for categorical data for the imputation models for univariate models comparing adult- and childhood-onset patients. Family history, derived from father, mother or sibling family history data was imputed as 'just another variable', and the number of imputation models was at least 5 or equal to the percentage of missing data for that independent variable in the univariate model. Complete data on age of onset on age, sex, atopic disease, and non-atopic disease were used as auxiliary variables for imputation. Imputation models also contained the variables in the univariate final estimation models.[17] The combination of penalized likelihood profiles (CLIP) method was used to pool imputation models for the estimation of results.[18] *P*-values were based on profile penalized log-likelihood. We adjudicated which results to value the most between the complete case analysis and multiple imputation sensitivity analysis by whether the sensitivity analysis result had a plausible direction of effect, a plausible magnitude according to the literature, and a reduction in the width of the 95% confidence interval demonstrating increased efficiency of the result (i.e., the power to detect a significant effect at the given sample size). If these three considerations were deemed acceptable, the multiple imputation sensitivity analysis result was valued more than the complete case analysis result, which may have had a higher risk of bias and is less efficient than a valid multiple imputation analysis.[19] All analyses were performed in R version 4.2.0. [R Team (2023). R Foundation of Statistical Computing, Vienna, Austria] using the logistf and mice packages along with Microsoft Excel [Microsoft Corporation (2018), Redmond, WA]. A p-value < 0.05 was considered significant.

Results

There was a total of 719 patient records from the adult allergy clinic, Siriraj Hospital between January 2009 to December 2019. Of these, exclusions included one patient for < 18 years old, three for lost medical records, and four for duplicates. Thus, 711 patients were included in the final analysis, of which 174 (24.5%) were patients with allergist-diagnosed FA (**Figure 1**). There were missing data in the electronic medical records database. Due to the length of telephone interviews, some were incomplete with subsequent loss of contact. Hence, there were missing data on the age of onset, trigger foods, history before diagnosis, and the characteristics of FER, and the frequencies of non-missing data.

Demographic, comorbidities, and aeroallergen sensitization

Among enrolled subjects, 711 patients visiting the clinic, the median age was 34.0 years (interquartile range 26.0, 49.0), and male was 30% (213/711). Non-FA patients were significantly older and had a significantly higher prevalence of non-atopic comorbidities including diabetes, hypertension, and dyslipidemia. They also had a higher prevalence of atopic comorbidities including allergic rhinitis, allergic conjunctivitis, and asthma. Interestingly, patients with FA had a significantly higher prevalence of sensitization to cockroach than non-FA patients (67.4% vs. 56.3%; $p = 0.016$).

Clinical characteristics of adult FA patients

Clinical characteristics of adult FA patients are described in **Table 1**. The median age was 31.0 years (interquartile range 24.0, 44.0). The median age of onset of FA was 25.0 (18.0, 38.0) years. Forty of 150 patients (26.7%) with FA had multiple FAs, defined as ≥ 2 structural unrelated, allergist-diagnosed FAs. Sixty-four of 174 (36.8%) initially presented with anaphylaxis. Before FA diagnosis was made, 97/171 (56.7%) reported at least 1 FA-associated anaphylaxis, and 76/171 (44.4%) reported having more than 1 anaphylactic episodes. The 3 leading causes associated with any reaction were shellfish (102/150, 68.0%), wheat (43/150, 28.7%), and fruit/vegetables (15/150, 10.0%) (**Figure 2A**). Amongst shellfish reactions in 102 patients, reactions to specific types of shellfish were 87 (85.3%) to shrimp, 27 (26.5%) to crab, 13 (12.8%) to oyster, 8 (7.8%) to squid, and 4 (3.9%) to crayfish.

The characteristics of first-ever reactions (FER) of FA were described. The median onset of reaction was 30 minutes (interquartile range (IQR) 15, 60). Of 98 patients with complete data, the vast majority (87.8%) had skin/mucosal involvement as the first recognized system involvement, followed by gastrointestinal system (6.1%). Seven patients had simultaneous multi-system involvement at the onset of the reaction. At any time after onset, nearly all patients (108/110, 98.2%) had skin/oral mucosal involvement, followed by respiratory (55/110, 50.0%), and cardiovascular (30/110, 27.3%) involvement upon the FER.

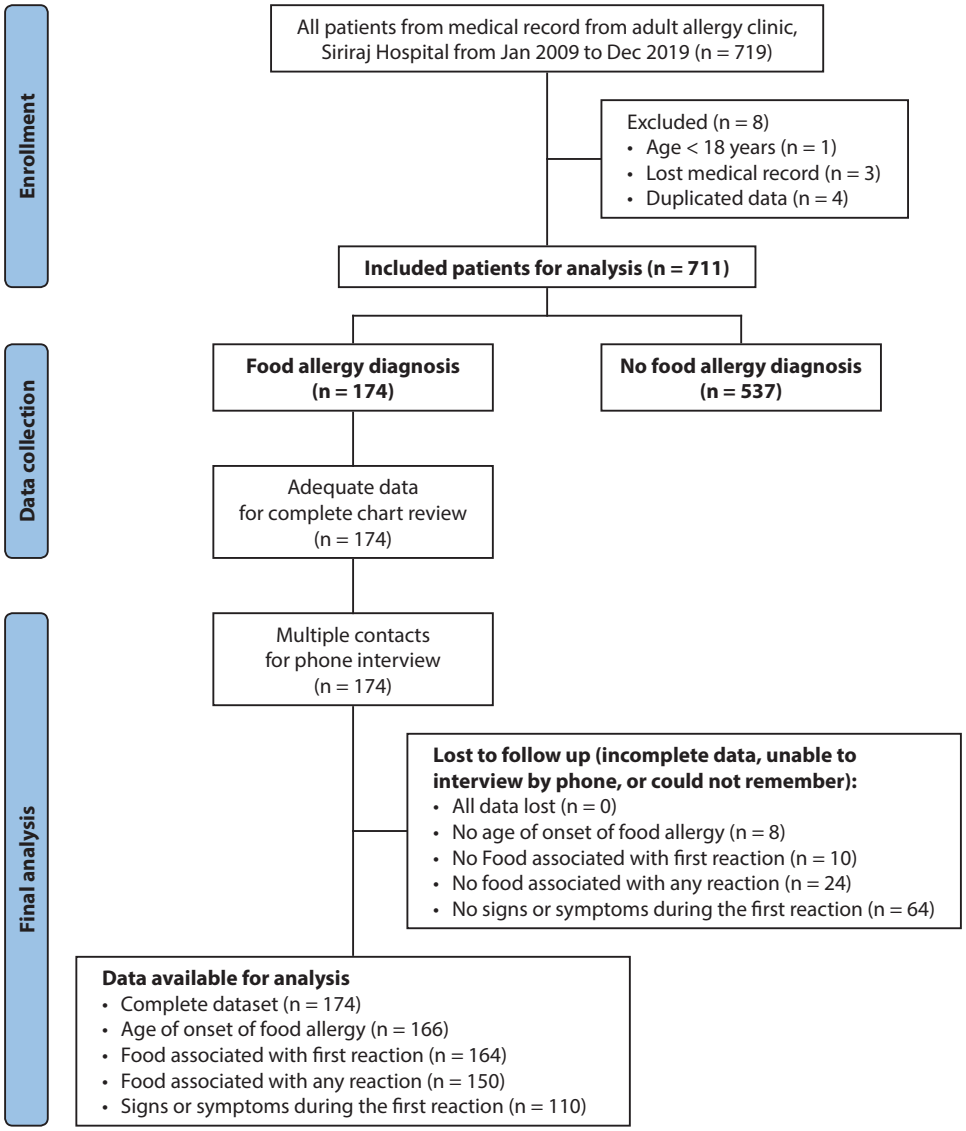


Figure 1. Flow of participants.

Table 1. Demographic and clinical characteristics of adult food allergy patients (N = 174).

Parameter	n of non-missing data	Food allergic adults (N = 174)
Male	174	51 (29.3)
Age, median (IQR), y	174	31.0 (24.0, 44.0)
Age of onset, median (IQR), y	166	25.0 (18.0, 38.0)
Multiple food allergies[a]	150	40 (26.7)
Anaphylaxis at first presentation	174	64 (36.8)
At least one anaphylaxis in life before food allergy diagnosis made	171	97 (56.7)
Multiple episodes of anaphylaxis before food allergy diagnosis made	171	76 (44.4)

Table 1. (Continued)

Parameter	n of non-missing data	Food allergic adults (N = 174)
Foods associated with any reaction		
• Shellfish	150	102 (68.0)
• Wheat	150	43 (28.7)
• Fruit and vegetables	150	15 (10.0)
• Peanut	150	6 (4.0)
• Soybean	150	4 (2.7)
• Finfish	150	4 (2.7)
• Cow's milk	150	2 (1.3)
• Pork	150	1 (0.7)

Notes:- All data are presented as n (%) unless stated otherwise.
[a]Defined as ≥ 2 structural unrelated, allergist-diagnosed food allergies.

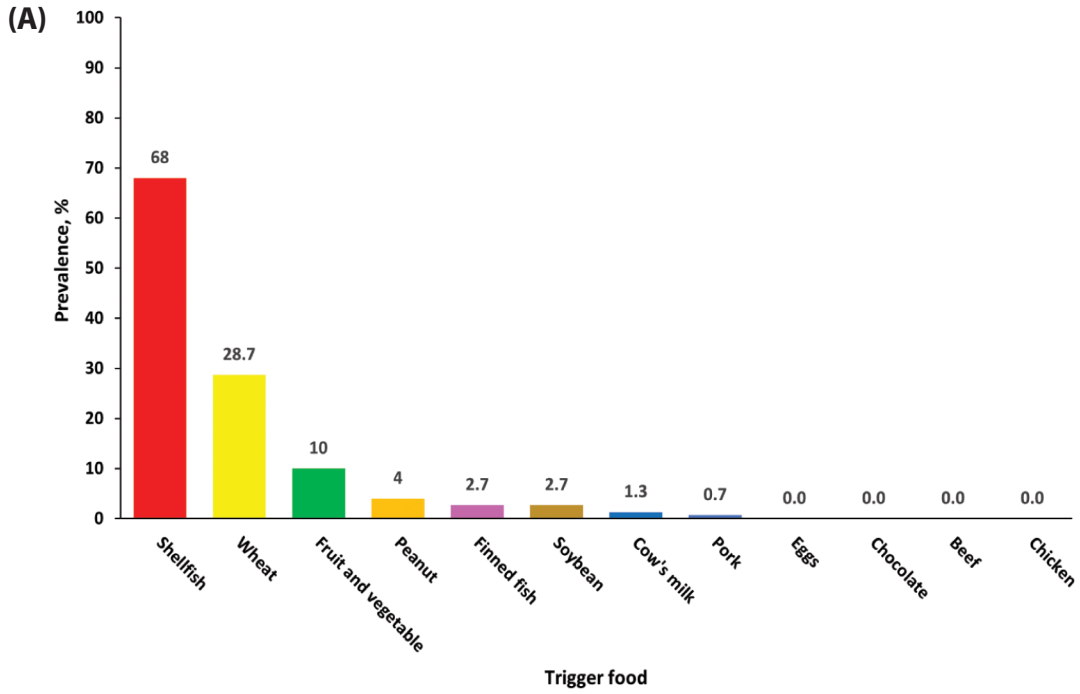


Figure 2.
(A) Prevalence of trigger foods associated with any reaction in all adult food-allergic patients (n = 150).
(B) Stacked area chart of distribution of foods associated with the first reaction stratified by age of onset (n = 157).

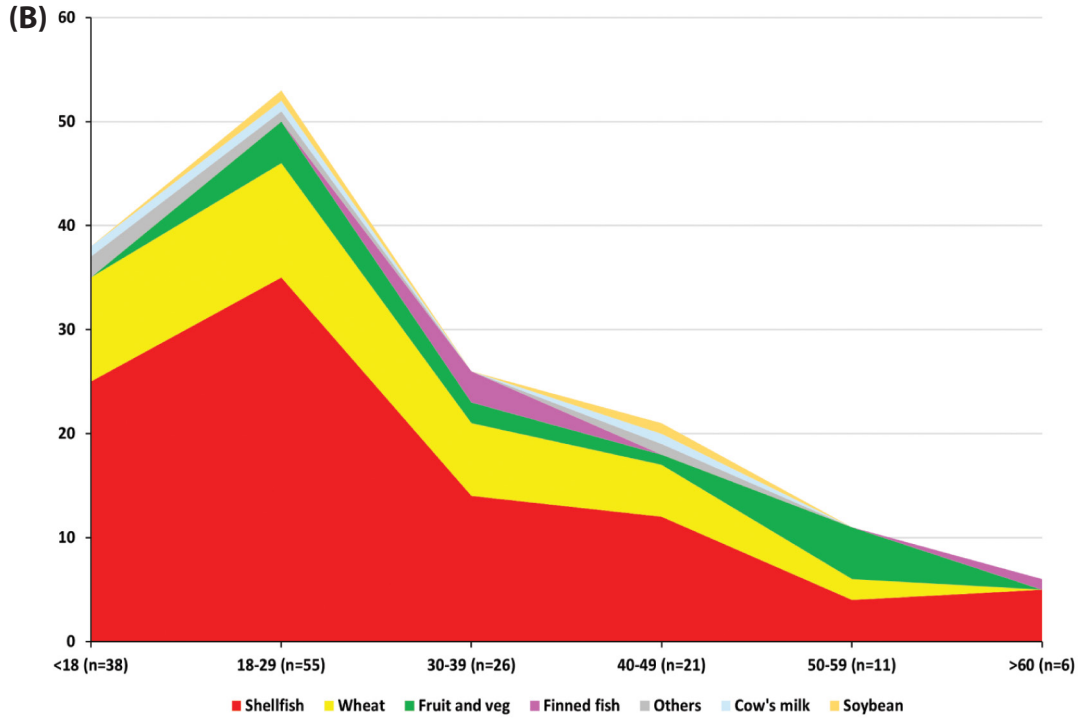


Figure 2. (Continued)

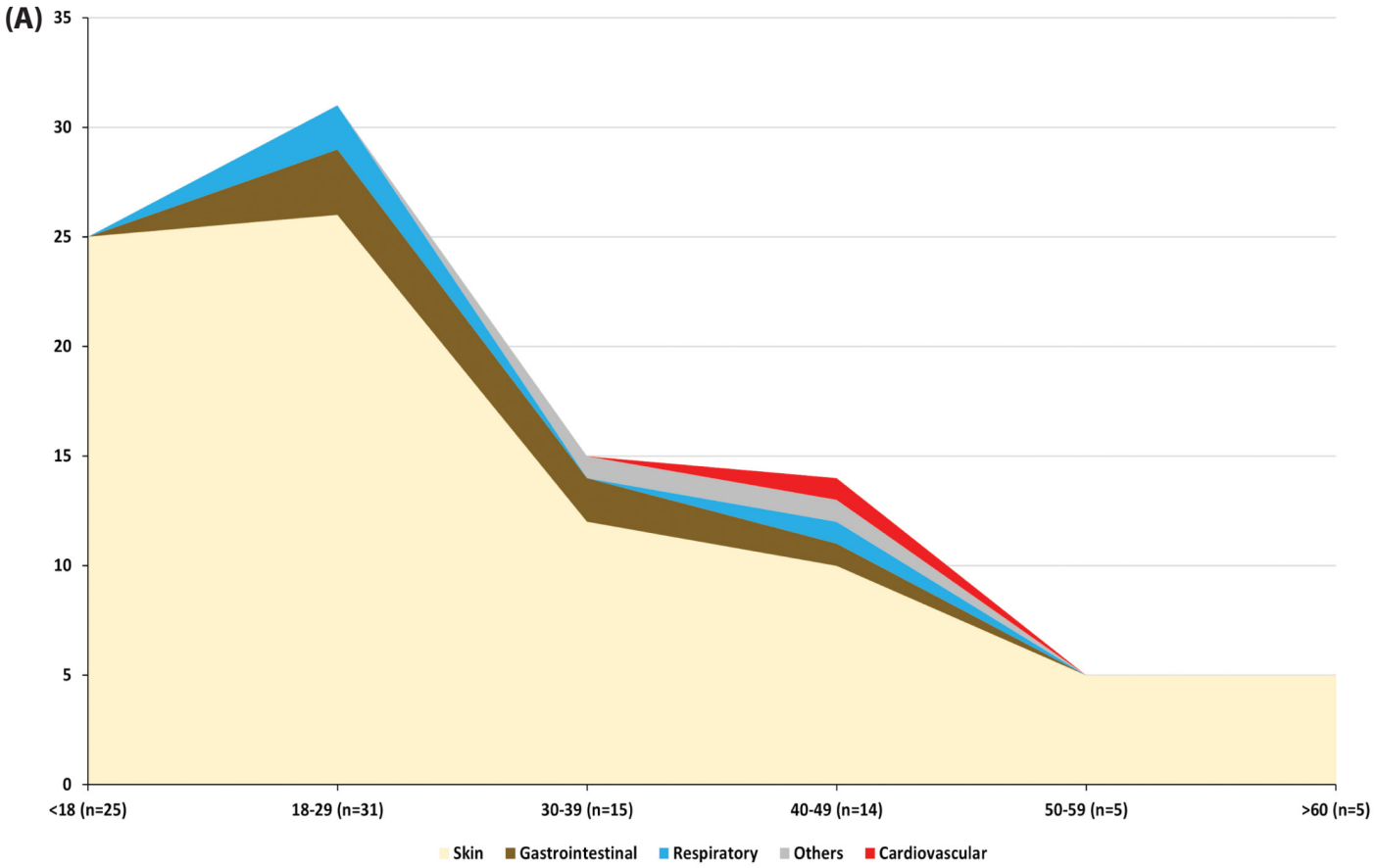


Figure 3.
(A) Stacked area chart of the first system involved in the first reaction stratified by age of onset (n = 95).
(B) Stacked area chart of the system involved in the first reaction stratified by age of onset.

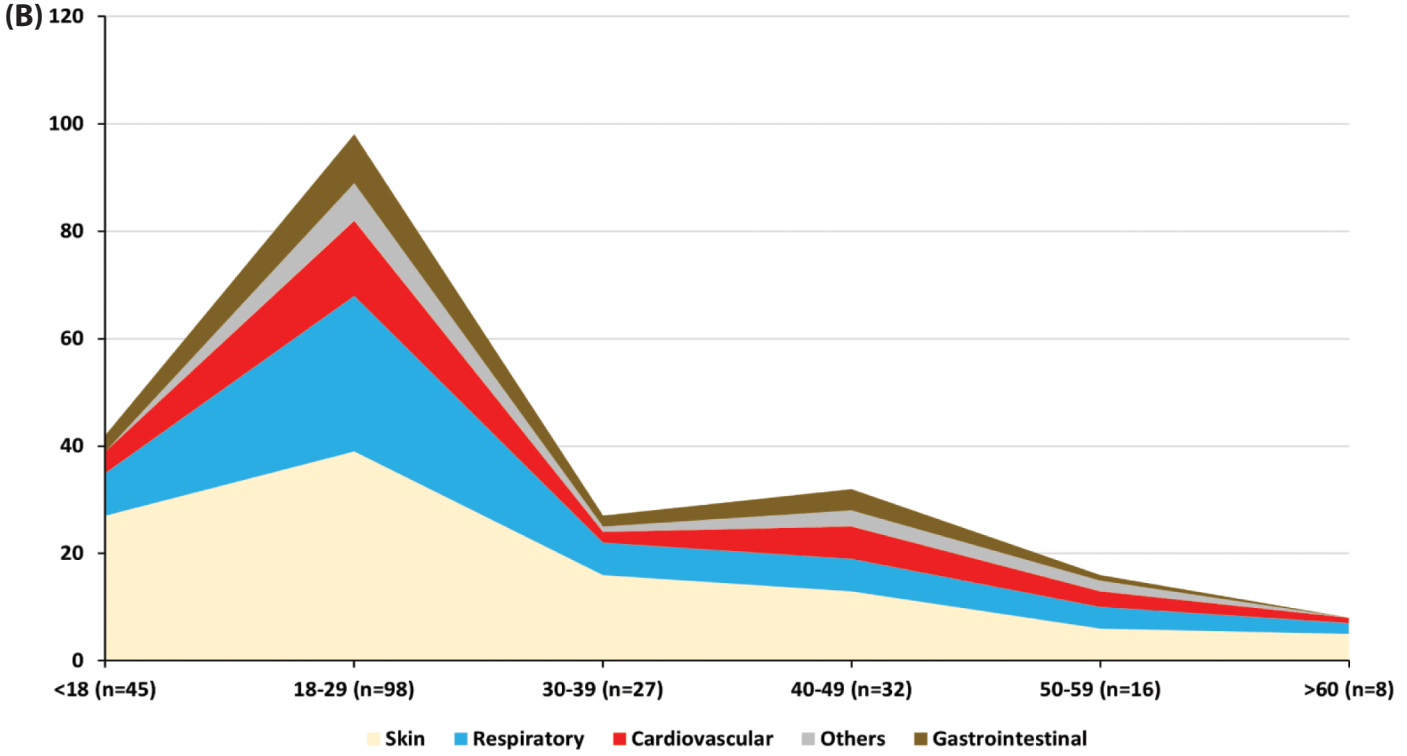


Figure 3. (Continued)

Characteristics of first-in-life reactions in adult patients with food allergy

The distribution of foods associated with the first reaction stratified by age of onset is displayed in **Figure 2B**. Shellfish ranked first in almost all age groups, followed by wheat, which had incidence up to the 5th decade of age. Notably, there were no incident cases of fruit and vegetable allergy at age of onset < 18 years while incidence occurred in adults up to the 5th decade of life. As the first recognized system in the first reaction, patients aged < 18 years and aged ≥ 50 years had exclusively skin/mucosal involvement. Those aged between 18 and 49 years old sporadically had other systems as the first recognized reaction (**Figure 3A**). Seven patients had multiple systems involvements at the onset of their first reaction, of which 6 of 7 were adult-onset. Overall ages of onset, skin/ mucosal involvement was the most common system involved during the first reaction. However, the respiratory system along with other systems was more common in most adults ages than in childhood (**Figure 3B**).

Comparison of characteristics between childhood- and adult-onset food allergy

The descriptive comparison between childhood- and adult-onset food allergy patients are shown in **Table 2**. The median age of onset was at 12.0 (7.0, 15.0 years) in childhood-onset patients and 30.0 (23.0, 42.0) years in adult-onset patients. The odds ratio comparison between a family history of food allergy and comorbidities in adult patients with childhood- or adult-onset food allergy is shown in **Table 3**. All results were non-significant except for a trend to the significance of lower odds of atopic dermatitis in adult-onset patients [odds ratio (OR) 0.32 (95% confidence interval (CI) 0.10, 1.01); p = 0.052]. Multiple imputation results on family history of food allergy and anaphylaxis before allergist's diagnosis were similar.

Comparing characteristics of first reactions, there was a trend to significance of anaphylaxis as the first reaction [OR 2.08 (95%CI 0.97, 4.75); p = 0.059]. Fruit and vegetables were significantly associated with adult-onset [OR 8.95 (95%CI 1.13, 1157); p = 0.034]. Adult-onset patients had significantly higher odds of respiratory or other systems involvement during the first reaction [OR 3.15 (95%CI 1.30, 8.25); p = 0.011 and OR 10.8 (95%CI 1.35, 1404); p = 0.019, respectively] while cardiovascular involvement showed a trend to significance [OR 2.49 (95%CI 0.88, 8.52); p = 0.086]. Multiple imputation results were similar except for cardiovascular system involvement during the first reaction, which was significant [OR 2.78 (95%CI 1.05, 9.15); p = 0.038]. Overall, atopic diseases were similar between both childhood- and adult-onset patients except for chronic urticaria (21.0% vs. 31.0%, respectively) and atopic dermatitis (15.0% vs. 6.0%, respectively). Adult-onset group had higher proportions of all non-atopic diseases than childhood-onset group. Interestingly, 5% of childhood-onset patients had dyslipidemia while 10% had other non-atopic diseases.

Table 2. Descriptive complete case analysis of the characteristics of childhood- and adult-onset food allergy patients.

Parameter	Age of onset					
	N	Pooled	n	Childhood (n = 39)	n	Adult (n = 127)
Current age, median (IQR), y	166	31.0 (24.0, 44.0)	39	24.0 (19.0, 29.0)	127	33.0 (26.0, 47.0)
Age of onset, median (IQR), y	166	25.0 (18.0, 38.0)	39	12.0 (7.0, 15.0)	127	30.0 (23.0, 42.0)
Male	166	50 (30.1)	39	15 (38.5)	127	35 (27.6)
Family history of food allergy	161	25 (15.5)	38	7 (18.4)	123	18 (14.6)
Paternal	161	11 (6.8)	38	4 (10.5)	123	7 (5.7)
Maternal	161	2 (1.2)	38	0 (0.0)	123	2 (1.6)
Sibling	161	14 (8.7)	38	3 (7.9)	123	11 (8.9)
Atopic and related disease						
Allergic rhinitis	166	105 (63.3)	39	26 (66.7)	127	79 (62.2)
Allergic conjunctivitis	166	15 (9.0)	39	3 (7.7)	127	12 (9.5)
Asthma	166	27 (16.3)	39	7 (18.0)	127	20 (15.8)
Chronic rhinosinusitis	166	7 (4.2)	39	2 (5.1)	127	5 (3.9)
Chronic urticaria	166	47 (28.3)	39	8 (20.5)	127	39 (30.7)
Drug allergy	166	26 (15.7)	39	6 (15.4)	127	20 (15.8)
Atopic dermatitis	166	13 (7.8)	39	6 (15.4)	127	7 (5.5)
Multiple anaphylaxes before diagnosis	164	76 (46.3)	39	14 (35.9)	125	62 (49.6)
At least one anaphylaxis before diagnosis	164	97 (59.2)	39	19 (48.7)	125	78 (62.4)
Characteristics of the first reaction in life						
First presentation with anaphylaxis	166	64 (38.6)	39	10 (25.6)	127	54 (42.5)
Food allergen associated with the first reaction						
Shellfish	157	95 (60.5)	38	25 (65.8)	119	70 (58.8)
Wheat	157	35 (22.3)	38	10 (26.3)	119	25 (21.0)
Fruit and vegetables	157	12 (7.6)	38	0 (0.0)	119	12 (10.1)
Cow's milk	157	3 (1.9)	38	1 (2.6)	119	2 (1.7)
Egg	157	0 (0.0)	38	0 (0.0)	119	0 (0.0)
Soybean	157	2 (1.3)	38	0 (0.0)	119	2 (1.7)
Peanut	157	2 (1.3)	38	0 (0.0)	119	2 (1.7)
Finned fish	157	4 (2.6)	38	0 (0.0)	119	4 (3.4)
Others	157	4 (2.6)	38	2 (5.3)	119	2 (1.7)
Chocolate	157	0 (0.0)	38	0 (0.0)	119	0 (0.0)
Beef	157	0 (0.0)	38	0 (0.0)	119	0 (0.0)
Chicken	157	0 (0.0)	38	0 (0.0)	119	0 (0.0)
Pork	157	0 (0.0)	38	0 (0.0)	119	0 (0.0)

Table 2. (Continued)

Parameter	Age of onset					
	N	Pooled	n	Childhood (n = 39)	n	Adult (n = 127)
The first system involved during the first reaction						
Skin or oral mucosa	95	83 (87.4)	25	25 (100)	70	58 (82.9)
Respiratory	95	3 (3.2)	25	0 (0.0)	70	3 (4.3)
Gastrointestinal	95	6 (6.3)	25	0 (0.0)	70	6 (8.6)
Cardiovascular	95	1 (1.1)	25	0 (0.0)	70	1 (1.4)
Others	95	2 (2.1)	25	0 (0.0)	70	2 (2.9)
System involved during the first reaction						
Skin or oral mucosa	108	106 (98.2)	27	27 (100.0)	81	91 (96.8)
Respiratory	108	55 (50.9)	27	8 (29.6)	81	47 (58.0)
Gastrointestinal	108	19 (17.6)	27	3 (11.1)	81	16 (19.8)
Cardiovascular	108	30 (27.8)	27	4 (14.8)	81	26 (32.1)
Others	108	13 (10.2)	27	0 (0.0)	81	13 (16.1)

Notes:- All data are presented as n (%) unless stated otherwise.

Table 3. Univariate logistic regression models comparing childhood- and adult-onset food allergy in adult food allergy patients (n = 166)

Parameter	Complete case analysis		Missing data imputation	
	Odds ratio (95%CI)	*P*-value	Odds ratio (95%CI)	*P*-value
Male	0.61 (0.29, 1.29)	0.193		
Coronary artery disease	0.94 (0.05, 137.8)	0.968		
Chronic obstructive pulmonary disease	0.94 (0.05, 137.8)	0.968		
Family history of food allergy[a]	0.74 (0.30, 1.98)	0.528	0.76 (0.31, 2.04)	0.570
Paternal	0.49 (0.15, 1.83)	0.275	0.53 (0.16, 1.96)	0.325
Maternal	1.58 (0.13, 220)	0.757	1.30 (0.11, 128)	0.892
Sibling	1.04 (0.32, 4.25)	0.955	1.12 (0.33, 4.69)	0.863
Atopic and related disease				
Allergic rhinitis	0.84 (0.39, 1.74)	0.634		
Allergic conjunctivitis	1.13 (0.36, 4.59)	0.847		
Asthma	0.83 (0.34, 2.20)	0.689		
Chronic rhinosinusitis	0.67 (0.15, 3.87)	0.623		
Chronic urticaria	1.65 (0.74, 4.06)	0.230		
Drug allergy	0.98 (0.39, 2.76)	0.972		
Atopic dermatitis	0.32 (0.10, 1.01)	0.052		
Multiple anaphylaxes before diagnosis[b]	1.73 (0.84, 3.67)	0.137	1.70 (0.83, 3.63)	0.146
At least one anaphylaxis before diagnosis[b]	1.74 (0.85, 3.58)	0.131	1.72 (0.84, 3.55)	0.137

Table 3. (Continued)

Parameter	Complete case analysis		Missing data imputation	
	Odds ratio (95%CI)	*P*-value	Odds ratio (95%CI)	*P*-value
The first reaction in life				
First presentation with anaphylaxis	2.08 (0.97, 4.75)	0.059		
Food allergen associated with the first reaction[c]				
Shellfish	0.75 (0.35, 1.58)	0.459	0.73 (0.34, 1.53)	0.410
Wheat	0.73 (0.32, 1.73)	0.468	0.66 (0.30, 1.54)	0.334
Fruit and vegetables	8.95 (1.13, 1157)	0.034*	10.0 (1.27, 1300)	0.024*
Cow's milk	0.53 (0.07, 5.94)	0.560	0.61 (0.07, 7.23)	0.667
Soybean	1.64 (0.13, 228)	0.739	1.62 (0.16, 178)	0.741
Peanut	1.64 (0.13, 228)	0.739	1.44 (0.11, 178)	0.823
Finned fish	3.00 (0.31, 401)	0.401	3.52 (0.38, 469)	0.320
Others	0.31 (0.05, 2.08)	0.212	0.33 (0.06, 2.10)	0.223
The first system involved during the first reaction[d,e]				
Skin or oral mucosa	0.09 (0.0007, 0.75)	0.020*	NC	
Respiratory	2.64 (0.24, 360)	0.478	2.17 (0.36, 60.2)	0.491
Gastrointestinal	5.14 (0.57, 679)	0.171	3.39 (0.64, 86.3)	0.184
Cardiovascular	1.10 (0.06, 163)	0.953	NC	
Others	1.86 (0.14, 260)	0.695	1.89 (0.26, 102)	0.679
System involved during the first reaction[f]				
Skin or oral mucosa	0.58 (0.004, 7.40)	0.711	0.71 (0.02, 5.61)	0.824
Respiratory	3.15 (1.30, 8.25)	0.011*	3.05 (1.36, 7.24)	0.006**
Gastrointestinal	1.76 (0.56, 7.19)	0.351	1.87 (0.64, 6.74)	0.266
Cardiovascular	2.49 (0.88, 8.52)	0.086	2.78 (1.05, 9.15)	0.038*
Others	10.8 (1.35, 1404)	0.019*	9.17 (1.28, 707)	0.022*

Notes:- Odds ratios are Firth's logistic regression penalized odds ratios. Confidence intervals are profile likelihood. [a]Missing data n = 5 (3%), [b]missing data n = 2 (1.2%), [c]missing data n = 9 (5.4%), [d]missing data = 71 (42.8%), [e]denominator n = 159 for missing data imputation models to include patient reporting only one system, [f]missing data n = 58 (34.9%).
Abbreviations: CI, confidence interval; NC, non-convergence. Significant at the > 0.05 level*, > 0.01 level**, and the < 0.001 level***.

Discussion

To the best of our knowledge, this is the first hospital-based, adult food allergy study in Thailand. The prevalence of allergist-diagnosed FA was 24.5% in our clinic. The three most common food triggers were shellfish (68.0%), wheat (28.7%), and fruits/vegetables (10.0%). Of the 166 food-allergic patients with complete data on age of onset, 76.6% were adult-onset, and 42.5% of adult-onset FA patients first presented with anaphylaxis.

Anaphylaxis during the FER was nearly twice as common in adult-onset patients compared with childhood ones. They also commonly had more non-skin/mucosal involvements. The odds of respiratory system or cardiovascular systems involvements were around 3 times and 2.8 times higher in adult-onset, compared with childhood-onset. Although cardiovascular system involvement was only trend to significance in the complete case analysis, it was significant in multiple imputation sensitivity analysis, which suggests that it is also more common in adult-onset FERs.

Adult-onset FA is an important emerging health burden. The mechanism of adult-onset FA was not fully elucidated. Oral tolerance is lost in previously tolerated patients. Current evidence suggested that adults had multiple routes of sensitization via alteration of gut, skin, and lung epithelium. Different routes of sensitization resulted in different molecular sensitization, clinical phenotypes, and possible course of the disease. Along with a period of abstention from the food allergens, after sensitization, adults might develop FA reactions to previously tolerated food.[3,20]

We observed a higher proportion of allergic rhinitis, conjunctivitis, asthma, and chronic rhinosinusitis in non-FA group. This is likely reflecting the nature of cases in our allergy clinic because respiratory allergies were the most common cases, referred to our clinic. Interestingly, allergist-diagnosed chronic urticaria (CU), was observed to be higher in FA group. The previous study generally considered food as a rare cause of CU (approximately 2% of cases).[21] Conversely, a high proportion of CU (28.7%) could be found in adults with FA. The CU prevalence is comparable to 27.8% CU prevalence in US adults with FA.[5] A recent meta-analysis showed that 37% of food-dependent exercise-induced anaphylaxis (FDEIA) patients also had concomitant CU.[22] The association between FA and CU was generally known as a multiple-morbidities concept like other atopic diseases.[23] Interestingly, these 2 diseases are mediated by mast cells. Although the recent concept showed that mast cells had distinct different subpopulations and functions,[24] there might be some shared mechanisms or common pathways which are needed to be explored in the future. Moreover, FA patients who have comorbid CU might complicate FA diagnosis in adult patients as they shared similar cutaneous manifestations. Delayed diagnosis of IgE-mediated reaction had previously been reported in a patient with CU.[25] Therefore, awareness of new-onset FA should be focused on all adult patients with food-related complaints to timely diagnose and halt possible future severe reactions.

The prevalence of food allergens in adult-onset FA is varied by region: shellfish, tree nut, and fin fish in one US allergy center from Kamdar et al.,[11] wheat, shellfish, and soy in US population-based study from Gupta et al.,[5] wheat, fish, crustaceans, fruits in Japanese adults from Ebisawa et al.[26] Recent data from European Anaphylaxis Registry reported wheat, shellfish, hazelnut, and soy.[27] The top three most prevalent trigger foods associated with any reaction in adult FA patients our study were shellfish, wheat, as well as fruits and vegetables. Our data showed that shellfish was the most common cause in both childhood and adult-onset groups. Interestingly, food allergens are not different between both adult-onset and childhood-onset FA in our study except fruits and vegetables which were observed to be 9- to 10-fold greater odds in adult-onset FA group compared with childhood-onset FA ones. However, this should be interpreted with caution as there is a small sample size in childhood-onset FA group.

In the present study, adult FA patients were more commonly sensitized to cockroach than non-FA ones, and shellfish is one of the most common trigger foods worldwide in both studies using patient self-reported FA as a definition and in studies using physician-diagnosed FA. Shellfish allergy might be secondary to sensitization to cockroach allergens.[28] Typically, tropomyosin has been reported as a cross-sensitizing allergen among patients with allergies to house dust mites, cockroaches, and shellfish.[29] However, our study was conducted as a cross-sectional retrospective study, and we did not specifically investigate the cross-reactive components. Our data showed shellfish was the most common causes in both childhood and adult-onset groups. The reasons for the development of shellfish allergy at different time points need to be investigated in future studies. The determinants and mechanisms of adult-onset FA largely remain unknown, and our results raise the possibility that it might be driven by some age-related eating habits or age-dependent determinants, such as prolonged dust mite sensitization or exposure.

Limited data exist for the prevalence of food allergy in the Asia region and studies comparing the clinical characteristic of adults FA with childhood vs adult-onset was very limited.[12,30] In our study, adult-onset FA had higher respiratory and cardiovascular involvement during their first FA presentation than the childhood-onset FA group. This is in contrast to a recent population-based, cross-sectional survey from the US, reporting that adult-onset-only FA had a less severe reaction, and lower healthcare utilization when compared to childhood-onset FA.[12] The difference could be explained by sampling bias as we collected data from the tertiary hospital, not a population-based level. FA adults with high severity are more likely to seek medical consultation or are referred to our hospital than those with mild symptoms. Moreover, the childhood-onset FA group also included patients who had both childhood-onset FA and new sensitization during adulthood which had a small sample size. Therefore, it may be less representative of generalization.

The prevalence of multiple food allergies (> 1 unrelated food allergen) was 26% among all adults with FA. Although, our result may not be directly comparable to the previous population-based studies (prevalence ranging from 17.5–77.8%),[5,31,32] multiple food allergies exist and may potentially and negatively impact on patients. The recent US population-based survey of multiple FA prevalence and characteristics revealed 4 major phenotypes of multiple FAs, using the latent class analyses (LCA), in both children and adults. These phenotypes are milk/egg dominant, seafood dominant, peanut/tree nut dominant, and a broadly multi-food-allergic group. In adults with multiple FA, allergic rhinitis was associated with a higher probability of being in the peanut/tree nut dominant group.[33] Although our study did not address this issue in detail, we look forward to seeing and understanding the phenotypes of multiple FA and its impacts on patients in our population to inform future research and interventions.

This study has several limitations. First, recall bias might occur with the nature retrospective cross-sectional study. However, our result gives reliable data on the ranking of food allergen prevalence as we used the allergists' diagnosis from our center. FA-mimicking conditions were frequently reported in adults, such as food intolerance, and a flare-up of CU, which might result in a false association between food and the occurrence of rash. Therefore, using an allergist's diagnosis would increase the validity of the diagnosis, and decrease the chance of misdiagnosis from patient-based information, unlike patient-reported surveys. Secondly, the prevalence has limited representative value and should be interpreted with caution because the denominator of the study population is patients attending the single-centered facility. The prevalence in our study might be higher than the general population as we gathered

the data from an allergy clinic where the presence of atopic background was likely higher than the general population and non-FA patients could be heterogeneous and differ from other allergy centers, thus, limiting their external validity. The data may reflect the patient characteristics in an allergy outpatient setting and may not generalize well to other settings, such as the emergency department. Thirdly, the size of the childhood-onset FA group is relatively small compared with adult-onset group. In our study, patients with both childhood- and adult-onset FA are counted in childhood-onset FA group, which had a small sample size. Therefore, it should be interpreted with caution. Fourth, although we performed missing data handling, there were relatively large proportions of missing data for the first system involved and the system involved in the first reaction in life models, so there is a greater risk of bias for these results. Fifth, results based on risk ratios are crude odds ratios and are not confounder-adjusted etiologic model estimates, which are desirable for assessments, such as adjusting results for comorbidities. This occurred because we did not have time/date stamps for establishing time dependencies between variables for good models. Finally, the sample size of the study is small. However, we chose Firth's logistic regression and profile likelihood confidence intervals in both complete case and multiple imputation models to obtain valid estimates in small sample size comparisons.

Conclusion

Shellfish, wheat, as well as fruit and vegetables were the most common trigger foods in adult FA patients. Anaphylaxis was common in the FER in adult-onset patients, and anaphylaxis was common before the allergist's diagnosis. Adult-onset FA patients also had more respiratory, cardiovascular and other systems involvements than childhood-onset ones. FA awareness, early diagnosis, and proper management are encouraged, and further studies focusing on the adult-onset food allergic patients are needed.

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Conflict of interest

All authors declare no personal or professional conflicts of interest relating to this article.

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