APJAI
Asian Pacific Journal of
Allergy and Immunology

ORIGINAL ARTICLE

Incidence, predictors, and treatment outcomes of biphasic anaphylaxis in the emergency department of a tertiary hospital: A 5-year retrospective study

Waratchaya Uawattanasakul,[1] Ploylarp Lertvipapath,[2] Thanachit Krikeerati,[3,4]* Chamard Wongsa,[3,4] Torpong Thongngarm,[3,4] Mongkhon Sompornrattanaphan[3,4]*

Abstract

Background: Biphasic anaphylaxis despite successful treatment has an incidence of 4-5% based on NIAID/FAAN criteria. Our study aimed to investigate the frequency and predictive factors associated with biphasic reactions within the emergency department (ED) at Siriraj Hospital.

Methods: This observational study assessed medical records of anaphylaxis and anaphylactic shock patients at Siriraj Hospital's ED from January 2015 to December 2019. Of these, a random sample was reviewed and validated by allergists. Telephone interviews were performed to collect more data. Uni- or biphasic response were analyzed descriptively. Prediction modeling was performed.

Results: Among 1888 ED anaphylaxis cases, 601 were randomly sampled; 239 patients completing interviews were analyzed. The incidence of biphasic reactions was 7.1% (17/239) of cases. Common triggers of biphasic responses were foods (57.7%), drugs (31%), other known allergens (5.9%). Shellfish, edible insects, and wheat were the leading food triggers. Biphasic responses were significantly associated with history of drug allergy, any allergic disease, allergic rhinitis, number of prior anaphylactic reactions, angioedema, less generalized erythema, less reaction to shellfish, reaction to NSAIDs, and no epinephrine giving at ED visit (all $p < 0.1$). From a 3-predictor prognostic model including drug/idiopathic reaction, duration from onset to first epinephrine > 60 minutes, and any cutaneous edema/angioedema with an area under the curve of 0.72 (95%CI 0.54, 0.90).

Conclusions: The incidence of biphasic response was 7.1%. Predictors of biphasic response were drug/idiopathic reaction, any cutaneous edema/angioedema, and time from onset to first epinephrine > 60 minutes.

Key words: Anaphylaxis, Asia-Pacific, Biphasic anaphylaxis, Drug allergy, Emergency department, Food allergy, Prevalence, Risk factors

Citation:
Uawattanasakul, W., Lertvipapath, P., Krikeerati, T., Wongsa, C., Thongngarm, T., Sompornrattanaphan, M. (2026). Incidence, predictors, and treatment outcomes of biphasic anaphylaxis in the emergency department of a tertiary hospital: A 5-year retrospective study. *Asian Pac J Allergy Immunol*, 44(2), 351-361. https://doi.org/10.12932/ap-101223-1745

Affiliations:
[1] Inpatient Pharmacy Division, Department of Pharmacy, Faculty of Medicine, Siriraj Hospital, Bangkok, Thailand
[2] Adverse Drug Reaction Unit, Division of Academic Affairs, Department of Pharmacy, Siriraj Hospital, Mahidol University, Bangkok, Thailand
[3] Division of Allergy and Clinical Immunology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand
[4] Faculty of Medicine Siriraj Hospital, Center of Research Excellence in Allergy and Immunology, Mahidol University, Bangkok, Thailand, certified by the WAO Centers of Excellence (COE)

* These authors are an essentially intellectual contributors (EIC) of this work.

Corresponding author:
Mongkhon Sompornrattanaphan
Division of Allergy and Clinical Immunology, Department of Medicine
Faculty of Medicine Siriraj Hospital, Mahidol University,
Bangkok 10700, Thailand
E-mail: mongkhon.som@mahidol.ac.th, bankallergymed@gmail.com

Abbreviation:

ED,	emergency department
FAAN	the Food Allergy and Anaphylaxis Network
ICD-10	International Classification of Diseases and Related Health Problem 10th Revision
JTFPP	the Joint Task Force on Practice Parameters
NSAIDs	non-steroidal anti-inflammatory drugs
WDEIA	wheat-dependent exercise-induced anaphylaxis

Introduction

Anaphylaxis represents a severe and life-threatening immediate hypersensitivity reaction, manifesting as the most severe end of the allergic reaction spectrum. As a global public health problem, anaphylaxis can be triggered by various substances, including food, insect venom, and medications such as the beta-lactam group and non-steroidal anti-inflammatory drugs (NSAIDs).[1] In Europe, the incidence of anaphylaxis ranges from 1.5 to 7.9 cases per 100,000 person-years.[2] In Asia, diverse incidence rates have been observed, including 2.3 cases per 100,000 person-years in Korea,[3] 4.68 cases per 100,000 person-years in Hong Kong.[4] Additionally, Taiwan reports an incidence, ranging from 12.71 to 13.23 cases per million population.[5]

Biphasic anaphylaxis is recurrence of symptoms within 72 hours after initial anaphylactic event, without additional exposure to allergen.[1,6] The prevalence of biphasic anaphylaxis has garnered considerable attention due to its variation in reported rates, ranging from less than 1% to 20% among patients. Notably, recent studies adopting the diagnostic criteria endorsed by the National Institute of Allergy and Infectious Diseases (NIAID) and the Food Allergy and Anaphylaxis Network (FAAN), or analogous criteria, have yielded more refined estimates. These contemporary investigations have revealed a narrower range of biphasic reaction rates, predominantly converging around 4% to 5%.[6]

The recent findings from the Joint Task Force on Practice Parameters (JTFPP) suggest an elevated risk of biphasic anaphylaxis associated with factors such as anaphylaxis triggered by an unknown source, drug-induced anaphylaxis in patients under 18 years of age, cutaneous manifestations, wide pulse pressure, severe initial anaphylaxis, anaphylaxis in pediatric patients treated with glucocorticoids, and requiring multiple doses of epinephrine.[6] Nonetheless, these conclusions are based on evidence of very low certainty derived from a range of retrospective observational studies characterized by varying sample sizes. These studies display a moderate to high degree of bias due to limitations, including the utilization of retrospective data, exclusions stemming from missing data, and constraints related to limited patient populations. However, the JTFPP suggests that clinicians consider integrating the severity of the initial anaphylaxis presentation and/or the use of multiple doses of epinephrine during treatment as indicators for assessing a patient's potential risk of developing biphasic anaphylaxis.[6]

Enhancing our comprehension of biphasic reaction frequency, potential severity, and related risk factors could aid emergency healthcare providers in gauging the necessity for post-anaphylactic reaction observation, thereby reducing unnecessary healthcare utilization. Therefore, we aimed to describe the incidence of biphasic reactions within the emergency department (ED) at Siriraj Hospital along with the factors that can predict their onset. Additionally, we describe the clinical manifestations of biphasic anaphylaxis and the real-world management strategies performed by the ED physicians.

Methods

Study design

The study was designed as a retrospective observational study covering the period from January 2015 to December 2019. Information about drugs administered and treatments provided was abstracted from the medical records of patients diagnosed with anaphylaxis and anaphylactic shock at the emergency room (ER) of Siriraj Hospital. The research protocol received ethical approval from the Siriraj Institutional Review Board (SIRB) [COA no. Si 177/2020, protocol no. 841/2562(IRB4)] Patients participating in the study provided informed consent via telephone. The study was conducted in accordance with the Declaration of Helsinki.

Participants

Diagnoses were assigned based on the guidelines outlined in the 10th Revision of the International Classification of Diseases and Related Health Problems (ICD-10). Our study focused on patients who had received a diagnosis within the specified timeframe of January 1, 2015, to December 30, 2019, and had sought medical attention in the emergency room (ER). The diagnostic codes utilized for inclusion were T780, T781, T782, and T886, as stipulated by the ICD-10 classification system. Cases involving patients diagnosed with anaphylaxis and anaphylactic shock at other medical facilities (referred cases) were deliberately excluded from our analysis. Additionally, patients who declined participation in telephone interviews were also not included in the study.

Patient data, including clinical histories and treatment records, were extracted from the medical record system (SI enterprise). We supplemented this information by conducting telephone interviews with patients using a standardized form and trained interviewers, ensuring a comprehensive understanding of cases involving biphasic anaphylaxis. The accuracy of the collected data was validated by allergists.

Definition of terms

After identifying subjects using the ICD-10 coding system, anaphylaxis diagnoses were made by allergists following the NIAID/FAAN diagnostic criteria.[7] Biphasic reactions were defined as any adverse reactions compatible with mast cell mediator release occurring within 72 hours after the complete resolution of the initial anaphylactic response, without exposure to additional allergens. Biphasic anaphylaxis, on the other hand, referred to biphasic reactions that also met the NIAID/FAAN diagnostic criteria. For the final analysis, patients with comprehensive datasets were divided into two groups: (1) the uniphasic group consisting of patients who did not experience any biphasic reactions, and (2) the biphasic group comprising

patients who exhibited any form of biphasic reactions. We incorporated the definition of severe anaphylaxis as hypoxia, hypotension, or neurologic compromise, defined by cyanosis or pulse oximetry ≤ 92% at any time, hypotension (SBP < 90 mmHg in adults), confusion, collapse, loss of consciousness, and incontinence, following the criteria set forth by Brown SG 2004.[8]

Retrospective chart review

Diagnoses for cases without post-ED allergist consultations were determined from medical records by allergists who identified potential allergens; discrepancies were resolved through discussion. Simple cases, such as anaphylaxis from known triggers (e.g., allergen immunotherapy, specific foods), were directly attributed, whereas multifaceted meal exposures were classified as "complex food" incidents. For cases undergoing allergist evaluation, confirmation used allergology tests (skin, prick-to-prick, specific IgE, basophil activation tests), with Omega-5-gliadin-specific IgE testing for suspected WDEIA or unidentified triggers, prior to considering a diagnosis of unknown or idiopathic anaphylaxis.

Statistical analyses

Descriptive statistics are presented, including categorical data displayed as frequencies (%) and continuous data expressed as mean [standard deviation (SD)] or median [interquartile range (IQR)] as appropriate. Statistical comparisons were conducted using t-tests or Mann-Whitney U-tests for continuous variables, as well as Chi-squared tests or Fisher exact tests for categorical variables, based on their relevance. Additionally, univariate analysis was carried out by logistic regression.

To develop a prognostic clinical prediction model designed to predict outcomes during the initial phase of anaphylactic reaction management, we faced limitations due to a scarcity of available biphasic anaphylaxis events. In response, we pre-selected predictors for inclusion in the full model approach to predictor selection. Notably, we intended to select time from onset to the initial administration of epinephrine as a predictor. Consequently, our sample size was constrained to patients possessing complete data for these two variables, and individuals who did not receive epinephrine during their emergency department visit were excluded from consideration. To determine the appropriate number of predictors for selection, we conducted a sample size analysis following the guidelines outlined by Riley et al. in 2019.[9]

Sample size calculation

The approach used for calculating the sample size in the clinical prediction model serves to prevent the potential inflation of optimistic outcomes within the development cohort model. This is achieved by determining the maximum degrees of freedom required to integrate predictors into the model while striving for a consistent heuristic shrinkage factor of ≥ 0.9. Additionally, this strategy is guided by the criteria of maintaining a minimal absolute difference of ≤ 0.05 in both apparent Nagelkerke's R2 and adjusted Nagelkerke's R2 values, along with a margin of error of ≤ 0.05 in overall risk estimates. With an estimated prevalence of 14%[6] and c-statistic of 0.79[10] and a sample size of 189 patients with complete data on time to first epinephrine, a 3-predictor model was feasible to ensure the robustness and dependability of our predictive modeling approach. These calculations were performed using the R package pmsampsize.

Results

A total of 1888 participants were initially enrolled based on ICD-10 criteria (codes T780, T781, T782, T886) from the Emergency Department (ED) of Siriraj Hospital, spanning from January 1, 2015, to December 31, 2019. Out of these, 601 cases were selected through a process of simple random sampling and subsequently validated by allergists. This validation process led to the identification of 400 verified cases, which were then subjected to further phone interviews. Eventually, comprehensive phone interviews were completed for 239 cases. Among these cases, 222 were classified into the uniphasic group, while the remaining 17 were classified into the biphasic group. The study patient flowchart is displayed in **Figure 1**.

Demographic data

Patient baseline characteristics and causes of anaphylaxis are summarized in **Table 1**. The median age upon recruitment was 35 years IQR (22.0, 56.0). 156 of 239 (65%) were female, and within this subgroup, only 1.3% were pregnant at the time when anaphylaxis episode occurred. More than 50% of the patients had history of allergic disease, including food allergies (28.5%), allergic rhinitis (23%), and drug allergies (13%). Notably, 30 out of 236 patients (12.6%) had experienced previous episodes of anaphylaxis. The mean ± SD number of previous anaphylaxis was 0.26 ± 1.07. Food-induced anaphylaxis was the primary cause, accounting for 57.7% (138/239) of cases, followed by drug-induced anaphylaxis at 31% (74/239). Of 138 patients experiencing food-induced anaphylaxis, shellfish stood as the most common trigger (33.1%), followed by edible insects (5.8%), and wheat (2.1%). In 16.3% of food-associated anaphylaxis cases, the triggers were identified as mixed or complex foods. Due to incomplete diagnostic evaluations in these patients, the offending allergens could not be determined. The causes of anaphylaxis related to drugs were NSAIDs (6.7%), beta-lactam antibiotics (4.2%), and non-beta-lactam antibiotics represented (2.1%).

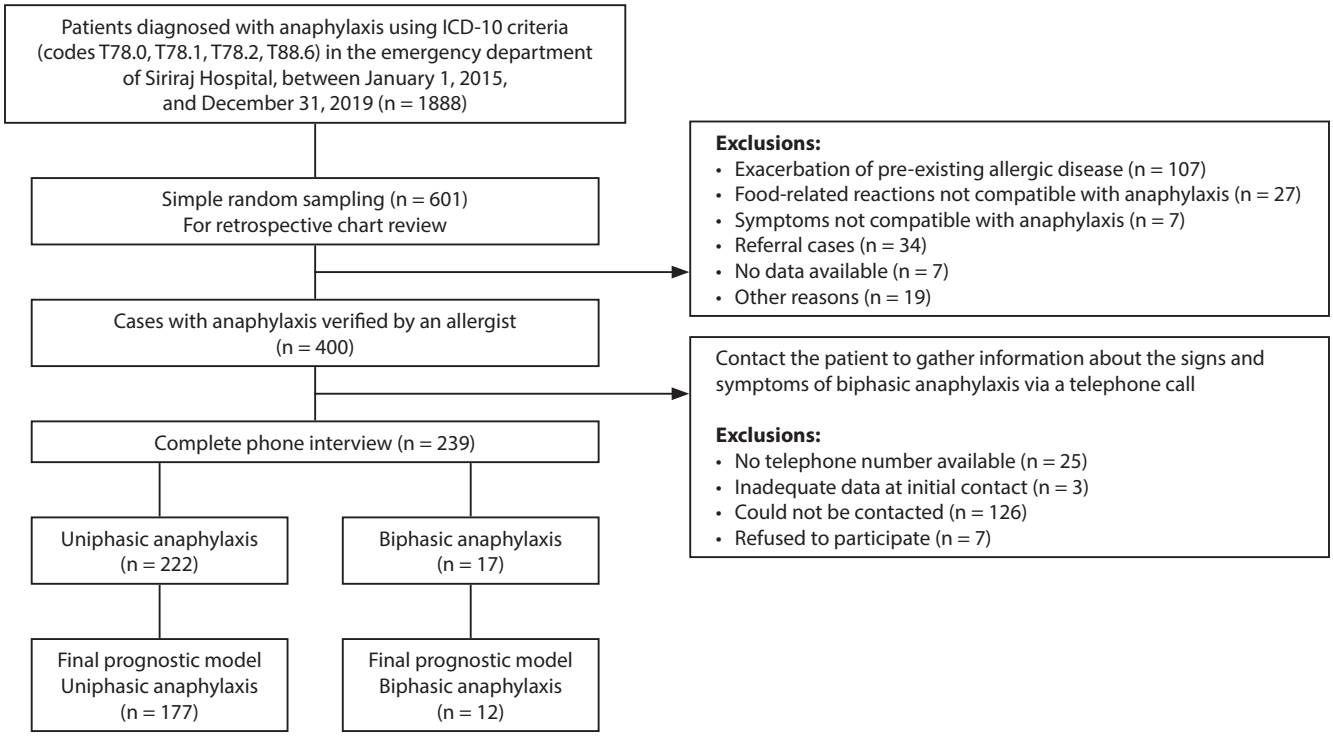

Figure 1. Flow diagram of the study selection process.

Abbreviation: ICD-10, International Classification of Diseases and Related Health Problem 10th Revision

Table 1. Patient baseline characteristics and causes of anaphylaxis.

Characteristic	Total	Total (N = 239)
Age at the event, median (interquartile), y	239	35.0 (22.0, 56.0)
Age at the event (categorical data)		
• < 18 y		34 (14.4)
• 18 to 34 y		83 (35.0)
• 35 to 54 y		54 (22.8)
• ≥ 55 y		66 (27.9)
Female sex	239	156 (65.3)
Pregnancy	156	2 (1.3)
Atopic comorbidities	239	131 (54.8)
• Any history of food allergy	239	68 (28.5)
• Any drug allergy	239	31 (13.0)
• Allergic rhinitis	239	55 (23.0)
• Asthma	239	26 (10.9)
• Atopic dermatitis	239	9 (3.8)
Any previous history of anaphylaxis	239	30 (12.6)
• Number of episode among patients with previous anaphylaxis (mean ± SD)	30	2.09 ± 1.64
Number of previous anaphylactic reactions, mean ± SD	239	0.26 ± 1.07

Characteristic	Total	Total (N = 239)
Cause of anaphylaxis		
Food	239	138 (57.7)
• Shellfish	239	79 (33.1)
• Edible insects	239	14 (5.8)
• Wheat	239	5 (2.1)
• Fruit/vegetable	239	1 (0.4)
• Mixed food component or incomplete investigation	239	39 (16.3)
Drug	239	74 (31.0)
• NSAIDs	239	16 (6.7)
• Antibiotic	239	15 (6.3)
- Beta-lactams	239	10 (4.2)
- Non-beta-lactams	239	5 (2.1)
• Other drugs	239	48 (20.1)
Other known cause	239	14 (5.9)
Unknown or idiopathic	239	10 (4.2)
React to drug or idiopathic	239	84 (35.2)

Abbreviation: NSAIDs, non-steroidal anti-inflammatory drugs; SD, standard deviation; y, year

Anaphylactic events

Thirty-seven patients (15.8%) experienced severe anaphylaxis according to the Brown SG 2004 classification. Initial ED visits revealed hypotension in 29 patients (12.3%). **Table 2** provides details of anaphylaxis manifestation and management in emergency department. Predominant clinical manifestations included the cutaneous system (95.4%), respiratory system (81.6%), and gastrointestinal system (44.4%). Cardiovascular system involvement was present in 20.5% (49 patients). More than half of the patients experienced a time interval exceeding 60 minutes between the onset of reaction and the initial epinephrine administration. Median (IQR) time from the onset of the reaction to epinephrine administration was 74.3 minutes (41.5, 131.1), whereas the median (IQR) time from ED arrival to first epinephrine was 10.9 minutes (4.4, 21.8). Only 8.7% (17 of 196) experienced a duration exceeding 60 minutes between ED arrival and first epinephrine dose. Epinephrine (90.8%) and corticosteroids (87.9%) were the most frequently administered treatments for anaphylaxis.

Table 2. Anaphylaxis manifestation and management in emergency department.

Characteristic	Total	Total N = 239
Severe anaphylaxis[a]	234	37 (15.8)
Parameter measured at initial ED visit		
• HR, median (IQR), min^{-1}	237	94 (82, 110)
• Systolic blood pressure, median (IQR), mmHg	236	123.5 (107, 143)
• Hypotension	235	29 (12.3)
• Diastolic blood pressure, mean ± SD, mmHg	236	72.6 ± 1.23
• Pulse pressure, median (IQR), mmHg	236	49.5 (39.0, 60.0)
• Wide pulse pressure at emergency department[b]	235	29 (12.3)
• RR, median (IQR), min^{-1}	223	22.0 (20.0, 24.0)
• SpO_2, median (IQR), %	234	98 (96, 99)
Initial signs and symptoms		
Any mucocutaneous sign or symptom	239	228 (95.4)
• Urticaria	239	137 (57.3)
• Angioedema (eyelids or lips)	239	106 (44.4)
• Face swelling	239	10 (4.2)
• Face erythema	239	15 (6.3)
• Generalized erythema	239	76 (31.8)
Any respiratory sign or symptom	239	195 (81.6)
• Dyspnea	239	146 (61.1)
• Chest pain	239	121 (50.6)
• Hoarseness	239	4 (1.7)
• Lung wheezing	239	63 (26.4)
Any gastrointestinal sign or symptom	239	106 (44.4)
• Vomiting	239	58 (24.3)
• Nausea	239	48 (20.1)
• Stomachache	239	41 (17.2)
• Diarrhea	239	37 (15.5)
Any cardiovascular system sign or symptom	239	49 (20.5)
• Dizziness	239	21 (8.8)
• Syncope	239	16 (6.7)
• Palpitation	239	13 (5.4)
• Hypotension	236	29 (12.3)
• Tachycardia	239	72 (30.1)
Duration		
• From onset of reaction to first epinephrine, median (IQR), min	189	74.3 (41.5, 131.1)
• Duration > 60 minutes between onset and first epinephrine	189	121 (64.0)
• From ED arrival to first epinephrine median (IQR), min	196	10.9 (4.4, 21.8)
• Duration > 60 minutes between ED arrival and first epinephrine	196	17 (8.7)
Agents administered at the emergency department		
Epinephrine		
• Giving epinephrine at ED	239	217 (90.8)
• Need ≥ 2 dose of epinephrine	238	15 (6.3)
• Intravenous epinephrine (non-cardiac arrest)	239	1 (0.4)
Bronchodilator, n (%)	239	54 (22.6)
Corticosteroid, n (%)	239	210 (87.9)

Abbreviation: ED, emergency department; IQR, interquartile range; SpO_2. Pulse oximetry
Note: [a]According to Brown SG, 2004 classification[8]; [b]defined as diastolic blood pressure ≤ one-half of systolic blood pressure

Biphasic reaction versus uniphasic reaction

Of 239, 17 cases (7.1%) experienced biphasic reaction. Median (range; min.-max.) time of biphasic reaction was 15 hours (6.2-47.6). **Table 3** compares between uniphasic and biphasic reactions. Univariate analysis demonstrated that patients with biphasic anaphylactic reactions had significantly more history of drug allergies [OR 3.14 (95%Cl 1.02, 9.63)] and allergic rhinitis [OR 3.31 (95%Cl 1.21, 9.04)], higher number of previous anaphylactic episodes [OR 1.34 (95%Cl 1.03, 1.74)], and more eyelid edema [OR 3.81 (95%Cl 1.39, 10.5) (all $p < 0.05$). Anaphylaxis causes in the biphasic group significantly tended to be drug-related or idiopathic [OR 2.86 (95%Cl 1.05, 7.81); $p = 0.04$]. Patients who did not receive epinephrine [OR 3.49 (95%Cl 1.03, 11.8); $p = 0.045$] were significantly more susceptible to biphasic reactions. Additionally, a significantly greater proportion of those receiving the initial epinephrine dose [OR 0.29 (95%Cl 0.08, 0.97), $p = 0.045$] were less prone to biphasic reactions.

3-predictor prognostic model of biphasic anaphylaxis

Table 4 shows a 3-predictor prognostic model of biphasic anaphylaxis by log odds linear including reaction related to drug/idiopathic cause, duration from onset to first epinephrine > 60 minutes, and any cutaneous edema/angioedema. Presence of all predictors had a predicted probability of biphasic response of 21.3% [area under the curve of 0.72 (95%CI 0.54, 0.90)].

Table 3. Univariate analysis of biphasic reaction.

Characteristic	Uniphasic group (n = 222)	Biphasic group (n = 17)	Odds ratio (95%CI)	*P*-value
Previous history				
• Any drug allergy	26 (11.7)	5 (29.4)	3.14 (1.02, 9.63)	0.045*
• Allergic rhinitis	47 (21.2)	8 (47.1)	3.31 (1.21, 9.04)	0.02*
• Number of previous anaphylactic reactions, median (IQR)/mean ± SD, n	0 (0, 0) / 0.21 ± 0.86	0 (0, 0) / 0.94 ± 2.54	1.34 (1.03, 1.74)	0.03*
Present anaphylactic episode characteristics				
• Eyelid angioedema	42 (18.9)	8 (47.1)	3.81 (1.39, 10.5)	0.009*
• Severe anaphylaxis[a]	36 (16.5)	1 (6.3)	0.34 (0.04, 2.63)	0.30
• Anaphylaxis with hypotension	28 (12.8)	1 (5.9)	0.79 (0.17, 3.63)	0.76
Cause of anaphylaxis				
• React to drug or idiopathic	74 (33.3)	10 (58.8)	2.86 (1.05, 7.81)	0.04*
Epinephrine status in ED				
• First dose of epinephrine given (%)	204 (91.9)	13 (76.5)	0.29 (0.08, 0.97)	0.045*
• Duration > 60 minutes between onset and first epinephrine	112 (63.3)	9 (75.0)	1.74 (0.46, 6.66)	0.42
• Received ≥ 2 dose of epinephrine	14 (6.3)	1 (5.9)	0.93 (0.11, 7.52)	0.95

Abbreviation: ED, emergency department; IQR, interquartile range; SpO_2. Pulse oximetry

*p-value < 0.05

[a]According to Brown SG, 2004 classification[8] which included hypoxia, hypotension, or neurologic compromise, defined by cyanosis or pulse oximetry ≤ 92% at any time, hypotension (SBP < 90 mmHg in adults), confusion, collapse, loss of consciousness, and incontinence

Table 4. Predicted probabilities of biphasic anaphylaxis by log odds linear combinations of predictors in the 3-predictor prognostic model. (n = 189)

Reaction to either drug or idiopathic reaction	Duration from onset to first epinephrine > 60 min	Any cutaneous edema or angioedema	Predicted probability of biphasic reaction
Yes	Yes	Yes	21.3%
Yes	Yes	No	8.5%
Yes	No	No	4.6%
No	Yes	Yes	6.2%
No	No	Yes	3.4%
No	Yes	No	2.2%
No	No	No	1.1%

Table 5. Clinical characteristics of patients experiencing biphasic reaction. (n = 17)

No	Age (year)	Sex	Comorbidities	Trigger	Initial symptoms	Treatment at ED	Time to Biphasic reaction (hour)	Biphasic symptoms	Hospital Revisit	Severity of biphasic reaction, compared with initial reactiona	Self-administered treatment/ treatment given
1	36	M	AR, Asthma	Unverified Drugs (NSAIDs, Roxithromycin)	Perioral AE, Facial edema, Bronchospasm, Nasal congestion and discharge, Nausea, Vomiting	EPI H1AH H2AH CS	7.5	Dyspnea	Yes	Milder	H1AH
2	53	F	Gallstone, Adenomyosis	Unverified Drugs (Metronidazole, Ciprofloxacin)	Urticaria, Dyspnea, Hypotension	H2AH H1AH CS	NA	Urticaria, Pruritus, Dyspnea	Yes	Similar	H1AH
3	68	F	Unverified FA	Food (Uninvestigated)	Urticaria, Periorbital and perioral AE, Facial edema, Dyspnea	H1AH CS	12.42	Rash, Mouth edema	No	Milder	H1AH
4	29	F	AR, Urticaria	Food (Fish)	Urticaria, Periorbital AE, Dyspnea, Chest pain, Diarrhea	EPI H1AH CS H2AH	NA	Urticaria, Periorbital AE, Dyspnea, Chest pain, Diarrhea	Yes	Similar	H1AH EPI
5	11	M	AR, Asthma, Verified Multiple FA (Shellfish, wheat, soy, peanut)	Food (Uninvestigated)	Urticaria, Periorbital AE, Dyspnea, Chest pain	Self-inject EPI H1AH CS	NA	Urticaria, Facial edema, Mouth edema, Dyspnea	No	Similar	H1AH
6	61	F	Endometrium cancer	Drugs (NSAIDs)	Pruritus, Periorbital and perioral AE, Tachypnea	EPI H1AH	NA	Mouth edema, Dyspnea, Chest pain	No	Milder	None
7	41	F	Urticaria	Idiopathic	Urticaria, Periorbital AE, Pruritus, Dyspnea	EPI CS	NA	Urticaria, Pruritus, Dyspnea	No	Milder	H1AH
8	39	F	Unverified FA	Food (Edible insect)	Generalized erythema, Pruritus, Periorbital AE, Abdominal pain, Diarrhea	EPI H1AH CS	NA	Pruritus, chest pain, numbness	No	Milder	H1AH
9	32	F	Urticaria	Idiopathic	Urticaria, Periorbital AE, Facial edema, Dyspnea, Chest pain, Palpitation Diarrhea, Nasal congestion	EPI H1AH CS H2AH	13	Pruritus, Facial edema, Chest pain	No	Milder	H1AH

Asian Pac J Allergy Immunol 2026;44:351-361 DOI 10.12932/AP-101223-1745

Table 5. (Continued)

No	Age (year)	Sex	Comorbidities	Trigger	Initial symptoms	Treatment at ED	Time to Biphasic reaction (hour)	Biphasic symptoms	Hospital Revisit	Severity of biphasic reaction, compared with initial reactiona	Self-administered treatment/ treatment given
10	32	F	None	Food (Uninvestigated, possible shrimp)	Globus sensation, Chest pain, Palpitation, Tachypnea, Numbness	H1AH CS	20	Periorbital AE, Dyspnea, Chest pain, Palpitation	Yes	Milder	H1AH
11	71	F	AR, Asthma, Unverified FA and DA, Bronchiectasis	Food (Uninvestigated, possible shrimp)	Rash, Pruritus, Facial edema and erythema, Bronchoconstriction Perioral AE, Dyspnea	EPI H1AH CS H2AH	47.62	Rash, Pruritus, dizziness	No	Milder	H1AH
12	29	F	Unverified DA (Penicillin)	Unverified Drug (Ciprofloxacin)	Urticaria, Periorbital AE, Chest pain, Nausea, Globus sensation	EPI H1AH CS	17	Urticaria, Eyelid edema, Dyspnea	No	Milder	H1AH
13	21	F	None	Unverified Drug (Cephalexin)	Urticaria, AE, Pruritus, Dyspnea, Chest pain, Dizziness	EPI H1AH H2AH CS	34.83	Pruritus, Dyspnea, Dizziness	No	Similar	H1AH
14	8	M	AR	Drugs (NSAIDs)	Periorbital AE, Bronchoconstriction, Dyspnea, Vomiting	EPI H1AH H2AH CS Hospitalized	8.5	Urticaria, Periorbital AE, Dyspnea, Bronchoconstriction	NA	Worse	EPI H1AH CS
15	30	M	None	Food (Uninvestigated)	Urticaria, Dyspnea, Vomiting	EPI H1AH H2AH CS	43.95	Urticaria, Generalized erythema, Dyspnea, Vomiting	Yes	Similar	H1AH CS
16	25	F	Unverified FA	Food (Uninvestigated)	Dyspnea, Chest pain, Nausea, Vomiting, Bronchoconstriction	EPI H1AH CS	12.17	Dyspnea, Dizziness, Vomiting	No	Milder	H1AH
17	32	F	AR, Multiple FA (Wheat, Shellfish), MDH	Drugs (Subcutaneous allergen immunotherapy)	Dyspnea, Nausea, Vomiting, Abdominal pain, Urticaria, Generalized erythema, Hypotension	EPI H1AH CS Hospitalized	6.17	Chest pain, Tachycardia, Numbness	NA	Similar	EPI H1AH CS

Abbreviations: AE, angioedema; AR, allergic rhinitis; CS, corticosteroids; DA, drug allergy; EPI, epinephrine; F, female; FA, food allergy; H1AH, H1-antihistamines; H2AH, H2-antihistamines; M, male; MDH, multiple drug hypersensitivity; NA, not applicable or not available; N, no; Y, yes;

[a]According to Brown SG, 2004 classification[8]

Clinical characteristics of patients experiencing biphasic anaphylaxis

Details of 17 patients with biphasic anaphylaxis are summarized in **Table 5**. The majority were female (13/17, 76.5%), with ages ranging from 8 to 71 years old. Five patients revisited the hospital (5/17, 29.4%), and 2 were hospitalized after the primary reaction (2/17, 11.8%). Only 6 of 11 (54.5%) were referred to an allergist for evaluation. In most cases, reactions were milder than the primary reaction (10/17, 58.8%), followed by a similar intensity to the primary reaction (6/17, 35.3%), with only one being worse than the primary reaction. Most cases (13/17, 76.5%) did not require an additional dose of epinephrine and were treated only with H1-antihistamines. One case was self-limiting.

Discussion

In our analysis of anaphylactic cases presenting to our emergency department from 2015 to 2019, we estimated the incidence of biphasic reactions to be 7.1% (17 out of 239 cases). This rate is consistent with the results of a comprehensive meta-analysis that included 27 studies, where the reported incidence of biphasic reactions was 4.6% (192 out of 4114 patients).[11] The accurate estimation of biphasic anaphylaxis incidence poses a challenge in retrospective studies and is likely to be an underestimate due to potential follow-up losses and variations in definitions.[12] The previous studies in Thailand has indicated a wide range of biphasic reaction incidence, from 1.4% to 21.3%, among anaphylaxis cases.[13,14] This variability is mirrored globally, with reported incidence rates of biphasic anaphylaxis ranging from less than 1% to as high as 20%.[6]

In the univariate analysis, we observed a significantly increased probability of biphasic anaphylaxis in cases triggered by drugs or with idiopathic origins ($p < 0.05$). This finding is consistent with the recent report published by the Joint Task Force on Practice Parameters (JTFPP).[6] Patients presenting with eyelid edema were observed to have an increased likelihood of experiencing biphasic anaphylactic reactions. This may be due to the underestimation of severity commonly associated with eyelid edema. Such underestimation often results in a preference for antihistamines over epinephrine, which can delay the administration of epinephrine. This delay is a potential factor contributing to the increased likelihood of a biphasic reaction. Our research also determined that a history of drug allergies, allergic rhinitis, and a higher frequency of previous anaphylactic episodes are linked to an increased risk of biphasic reactions. However, the possibility of selection bias in these results must be acknowledged. Individuals with detailed medical histories are more likely to seek medical care while those without such documentation might be underrepresented in follow-up data. On the other hand, patients who received an initial dose of epinephrine were less prone to biphasic reactions. This supports the Joint Task Force on Practice Parameters (JTFPP) clinical guidelines, which emphasize the critical role of prompt epinephrine administration in the treatment of anaphylaxis.[6]

Our prognostic model, incorporating factors such as drug-related or idiopathic triggers, a delay in epinephrine administration exceeding 60 minutes, and the presence of cutaneous edema/angioedema, indicates a 21.3% predicted probability of biphasic response when all three predictors are present. These results underline the need for prolonged clinical observation and vigilant follow-up in patients exhibiting these risk factors. In our study group, the median time to biphasic anaphylaxis onset was 15 hours, with a range of 6.2 to 47.6 hours, suggesting that a 24-hour observation period may be more suitable for detecting biphasic reactions. This finding contrasts with the conclusion of Kim et al., based on a meta-analysis of 12 studies involving 2890 patients, which suggested that an observation period of 6-12 hours might be sufficient.[15] Additionally, it is advisable to provide epinephrine in prefilled syringes or autoinjectors, along with a detailed action plan, for patients deemed at an increased risk of experiencing a biphasic reaction.

Severity of biphasic reaction can unpredictably be milder, similar, or more severe than initial reaction.[16] However in our study, the severity of biphasic reaction tended to be milder than primary reaction which is consistent with previous findings.[17-19] Most cases of biphasic anaphylaxis in our study were managed with H1-antihistamines, and one case resolved spontaneously. A well-written initial emergency action plan could be offered to patients, reducing the need for unnecessary hospital visits. More than half of the patients who experienced a biphasic reaction were not referred for evaluation by allergists. For individuals with a food allergy, additional assessment is necessary to identify cross-reactive foods, especially in cases of fruit allergy.[20] The prescription of self-carry epinephrine may also be necessary.[1,20,21]

In terms of public health initiatives, our study showed that the median time to administer epinephrine after symptom onset was 74.3 minutes, indicating a significant delay. Some patients initially presented with a urticarial rash that briefly improved with H1-antihistamines before rapidly progressing to systemic symptoms. Traffic issues in our country may also contribute to delayed treatment. We recommend that anaphylaxis patients carry epinephrine and advocate for its availability in key public locations like schools and workplaces, with trained personnel on hand. Additionally, an observation in our study was the high prevalence of edible insect-associated anaphylaxis, ranking second among food-related anaphylactic reactions. This finding appears to be a unique characteristic of food allergens in our region, particularly when compared to data from other parts of the Asia-Pacific region.[22] Our institution, Siriraj Hospital, a tertiary care center, which is situated near community markets similar to other regions in Thailand, in which edible insects are commonly bought and consumed as a popular exotic food item.[23] This dietary preference in our region could be a contributing factor to the observed incidence of insect-associated anaphylaxis. It is also important to consider histamine intolerance as a differential diagnosis in cases of insect consumption.

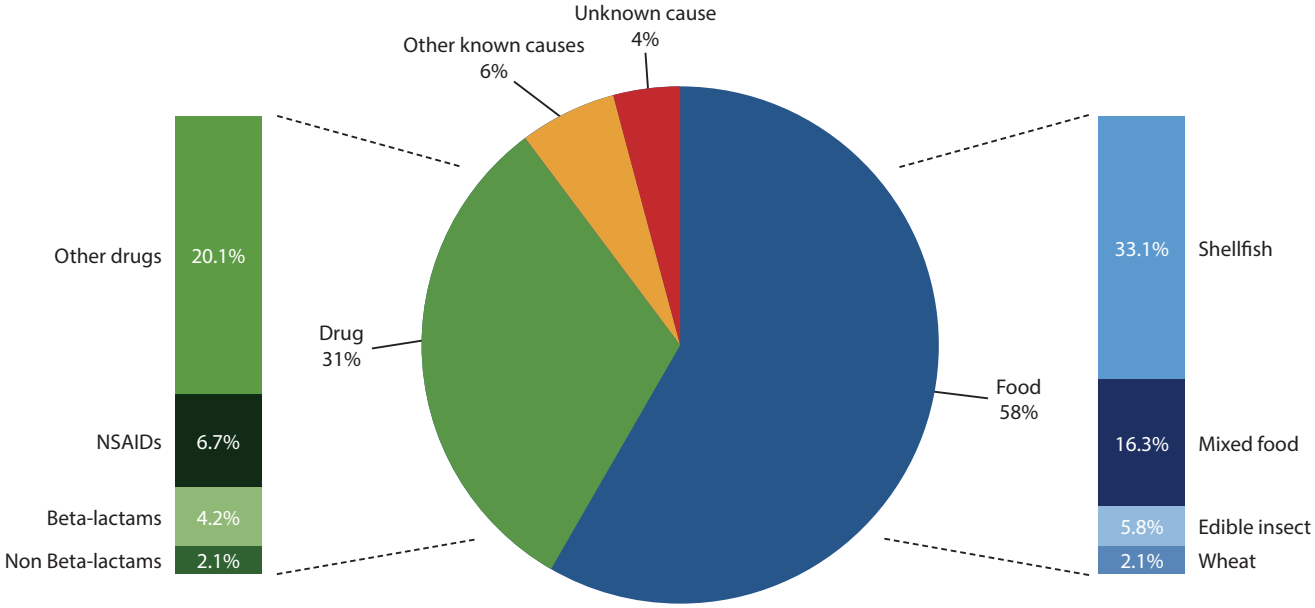

Figure 2. Triggers of anaphylaxis. (n = 239)

Abbreviation: NSAID, non-steroidal anti-inflammatory drug. Other drugs included allergen immunotherapy (n = 19), iodinated radiocontrast (n = 15), vaccines (n = 9), contraceptive drugs (n = 3), and antithyroid drugs (n = 2). Other known causes included reactions to insect stings or bites (n = 9), exercise (n = 4), and snakebites (n = 1).

Studies conducted by our institution have measured contaminated histamine levels in edible insects sold in Thailand, which could lead to severe reactions that mimic anaphylaxis. Such incidents have been reported as outbreaks in various regions across Thailand, prompting public health warnings.[24,25] Furthermore, there is evidence suggesting potential cross-reactivity between insect and shellfish allergens, particularly through tropomyosin components.[26] This area warrants further research.

Our data also showed that mixed food items accounted for up to 16.3% of the cases, underscoring the complexities involved in identifying allergens in Asian cuisines, which often have complex dishes and meals in ingredients used. This highlights the importance of comprehensive investigations to accurately determine the triggers of anaphylaxis for precise diagnosis. A recently published prospective cohort study in Hong Kong involving adults used a well-established multidisciplinary diagnostic pathway, including evaluations by allergists. The study identified food as the primary anaphylaxis trigger (63%), which is similar to our findings. However, food-dependent exercise-induced anaphylaxis (FDEIA) constituted a significant proportion in Hong Kong, which was limitedly evaluated in our retrospective study.[27]

The present study has several limitations inherent to its retrospective chart reviews and self-report questionnaires which may introduce biases like non-response, recall, and misclassification, compromising accuracy. Selection bias and loss to follow-up could have impacted the results, along with the presence of missing data. Additionally, the conclusions regarding triggers were primarily based on allergist diagnoses, and not all cases underwent a complete investigation. This is particularly noteworthy given that mixed foods, potentially harboring specific causative agents, were reported in as many as 16.3% of cases. However, the lack of comprehensive workups precluded definitive identification of these triggers. Another limitation is the relatively low incidence of anaphylaxis observed in our study, which may restrict the applicability of our predictive model. To confirm its validity, the model developed in the present study requires external validation.

In conclusion, our findings suggest that potential predictors of a biphasic response include drug/idiopathic reactions, any cutaneous edema/angioedema, and a time from onset to the first epinephrine administration exceeding 60 minutes. However, the applicability of these findings is constrained by the previously mentioned limitations. Given the current absence of reliable predictors for biphasic reactions and the risk of complications from both anaphylaxis and its treatment, close monitoring following an anaphylaxis event remains critically important.

Funding

This study is supported by Siriraj Research Development Fund (Managed by Routine to Research: R2R), Grant Number (IO): R016335018

Institutional Review Board Statement

This study was approved by the Siriraj Institutional Review Board (SIRB), Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand 841/2562 (IRB4).

Informed Consent Statement

Patients participating in the study provided informed consent via telephone, a procedure that was ethical authorization by the IRB.

Data Availability Statement

Not applicable

Acknowledgments

We would like to thank Dr. Anthony Tan for editing the English language and statistical analyses.

Conflicts of Interest

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

Author Contributions

- Conceptualization, W.U., P.L., T.K., M.S.
- Methodology, W.U., P.L., M.S.
- Software, W.U., P.L., M.S.
- Validation, W.U., P.L., T.K., M.S.
- Formal analysis, W.U., P.L., T.K., M.S.
- Investigation, W.U., P.L., T.K., C.W., T.T., M.S.
- Resources, T.T., M.S.
- Data curation, W.U., P.L., T.K.
- Writing—original draft preparation, W.U., P.L., T.K., C.W., T.T., M.S.
- Writing—review and editing, W.U., P.L., T.K., C.W., T.T., M.S.
- Visualization, P.L., T.K., M.S.
- Supervision, T.K., C.W., T.T., M.S.
- Project administration, M.S.
- Funding acquisition, W.U., P.L., M.S.
- All authors have read and agreed to the published version of the manuscript. All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agreed to be accountable for all aspects of the work.

References

1. Cardona V, Ansotegui IJ, Ebisawa M, El-Gamal Y, Fernandez Rivas M, Fineman S, et al. World allergy organization anaphylaxis guidance 2020. World Allergy Organ J. 2020;13(10):100472.
2. Panesar SS, Javad S, de Silva D, Nwaru BI, Hickstein L, Muraro A, et al. The epidemiology of anaphylaxis in Europe: a systematic review. Allergy. 2013;68(11):1353-61.
3. Yang MS, Lee SH, Kim TW, Kwon JW, Lee SM, Kim SH, et al. Epidemiologic and clinical features of anaphylaxis in Korea. Ann Allergy Asthma Immunol. 2008;100(1):31-6.
4. Li PH, Leung ASY, Li RMY, Leung TF, Lau CS, Wong GWK. Increasing incidence of anaphylaxis in Hong Kong from 2009 to 2019-discrepancies of anaphylaxis care between adult and paediatric patients. Clin Transl Allergy. 2020;10(1):51.
5. Liu FC, Chiou HJ, Kuo CF, Chung TT, Yu HP. Epidemiology of anaphylactic shock and its related mortality in hospital patients in Taiwan: a nationwide population-based study. Shock. 2017;48(5):525-31.
6. Shaker MS, Wallace DV, Golden DBK, Oppenheimer J, Bernstein JA, Campbell RL, et al. Anaphylaxis-a 2020 practice parameter update, systematic review, and Grading of Recommendations, Assessment, Development and Evaluation (GRADE) analysis. J Allergy Clin Immunol. 2020;145(4):1082-123.
7. Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006;117(2):391-7.
8. Brown SG. Clinical features and severity grading of anaphylaxis. J Allergy Clin Immunol. 2004;114(2):371-6.
9. Riley RD, Snell KI, Ensor J, Burke DL, Harrell FE Jr, Moons KG, et al. Minimum sample size for developing a multivariable prediction model: PART II - binary and time-to-event outcomes. Stat Med. 2019;38(7):1276-96.
10. Lee S, Peterson A, Lohse CM, Hess EP, Campbell RL. Further evaluation of factors that may predict biphasic reactions in Emergency department anaphylaxis patients. J Allergy Clin Immunol Pract. 2017;5(5):1295-301.
11. Lee S, Bellolio MF, Hess EP, Erwin P, Murad MH, Campbell RL. Time of onset and predictors of biphasic anaphylactic reactions: a systematic review and meta-analysis. J Allergy Clin Immunol Pract. 2015;3(3):408-16.e1-2..
12. Turner PJ, Campbell DE, Motosue MS, Campbell RL. Global trends in anaphylaxis epidemiology and clinical implications. J Allergy Clin Immunol Pract. 2020;8(4):1169-76.
13. Rangkakulnuwat P, Sutham K, Lao-Araya M. Anaphylaxis: ten-year retrospective study from a tertiary-care hospital in Asia. Asian Pac J Allergy Immunol. 2020;38(1):31-9.
14. Sricharoen P, Sittichanbuncha Y, Wibulpolprasert A, Srabongkosh E, Sawanyawisuth K. What clinical factors are associated with biphasic anaphylaxis in Thai adult patients? . Asian Pac J Allergy Immunol. 2015;33(1):8-13.
15. Kim TH, Yoon SH, Hong H, Kang HR, Cho SH, Lee SY. Duration of observation for detecting a biphasic reaction in anaphylaxis: a meta-analysis. Int Arch Allergy Immunol. 2019;179(1):31-6.
16. Gupta RS, Sehgal S, Brown DA, Das R, Fierstein JL, Casale TB, et al. Characterizing biphasic food-related allergic reactions through a US food allergy patient registry. J Allergy Clin Immunol Pract. 2021;9(10):3717-27.
17. Nomura T, Sekii H, Sugita M, Nakahara S. Association between biphasic reactions and the systems of symptoms and treatment in patients with anaphylaxis hospitalized from the emergency department. Acute Med Surg. 2020;7(1):e599.
18. Oya S, Nakamori T, Kinoshita H. Incidence and characteristics of biphasic and protracted anaphylaxis: evaluation of 114 inpatients. Acute Med Surg. 2014;1(4):228-233.:228-33.
19. Scranton SE, Gonzalez EG, Waibel KH. Incidence and characteristics of biphasic reactions after allergen immunotherapy. J Allergy Clin Immunol. 2009;123(2):493-8.
20. Krikeerati T, Rodsaward P, Nawiboonwong J, Pinyopornpanish K, Phusawang S, Sompornrattanaphan M. Revisiting fruit allergy: prevalence across the globe, diagnosis, and current management. 2023;12(22):4083.
21. Muraro A, Worm M, Alviani C, Cardona V, DunnGalvin A, Garvey LH, et al. European Academy of Allergy and Clinical Immunology, Food Allergy, Anaphylaxis Guidelines Group. EAACI guidelines: anaphylaxis (2021 update). Allergy. 2022;77(2):357-77.
22. Tham EH, Leung ASY, Pacharn P, Lee S, Ebisawa M, Lee BW, et al. Anaphylaxis - lessons learnt when East meets West. Pediatr Allergy Immunol. 2019;30(7):681-8.
23. Krongdang S, Phokasem P, Venkatachalam K, Charoenphun N. Edible insects in Thailand: an overview of status, properties, processing, and utilization in the food industry. Foods. 2023;12(11):2162.
24. Chomchai S, Chomchai C. Histamine poisoning from insect consumption: an outbreak investigation from Thailand. Clin Toxicol (Phila). 2018;56(2):126-31.
25. Chomchai S, Laoraksa P, Virojvatanakul P, Boonratana P, Chomchai C. Prevalence and cluster effect of self-reported allergic reactions among insect consumers. Asian Pac J Allergy Immunol. 2020;38(1):40-6.
26. De Marchi L, Wangorsch A, Zoccatelli G. Allergens from edible insects: cross-reactivity and effects of processing. Curr Allergy Asthma Rep. 2021;21(5):35.
27. Chiang V, Mak HWF, Yeung MHY, Kan AKC, Au EYL, Li PH. Epidemiology, outcomes, and disproportionate burden of food-dependent exercise-induced anaphylaxis from the Hong Kong Multidisciplinary Anaphylaxis Management Initiative (HK-MAMI). J Allergy Clin Immunol Glob. 2023;2(3):100127.