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Recurrence rate and risk factors of recurrent anaphylaxis: A ten-year retrospective cohort study

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Abstract

Background: Few studies have investigated the risk factors for recurrent anaphylaxis. Identifying these factors may help patients implement preventive measures.

Objective: To determine the rate and risk factors for recurrent anaphylaxis, assess the time to recurrence, and compare the characteristics, triggers, and clinical manifestations between recurrent and non-recurrent cases.

Methods: A retrospective cohort study was conducted at Naresuan University Hospital from March 2011 to February 2021, using medical records of patients with ICD-10–confirmed anaphylaxis. Risk factors for recurrence were analyzed using Cox proportional hazards regression model.

Results: A total of 439 anaphylactic episodes were identified in 381 patients (49 children, 332 adults). Of these, 42 patients (11.2%) experienced 58 recurrent episodes (7/49 [14.3%] children, 35/332 [10.6%] adults). Food and medications were the most and second most common triggers. The median time to recurrence was 9.9 months (IQR: 3.1–18.8), while the median follow-up duration for non-recurrent cases was 41.8 months (IQR: 23.8–61.8). The recurrent anaphylaxis rate was 4.1 events per 100 person-years. Statistically significant risk factors included a history of food, a history of insect, a history of drug allergies, chest discomfort, and severe anaphylaxis (HR [95%CI]: 3.31 [1.50-7.29], p = 0.003; 4.96 [1.47–16.82], p = 0.010; 5.87 [2.64–13.07], p < 0.001; 2.43 [1.19-4.99], p = 0.015; and 2.29 [1.07-4.88], p = 0.033, respectively). Conversely, palpitations were associated with a lower risk of recurrence (HR 0.11 [0.01–0.86], p = 0.036).

Conclusion: Identifying risk factors in anaphylaxis patients enhances medical care and aids in preventing recurrence.

Key words: Recurrent anaphylaxis, recurrent rate, risk factors, allergy, Thailand

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Introduction

Anaphylaxis is a severe, potentially life-threatening condition caused by a systemic allergic reaction. It requires immediate recognition and medical intervention to prevent fatal outcomes. The lifetime prevalence of anaphylaxis ranges from 0.3% to 5.1%.[1,2] The global incidence is estimated to be between 50 and 112 episodes per 100,000 person-years, with a pediatric incidence ranging from 1 to 761 per 100,000 person-years.[1-3] In Thailand, studies conducted in Bangkok, Chiang Mai, and Phitsanulok reported anaphylaxis rates ranging from 3.9 to 652 episodes per 100,000 outpatient and emergency visits per year.[4-8]

In recent years, both fatality rates due to drug-induced anaphylaxis and hospitalizations due to anaphylaxis have significantly increased, particularly in the United States and Australia.[9-11] Moreover, studies have demonstrated an increasing trend in anaphylaxis-related emergency department visits over the past decade.[8,10,12] These trends underscore the need for healthcare professionals to promptly recognize, intervene, and implement preventive measures. One important aspect that warrants further attention is recurrent anaphylactic reaction and its associated risk factors.

Recurrent anaphylaxis affects 26.5 to 54% of anaphylactic patients over follow-up periods ranging from 1.5 years to 24 years.[10] A study in children reported an annual recurrence rate of 17.6%.[13] Moreover, studies on anaphylaxis recurrence rate have shown variability, ranging from 6.6 to 90 episodes per 100 person-years in pediatric populations,[14] while recurrence rates across all age groups range from 1.4 to 57 events per 100 person-years.[15-18]

Identifying risk factors for recurrent anaphylaxis can help patients take precautionary measures to mitigate their risk. However, studies on risk factors for recurrent anaphylaxis remain limited. One observational cohort study identified a history of atopic dermatitis, presence of cough or oral pruritus, and steroid therapy as significant risk factors associated with recurrence.[18] This study aimed to determine the rate and risk factors of recurrent anaphylactic reactions, assess the time to recurrence, and compare the characteristics, triggers, and clinical manifestations between patients with recurrent and non-recurrent episodes. Understanding these factors is crucial for improving patient outcomes and preventing fatal episodes.

Methods

As part of an anaphylaxis survey conducted at Naresuan University Hospital, Phitsanulok—one of the largest university hospitals in lower northern Thailand—between March 2011 and February 2021,[8] we further conducted a retrospective cohort study reviewing medical records of patients diagnosed with recurrent and non-recurrent anaphylaxis. Anaphylaxis cases were identified using ICD-10 codes from electronic medical records, including T78.0 (anaphylactic shock due to an adverse food reaction), T78.2 (unspecified anaphylactic shock), T80.5 (anaphylactic shock due to serum), and T88.6 (anaphylactic shock due to an adverse drug effect). Diagnosis were confirmed based on the clinical criteria proposed by the second U.S. National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network (NIAID/FAAN).[19] Patients diagnosed with anaphylaxis in the emergency department (ED), outpatient department, and inpatient wards were included in this 10-year study period.

Extracted data from the medical records of patients, both with and without recurrent anaphylaxis, encompassed: demographic information, pre-existing medical conditions, atopic tendencies, prior history of allergy, triggers, anaphylactic manifestations, the interval between allergen exposure and symptom onset, therapeutic interventions, patient outcomes, and allergy assessments. The total number of recurrent reactions during the study period for each patient was recorded.

The severity of anaphylaxis was evaluated based on the presence of at least one of the following: hypotension, cardiovascular collapse, respiratory failure or cyanosis, and loss of consciousness.[8,20] Hypotension was defined as systolic blood pressure < 70 mmHg in patients aged 1 month to 1 year; < 70 + (age in years × 2) mmHg in patients aged > 1 to 10 years; and < 90 mmHg in patients aged > 10 years. Cyanosis was considered if pulse oximetry saturation (SpO_2) was less than 95%. Risk factors for recurrence and the time to recurrent anaphylaxis were assessed. Recurrent anaphylaxis was defined as the recurrence of symptoms meeting the NIAID/FAAN criteria. Patients under 16 years of age were classified as children.

This study was reviewed and approved by the Naresuan University Institutional Review Board (NU-IRB), with ethics approval certification number P3-0097/2564. The NU-IRB Committee granted permission to conduct the study using patient medical records and waived the requirement for patient consent.

Statistics

All data were analyzed using both descriptive and inferential statistics with the STATA software package, version 18.0. Categorical variables were presented as frequencies and percentages, and continuous variables as medians and interquartile ranges (IQR). Comparisons between patients with and without recurrent anaphylaxis were performed using Fisher's exact test. Medians of two independent groups were compared using the Mann-Whitney U test. Time to event analysis was conducted to estimate time to recurrence and follow-up duration. The recurrence rate of anaphylaxis was calculated as events per 100 person-years. The association of risk factors with time to recurrence was analyzed utilizing the Cox proportional hazards regression model, with results expressed as hazard ratios (HR) and 95% confidence intervals (CIs). A multivariable Cox proportional hazards regression analysis was performed to identify potential risk factors for recurrent anaphylaxis. The Kaplan-Meier method was used to generate a recurrence rate curve (failure function) in relation to significant different risk factors. A two-sided p-value < 0.05 was considered statistically significant.

Results

A total of 820 potential anaphylaxis episodes from 715 consecutive patients were identified through a review of electronic medical records coded with ICD-10 diagnoses for anaphylaxis at Naresuan University Hospital from March 2011 to February 2021. Due to a transition in the hospital's Medical Information System (MIS) from fully paper-based to a hybrid electronic-paper system, storage limitations necessitated the removal of paper-based records of patients who had not visited the hospital in over five years. Consequently, 264 medical records (286 episodes, 36.9%), including seven inpatient episodes, could not be retrieved. Among the 451 available medical records (534 episodes), 50 records (75 episodes, 7.0%) contained insufficient medical information, and 20 patients (20 episodes, 2.8%) were excluded for not meeting the NIAID/FAAN clinical diagnostic criteria. The final analysis included 439 anaphylaxis episodes from 381 patients, including eight inpatient episodes. Of these, 57 episodes (13%) occurred in children, while 382 episodes (87%) occurred in adults. The selection process for medical records is presented in the study flow diagram (**Figure 1**).

Characteristics, Triggers, and Clinical Presentation of Recurrent and Non-Recurrent Anaphylaxis Episodes

Among 439 anaphylaxis episodes, 58 (13.2%) were recurrent episodes, with 8 (13.8%) occurring in children and 50 (86.2%) in adults. In contrast, 381 (86.8%) were non-recurrent episodes, including 49 (12.9%) in children and 332 (87.1%) in adults. **Table 1** presents the characteristics of recurrent and non-recurrent episodes. No significant difference in age was observed between the two groups. However, patients in the recurrent group had a significantly higher rates of prior food, insect-sting, and drug allergies, and chronic urticaria compared to those in the non-recurrent group (56.9% vs. 27.3%, $p < 0.001$; 8.6% vs. 2.6%, $p = 0.036$; 39.7% vs. 27.3%, $p < 0.001$; 10.3% vs. 3.2%, $p = 0.021$, respectively). No significant differences were found between the two groups in terms of sex, allergic rhinitis, asthma, atopic dermatitis, underlying cardiovascular diseases, or family history of atopic conditions. However, females, allergic rhinitis, and asthma were more frequently reported in the recurrent group.

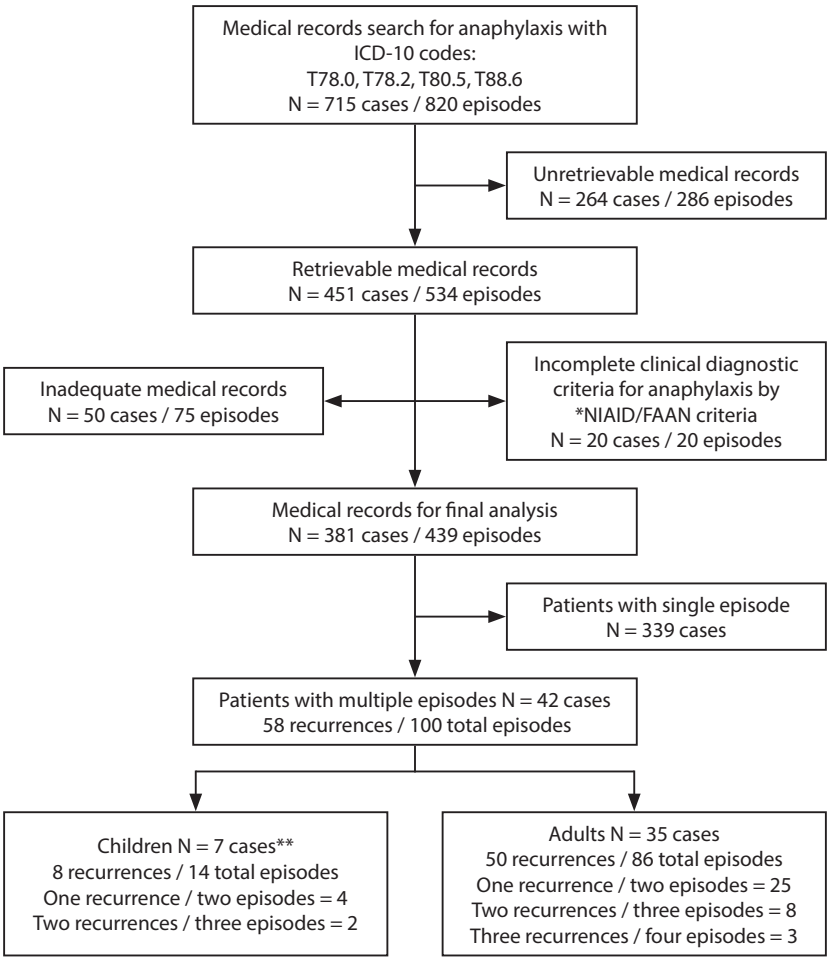

Figure 1. Study flowchart of medical record selection process.

*The second U.S. National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network
**One child experienced their first anaphylaxis episode before the age of 16 (classified in the pediatric group) and a recurrent episode at age 16 or older (classified in the adult group).

Table 1. Characteristics of recurrent vs. non-recurrent anaphylaxis episodes; number of episodes (%)

Characteristics	Recurrent anaphylaxis			Non-recurrent anaphylaxis			*p*-value
	Total (n = 58)	Children (n = 8)	Adult (n = 50)	Total (n = 381)	Children (n = 49)	Adult (n = 332)	
Sex: Male	19 (32.8)	2 (25.0)	17 (34.0)	160 (42.0)	29 (59.2)	131 (39.5)	0.199
Median age (year, IQR)	23 (20-47)	11.5 (8.5-14)	25.5 (21-49)	22 (19-35)	7 (4-12)	23 (20-41)	0.196
Atopic diseases	16 (27.6)	2 (25.0)	14 (28.0)	68 (17.9)	15 (30.6)	53 (16.0)	0.105
- Allergic rhinitis	10 (17.2)	2 (25.0)	8 (16.0)	47 (12.3)	8 (16.3)	39 (11.8)	0.297
- Allergic conjunctivitis	0	0	0	2 (0.5)	0	2 (0.6)	1.000
- Asthma	7 (12.1)	2 (25.0)	5 (10.0)	23 (6.0)	9 (18.4)	14 (4.2)	0.097
- Atopic dermatitis	1 (1.7)	0	1 (2.0)	6 (1.6)	2 (4.1)	4 (1.2)	1.000
- History of food allergy	33 (56.9)	5 (62.5)	28 (56.0)	104 (27.3)	15 (30.6)	89 (26.8)	< 0.001
Chronic urticaria	6 (10.3)	0	6 (12.0)	12 (3.2)	1 (2.0)	11 (3.3)	0.021
History of insect sting allergy	5 (8.6)	1 (12.5)	4 (8.0)	10 (2.6)	1 (2.0)	9 (2.7)	0.036
History of drug allergy	23 (39.7)	0	23 (46.0)	104 (27.3)	15 (30.6)	89 (26.8)	< 0.001
Underlying cardiovascular disease	6 (10.3)	0	6 (12.0)	40 (10.5)	1 (2.0)	39 (11.8)	1.000
Family history of atopic conditions	54 (93.1)	8 (100)	46 (92.0)	353 (92.7)	37 (75.5)	316 (95.2)	1.000

Regarding anaphylaxis triggers, recurrent episodes were more frequently associated with food and medication than non-recurrent episodes; however, these differences were not statistically significant, as shown in **Table 2** (53.5% vs. 48.3%, p = 0.484; 17.2% vs. 13.4%, p = 0.418, respectively). Among food-related triggers, clams/mussels, and crab were reported more frequently in the recurrent group than in the non-recurrent group (6.9% vs. 2.9%, p = 0.122; 3.5% vs. 1.8%, p = 0.338, respectively). Conversely, fried insects were less frequently associated with recurrent anaphylaxis compared to non-recurrent cases (3.5% vs. 8.1%, p = 0.288). Among medication-related triggers, antibiotics and radiocontrast media were more common in recurrent cases, but the differences were not statistically significant. Three patients experienced recurrent anaphylaxis due to antibiotics. One patient had anaphylaxis to the same drug (ceftriaxone) in each episode, while two patients had different antibiotics as triggers in their first and second episodes—dicloxacillin and amoxicillin in one case, and an unknown cause and norfloxacin in the other. Additionally, two patients experienced recurrent anaphylaxis due to radiocontrast media. One patient had anaphylaxis to different contrast agents in each episode (Ultravist and Xenetix), while another patient experienced a second recurrence triggered by Ultravist following a first recurrence caused by ceftriaxone. Interestingly, insect stings were significantly less common in recurrent anaphylaxis cases (1/58, 1.7%) compared to non-recurrent cases (43/381, 11.3%; p = 0.018), with bee stings being the most common cause. Cofactors such as exercise, infection, stress, sleep deprivation, and menstruation were less frequently reported in recurrent episodes than in non-recurrent episodes, with no significant differences.

In terms of clinical presentation, skin manifestations such as itching, flushing, urticaria, angioedema, and maculopapular rash were the most common presenting symptoms, with no statistically significant differences between the two groups. Patients who presented with maculopapular rash also exhibited other skin findings consistent with the NIAID/FAAN criteria, such as pruritus, flushing, urticaria, and angioedema. However, angioedema was observed less frequently in recurrent anaphylaxis episodes (**Table 3**). Respiratory symptoms were more prevalent in recurrent episodes, with chest discomfort, cough, and the sensation of a lump in the throat occurring at significantly higher rates than in non-recurrent episodes (65.5% vs. 50.7%, p = 0.047; 8.6% vs. 2.9%, p = 0.047; 10.3% vs. 3.2%, p = 0.021, respectively). Despite a higher observed frequency of cyanosis, wheezing, and ocular symptoms such as conjunctival injection in the recurrent anaphylaxis group, these differences were not statistically significant when compared to the non-recurrent group (**Table 3**). Both groups exhibited similar frequencies of gastrointestinal symptoms. Notably, Cardiovascular manifestations were generally less frequent in recurrent episodes than in non-recurrent episodes. Moreover, among these cardiovascular symptoms, palpitations occurred significantly less often in non-recurrent episodes (1.7% vs. 9.5%, p = 0.044). Recurrent anaphylaxis was associated with more severe symptoms than non-recurrent anaphylaxis (31% vs. 27.6%, p = 0.638); however, the onset of symptoms within 30 minutes was similar between the two groups. A total of 11 out of 58 recurrent anaphylaxis episodes underwent allergy testing. Of these, 5 patients (5/42, 11.9%) had testing after the initial episode, 2 patients underwent testing after their first recurrence, another 2 after their second recurrence,

Table 2. Triggers of recurrent anaphylaxis compared to non-recurrent anaphylaxis episodes; number of episodes (%)

Triggers	Recurrent anaphylaxis			Non-recurrent anaphylaxis			*p*-value
	Total (n = 58)	Children (n = 8)	Adult (n = 50)	Total (n = 381)	Children (n = 49)	Adult (n = 332)	
Foods	31 (53.5)	6 (75.0)	25 (50.0)	184 (48.3)	27 (55.1)	157 (47.3)	0.484
- Milk	0	0	0	4 (1.1)	2 (4.1)	2 (0.6)	1.000
- Egg	1 (1.72)	1 (12.5)	0	3 (0.8)	0	3 (0.9)	0.434
- Wheat	1 (1.7)	1 (12.5)	0	6 (1.6)	2 (4.1)	4 (1.2)	1.000
- Fish	1 (1.7)	0	1 (2.0)	6 (1.6)	1 (2.0)	5 (1.5)	1.000
- Clams/Mussels	4 (6.9)	0	4 (8.0)	11 (2.9)	0	11 (3.3)	0.122
- Shrimp	12 (20.7)	2 (25.0)	10 (20.0)	73 (19.2)	13 (26.5)	60 (18.1)	0.858
- Squid	1 (1.7)	0	1 (2.0)	10 (2.6)	3 (6.1)	7 (2.1)	1.000
- Crab	2 (3.5)	1 (12.5)	1 (2.0)	7 (1.8)	2 (4.1)	5 (1.5)	0.338
- Fired insects	2 (3.5)	1 (12.5)	1 (2.0)	31 (8.1)	5 (10.2)	26 (7.8)	0.288
- Ant eggs	0	0	0	3 (0.8)	0	3 (0.9)	1.000
Insect sting	1 (1.7)	0	1 (2.0)	43 (11.3)	6 (12.2)	37 (11.1)	0.018
- Bees	0	0	0	16 (4.2)	1 (2.0)	15 (4.5)	0.146
- Wasp	0	0	0	3 (0.8)	1 (2.0)	2 (0.6)	1.000
- Vespid	0	0	0	5 (1.3)	2 (4.1)	3 (0.9)	1.000
- Ant	1 (1.7)	0	1 (2.0)	2 (0.5)	1 (2.0)	1 (0.3)	0.347
Medication	10 (17.2)	0	10 (20.0)	51 (13.4)	4 (8.2)	47 (14.2)	0.418
- Antibiotic	3 (5.2)	0	3 (6.0)	16 (4.2)	0	16 (4.8)	0.727
- NSAIDS	2 (3.5)	0	2 (4.0)	14 (3.7)	0	14 (4.2)	1.000
- Radiocontrast Media	2 (3.5)	0	2 (4.0)	5 (1.3)	1 (2.0)	4 (1.2)	0.233
Cofactor*	4 (6.9)	1 (12.5)	3 (6.0)	35 (9.2)	1 (2.0)	34 (10.2)	0.804

*Cofactors include exercise, infection, stress, sleep deprivation, and menstruation.

Table 3. Clinical features and treatment of recurrent vs. non-recurrent anaphylaxis episodes; number of episodes (%)

	Recurrent anaphylaxis			Non-recurrent anaphylaxis			*p*-value
	Total (n = 58)	Children (n = 8)	Adult (n = 50)	Total (n = 381)	Children (n = 49)	Adult (n = 332)	
1. Clinical manifestation							
- Skin and Mucosal symptoms	57 (98.3)	7 (87.5)	50 (100)	370 (97.1)	47 (95.9)	323 (97.3)	1.000
- Itch	33 (56.9)	2 (25.0)	31 (62.0)	234 (61.4)	29 (59.2)	205 (61.8)	0.564
- Flush/erythema	14 (24.1)	1 (12.5)	13 (26.0)	79 (20.7)	5 (10.2)	74 (22.3)	0.605
- Urticaria	25 (43.1)	1 (12.5)	24 (48.0)	169 (44.7)	26 (53.1)	143 (43.1)	0.888
- Angioedema	17 (29.3)	4 (50.0)	13 (26.0)	145 (38.1)	25 (51.0)	120 (36.1)	0.243
- Maculopapular rash	18 (31.0)	0	18 (36.0)	114 (29.9)	14 (28.6)	100 (30.1)	0.878
- Respiratory symptoms	48 (82.8)	6 (75.0)	42 (84.0)	287 (75.3)	31 (63.3)	256 (77.1)	0.248
- Chest discomfort	38 (65.5)	6 (75.0)	32 (64.0)	193 (50.7)	13 (26.5)	180 (54.2)	0.047
- Dyspnea	22 (37.9)	0	22 (44.0)	134 (35.2)	14 (28.6)	120 (36.1)	0.769

Table 3. (Continued)

	Recurrent anaphylaxis			Non-recurrent anaphylaxis			*p*-value
	Total (n = 58)	Children (n = 8)	Adult (n = 50)	Total (n = 381)	Children (n = 49)	Adult (n = 332)	
- Wheeze	14 (24.1)	1 (12.5)	13 (26.0)	64 (16.8)	18 (36.7)	46 (13.9)	0.196
- Cough	5 (8.6)	1 (12.5)	4 (8.0)	11 (2.9)	1 (2.0)	10 (3.0)	0.047
- Rhinorrhea	5 (8.6)	1 (12.5)	4 (8.0)	30 (7.9)	7 (14.3)	23 (6.9)	0.796
- Nasal congestion	4 (6.9)	2 (25.0)	2 (4.0)	31 (8.1)	3 (6.1)	28 (8.4)	1.000
- Cyanosis (SpO_2 < 92%)	5 (8.6)	0	5 (10.0)	24 (6.3)	3 (6.1)	21 (6.3)	0.567
- Lump in the throat	6 (10.3)	0	6 (12.0)	12 (3.2)	1 (2.0)	11 (3.3)	0.021
- Eye symptoms	4 (6.9)	0	4 (8.0)	18 (4.7)	3 (6.1)	15 (4.5)	0.514
- Itchy eye	0	0	0	5 (1.3)	2 (4.1)	3 (0.9)	1.000
- Tearing	0	0	0	5 (1.3)	2 (4.1)	3 (0.9)	1.000
- Injected conjunctiva	4 (6.9)	0	4 (8.0)	12 (3.2)	2 (4.1)	10 (3.0)	0.247
- Gastrointestinal symptoms	40 (69.0)	6 (75.0)	34 (68.0)	255 (66.9)	34 (69.4)	221 (66.6)	0.881
- Nausea	20 (34.5)	4 (50.0)	16 (32.0)	125 (32.8)	18 (36.7)	107 (32.2)	0.881
- Vomiting	11 (19.0)	4 (50.0)	7 (14.0)	91 (23.9)	26 (53.1)	65 (19.6)	0.505
- Diarrhea	15 (25.9)	2 (25.0)	13 (26.0)	106 (27.8)	9 (18.4)	97 (29.2)	0.875
- Abdominal pain	27 (46.6)	4 (50.0)	23 (46.0)	152 (39.9)	18 (36.7)	134 (40.4)	0.390
- Cardiovascular symptoms	15 (25.9)	2 (25.0)	13 (26.0)	133 (34.9)	6 (12.2)	127 (38.3)	0.184
- Syncope	4 (6.9)	2 (25.0)	2 (4.0)	25 (6.6)	0	25 (7.5)	1.000
- Dizziness	7 (12.1)	0	7 (14.0)	56 (14.7)	1 (2.0)	55 (16.6)	0.691
- Palpitation	1 (1.7)	0	1 (2.0)	36 (9.5)	1 (2.0)	35 (10.5)	0.044
- Arrhythmia	0	0	0	6 (1.6)	2 (4.1)	4 (1.2)	1.000
- Hypotension	4 (6.9)	0	4 (8.0)	49 (12.9)	2 (4.1)	47 (14.2)	0.278
- Tachycardia	4 (6.9)	0	4 (8.0)	27 (7.1)	3 (6.1)	24 (7.2)	1.000
- Neurological symptoms	1 (1.7)	0	1 (2.0)	11 (2.9)	0	11 (3.3)	1.000
- Anxiety	1 (1.7)	0	1 (2.0)	2 (0.5)	0	2 (0.6)	0.347
- Unconsciousness	0	0	0	6 (1.6)	0	6 (1.8)	1.000
2. Time from exposure to onset of symptoms ≤ 30 minutes	21 (36.2)	4 (50.0)	17 (34.0)	161 (42.3)	19 (38.8)	142 (42.8)	0.618
3. Treatment							
- Epinephrine	56 (96.6)	7 (87.5)	49 (98.0)	376 (98.7)	47 (95.9)	329 (99.1)	0.233
- Antihistamine	57 (98.3)	8 (100)	49 (98.0)	381 (100)	49 (100)	332 (100)	0.132
- Systemic corticosteroid	58 (100)	8 (100)	50 (100)	374 (98.2)	47 (95.9)	327 (98.5)	0.601
- Nebulized beta-agonist	12 (20.7)	1 (12.5)	11 (22.00)	57 (15.0)	17 (34.7)	40 (12.1)	0.251
- Oxygen supplement	8 (13.8)	0	8 (16.0)	47 (12.3)	4 (8.2)	43 (13.0)	0.831
4. Severe anaphylaxis*	18 (31.0)	2 (25.0)	16 (32.0)	105 (27.6)	10 (20.4)	95 (28.6)	0.638

*Severe anaphylaxis defined as any one of the following symptoms: hypotension, cardiovascular collapse, respiratory failure or cyanosis, and loss of consciousness

and 1 patient was tested after both the first and second recurrences. In comparison, allergy testing was performed in 33 out of 339 patients with non-recurrence (9.7%) following the index event. Among the 37 recurrence patients who did not have testing after their initial episode, only 7 had a documented history of exposure to the same allergen trigger, while the remaining episodes involved different or unidentified allergens. Self-injectable epinephrine was prescribed after the initial episode in 4 patients (4/42, 9.5%).

Risk Factors and Rate of Recurrent Anaphylaxis

Among 381 anaphylaxis patients (49 children, 332 adults), 42 (11.0%) experienced a total of 58 recurrent episodes (7/49 [14.3%] children and 35/332 [10.6%] adults). Seven children experienced a total of eight recurrent episodes: four had one recurrent episode each, while two had two recurrent episodes. Among the 35 adults, 25 experienced one recurrent episode, eight had two episodes, and three had three recurrent anaphylaxis episodes (**Figure 1**). One child had their first anaphylaxis episode before the age of 16 (classified in the pediatric group) and experienced a recurrent episode at age 16 or older (classified in the adult group). The median time (IQR) to recurrence after the index anaphylaxis episode was 9.9 (3.1–18.8) months, with no statistically significant difference between children and adults (p = 0.991) The median (IQR) follow-up duration for non-recurrent cases was 41.8 (23.8–61.3) months. The recurrence rate of anaphylaxis was 4.1 events per 100 person-years, with no statistically significant difference between adults and children.

The potential risk factors for recurrent anaphylaxis were selected for multivariable Cox proportional hazards regression analysis based on a review of literature, clinical relevance, and variables that showed statistical significance in the univariable Cox regression analysis (p-value < 0.20). Both univariable and multivariable Cox proportional hazards regression analyses identified several significant risk factors associated with recurrent anaphylaxis as presented in **Table 4** and **Figure 2**. A history of food allergy,

Table 4. Risk factors associated with recurrent anaphylaxis using univariable and multivariable Cox proportional Hazard regression models.

	Univariable Hazard ratio (95%CI)	p-value	Multivariable Hazard ratio (95%CI)	p-value
History of food allergy	2.88 (1.71-4.85)	< 0.001	3.31 (1.50-7.29)	0.003
History of insect allergy	2.12 (0.84-5.30)	0.110	4.96 (1.47-16.82)	0.010
History of drug allergy	3.11 (1.84-5.27)	< 0.001	5.87 (2.64-13.07)	< 0.001
Underlying atopic diseases	1.76 (0.99-3.13)	0.056	0.86 (0.32-2.37)	0.776
Underlying asthma	1.85 (0.84-4.08)	0.127	0.84 (0.22-3.18)	0.792
Underlying cardiovascular disease	0.94 (0.40-2.20)	0.890	0.59 (0.21-1.70)	0.330
Age				
Age ≥ 16 years	0.88 (0.42-1.87)	0.747	0.47 (0.14-1.59)	0.225
Age < 16 years	1.13 (0.53-2.39)	0.747	2.12 (0.63-7.10)	0.225
Trigger				
Food	1.22 (0.73-2.04)	0.459	1.66 (0.48-5.70)	0.423
Medication	1.49 (0.75-2.94)	0.255	2.02 (0.48-8.46)	0.338
Presenting symptoms				
Urticaria	0.97 (0.58-1.63)	0.908	0.86 (0.44-1.70)	0.672
Angioedema	0.70 (0.40-1.23)	0.210	0.47 (0.21-1.04)	0.063
Cough	2.36 (0.94-5.92)	0.067	3.07 (0.92-10.27)	0.068
Chest discomfort	1.76 (1.02-3.02)	0.041	2.43 (1.19-4.99)	0.015
Lump in the throat	2.40 (1.03-5.60)	0.043	2.53 (0.81-7.93)	0.112
Palpitation	0.18 (0.03-1.31)	0.091	0.11 (0.01-0.86)	0.036
Atopic dermatitis	0.94 (0.13-6.81)	0.948	1.6 (0.16-15.54)	0.687
Time from exposure to onset ≤ 30 minutes	0.80 (0.43-1.47)	0.467	0.86 (0.42-1.75)	0.676
Self-injectable epinephrine prescription upon discharge	1.74 (0.90-3.36)	0.102	2.45 (0.73-8.18)	0.146
Severe anaphylaxis	1.15 (0.66-2.01)	0.619	2.29 (1.07-4.88)	0.033

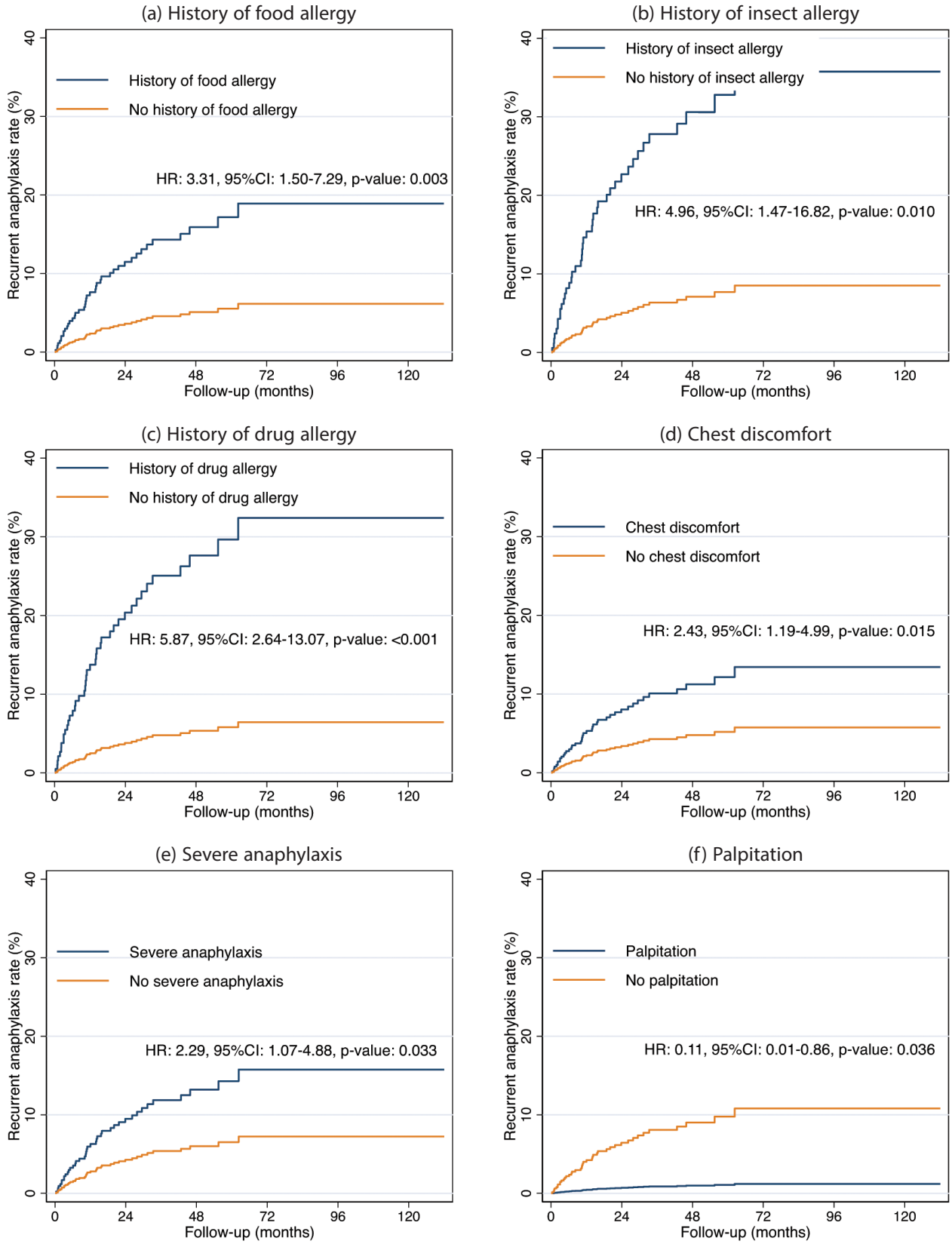

Figure 2. Kaplan-Meier curves for recurrent anaphylaxis rate in relation to 6 different statistically significant risk factors: (a) history of foods allergy, (b) history of insect allergy, (c) history of drug allergy, (d) chest discomfort, (e) severe anaphylaxis, and (f) palpitation.

Abbreviations: HR, Hazard Ratio; CI, Confident interval.

a history of insect allergy, and a history of drug allergy were significantly associated with an increased risk of recurrence (HR 3.31 [95%CI 1.50-7.29], p = 0.003; HR 4.96 [95%CI 1.47–16.82], p = 0.010; HR 5.87 [95%CI 2.64–13.07], p < 0.001, respectively). Similarly, presenting symptoms of chest discomfort and severe anaphylaxis, defined as any one of the following symptoms: hypotension, cardiovascular collapse, respiratory failure or cyanosis, or loss of consciousness, were significant clinical predictors of recurrence (HR 2.43 [95%CI 1.19-4.99], p = 0.015; HR 2.29 [95%CI 1.07-4.88], p = 0.033, respectively). Additionally, the Kaplan-Meier survival curve indicated that patients with a history of food, insect, and drug allergies, as well as those with chest discomfort and severe anaphylaxis, experienced significantly higher recurrence rates—3.3, 5.0, 5.9, 2.4, and 2.3 times greater, respectively—compared to those without these risk factors (**Figure 2**). Conversely, palpitations were significantly associated with a decreased risk of recurrent anaphylaxis (HR 0.11 [95%CI 0.01–0.86], p = 0.036). Other potential factors analyzed in the multivariable proportional hazards model, including underlying atopic diseases, asthma, atopic dermatitis, cardiovascular diseases, age (children vs. adults), specific triggers (food or medication), other presenting symptoms (urticaria, angioedema, cough, lump in the throat), symptom onset within 30 minutes, and post-discharge epinephrine prescription, were not statistically significant predictors of recurrence (**Table 4**).

Discussion

This study is the first to examine the recurrence rate of anaphylaxis and its associated risk factors in Thailand, a Southeast Asian country. Few studies worldwide have investigated the risk factors related to recurrent anaphylaxis, with variations in study design, population, follow-up duration, and statistical methods.[13,16,17,21,22] The annual recurrence rate in our study was 11.0% among anaphylaxis patients (13.2% among anaphylaxis episodes), comparable to the 11% recurrence rate among children hospitalized in pediatric intensive care units (PICU) for anaphylaxis in a French study.[15] This rate is lower than the 17.6% recurrence rate in children reported in the Cross-Canada Anaphylaxis Registry[13] and the 18% recurrence rate for food-related anaphylaxis in pediatric emergency care.[21] However, our recurrence rate is higher than the 8% observed in both children and adults in the Rochester Epidemiologic Project.[22]

By measuring time to the recurrent events to calculate an accurate recurrence rate, our study estimated a recurrence rate of 4.1 episodes per 100 person-years, consistent with rates reported in studies from Minnesota (2.6 episodes per 100 person-years),[22] Spain (3.2 episodes per 100 person-years),[17] and French PICUs (1.4 episodes per 100 person-years).[15] However, this rate is lower than the 9.1 episodes per 100 person-years in a pediatric food anaphylaxis study and the 57 episodes per 100 person-years reported in an Australian prospective study.[16,21] These differences likely stem from variations in study design (retrospective vs. prospective, cross-sectional vs. cohort), population settings, (emergency departments, allergy clinics, community-based specialist practices, intensive care units, community hospitals), and age, racial, cultural, and dietary factors.[8,15-17,21,22] Genetic predisposition, prevalence of allergic diseases, and types of allergenic agents may also contribute to these differences.

Our study revealed a low rate of allergy work-ups (46/381, 12.1%), including skin prick tests, serum-specific IgE tests, and oral food/drug challenge, as well as a low rate of self-injectable epinephrine prescriptions (11.4%) after initial anaphylaxis.[8] These factors may have contributed to recurrence. Although the recurrent group had a slightly higher allergy testing rate (11.9% [5/42]) than the non-recurrent group (9.7% [33/339]), this difference was minimal. The limited number of both allergy workups and self-injectable epinephrine prescriptions was likely due to several factors, including the limited availability of specialists at our hospital (only one pediatric allergist and no adult allergist), the absence of scheduled follow-up appointments to specialist, and failure of some patients to attend follow-up appointments.

Regarding the characteristics of our patients, females were more common in the recurrent anaphylaxis group, similar to an Australian prospective survey,[16] though most studies reported a male predominance.[13,15,22] This difference may be partly explained by the higher overall prevalence of anaphylaxis in females (59.2%) in our study population.[8] Patients with recurrent anaphylaxis in our study had higher rates of atopic diseases, including allergic rhinitis, asthma, and urticaria, as well as a statistically significant history of food, insect, and drug allergies. compared to those with non-recurrent events. This finding is consistent with previous studies showing a higher prevalence of atopy in recurrent cases.[13,15,16,23,24] A study also found that atopic patients were more likely to experience recurrent anaphylaxis.[17] However, our study observed a lower prevalence of atopic dermatitis in recurrent cases.

Food remained the most common trigger of recurrent anaphylaxis in this study, consistent with most previous studies.[13,15-17,22,23] Among food-related triggers, clams/mussels and crab were more frequently identified in the recurrent group than in the non-recurrent group. Interestingly, peanut allergy was not observed in our study, despite being the leading cause of recurrent anaphylaxis in many countries, including Canada, the USA, and France.[13,15,21,22] The types of food triggers likely reflect variations in dietary habits, genetic predisposition to allergies, and environmental exposures. This study also identified medication as the second most common trigger of recurrent anaphylaxis, with a higher prevalence in recurrent episodes than in non-recurrent cases, which aligns with findings from some previous reviews.[15,22] Among medication-related triggers, radiocontrast media was notably more prevalent in recurrent episodes.

Among clinical presenting symptoms, respiratory symptoms, such as wheezing, cyanosis, and injected conjunctivae, were more frequent in recurrent group than in the non-recurrent group, with chest discomfort, cough, and a lump in the throat being statistically significant symptoms. These symptoms may serve as warning signs for predicting recurrent events. Interestingly, cardiovascular symptoms like palpitations and hypotension were less frequent in recurrent episodes than in non-recurrent cases. Our study is comparable to one investigation which identified cough as one of the predominant clinical symptoms of recurrent anaphylaxis.[22]

The median (IQR) follow-up time for patients without recurrent events was 41.8 (23.8–61.8) months or 3.5 (1.98–5.15) years, which is comparable to a previous observational cohort study in Minnesota (median 3.1 years; IQR 1.3–5.7 years).[22] Most studies with different designs reported follow-up durations ranging from 2 to 7 years.[13,15-17,24] Patients with recurrent anaphylaxis experienced recurrence within a relatively short period, with a median time from the index event to recurrence of 10 months (IQR: 3 months to 1.5 years), which is slightly longer than the Minnesota study (7 months; IQR 1–48 months).[22] These findings highlight the need for early management and prevention strategies for patients at high risk of recurrence.

Based on the Kaplan-Meier survival curve and multivariable Cox regression analysis, anaphylactic patients with a history of food, a history of insect, and a history of drug allergies had a significantly increased risk of recurrence and a higher recurrent rate compared to those without these risk factors. These risk factors align with previous studies, which identified a history of asthma,[13,15,24] a history of atopic dermatitis,[15,22] and a history of food allergy[15,23] as significant risk factors. Some studies also found allergic rhinitis, asthma, age < 18 years, and food triggers to be significant risk factors.[13,15,17,23,25] In contrast, our study did not find allergic rhinitis, asthma, cardiovascular diseases, specific food or medication triggers, or age to be statistically significant risk factors.

Importantly, our study identified the presenting symptoms of chest discomfort and severe anaphylactic symptoms (any one of the following symptoms: hypotension, cardiovascular collapse, respiratory failure or cyanosis, and loss of consciousness) as significant risk factors for recurrent anaphylaxis. This finding is particularly crucial, as limited research has explored the association between presenting symptoms and recurrence risk. A study by Lee et al. reported cough and oral pruritus as significant predictors for recurrence.[22] Similarly, in our univariable Cox proportional hazards regression analysis, cough and a sensation of a lump in the throat were associated with an increased risk of recurrence (HR 2.36 [95%CI 0.94-5.92], p = 0.067, HR 2.40 [95%CI 1.03-5.60], p = 0.043, respectively); nonetheless, multivariable analysis did not demonstrate statistical significance. These severe anaphylactic symptoms, along with certain respiratory symptoms, such as cough, chest discomfort, and a lump in the throat, are likely predictors for recurrence and should prompt healthcare providers to prepare for and counsel patients on preventing future recurrences. Early intervention should include epinephrine auto-injector prescription upon discharge home and referring patients to an allergist for evaluation and confirmation of the trigger. Conversely, presenting symptom of palpitation was associated with a lower risk of recurrence, potentially aiding clinicians in assessing the reduced likelihood of future anaphylactic events.

This study is subject to several limitations. The retrospective design, utilizing 10-year hospital medical records, coupled with storage scarcity for paper-based medical records, which resulted in incomplete and unretrievable data may have influence the interpretation of the results. Moreover, screening medical records using ICD-10 codes specific to anaphylaxis may have excluded a small number of patients who were diagnosed under related codes, such as T78.3 (angioneurotic edema, laryngeal edema, Quincke edema, urticaria-larynx), T78.4 (allergy, unspecified), T78.9 (adverse effect, unspecified), and T80.9 (unspecified complication following infusion, transfusion, and therapeutic injection). Despite these limitations, this study represents the first survey on investigation into recurrent anaphylaxis rate and its risk factors in Thailand. Furthermore, the inclusion of a relatively large population compared to previous Thai studies enhances the significance of our findings. Future epidemiological surveys and improved study design may improve data collection and results.

Conclusion

This study demonstrated a recurrent anaphylaxis rate of 4.1 episodes per 100 person-years, with a median time from the index event to recurrence of 10 months, highlighting a relatively rapid recurrence interval. Patients without recurrence were followed for a median of 3.5 (1.98–5.15) years. Food and medications were identified as the primary triggers for recurrence. A statistically significant association was found between recurrent anaphylaxis and a history of food, a history of drug, and a history of insect allergies, as well as the initial presentation of chest discomfort and severe anaphylactic symptoms. Patients with these risk factors may be at higher risk for recurrence. Conversely, patients with palpitations appeared to have a lower likelihood of recurrence. These findings emphasize the necessity for proactive management strategies in anaphylaxis patients, particularly those exhibiting high-risk profiles, to mitigate the occurrence of subsequent episodes.

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Conflict of Interest

The authors have no conflict of interest to disclose.

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- All authors have read and approved the final manuscript.

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