ORIGINAL ARTICLE

Biphasic Anaphylaxis in Urban Emergency Patients: A Prospective Cohort Study

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Background: Despite the rising rates of anaphylaxis globally, the optimal observation period in emergency departments (EDs) remains unclear. A wide range of biphasic reaction prevalence (0.5% to 21%) and onset (0.2 to 72 h) has been reported, leading to unnecessary prolonged stays, emergency room crowding, and anxiety for patients. Thus, risk stratification could offer potential solutions.

Objective: To evaluate the incidence and onset of biphasic anaphylaxis in emergency patients.

Materials and Methods: This prospective study included patients with anaphylaxis aged ≥18 years who were admitted to an urban Thai tertiary ED between July 1, 2022, and December 31, 2023. Patients were discharged after 6 h and received phone follow-ups at 12, 24, 48, and 72 h. The patients with asthma or chronic obstructive pulmonary disease were excluded.

Results: 76 patients were included in the present study. Among them, 2 (2.63%) patients experienced biphasic anaphylaxis at 10 and 14.5 h after the initial resolution without requiring hospitalization or additional resuscitation. No biphasic reactions occurred within the 6 h observation period. Five patients returned to the ED within 24 h for nonanaphylactic urticaria. Food was the most common trigger of anaphylaxis, and urticaria was the dominant manifestation. The median time from symptom onset to ED arrival was 1.25 h (0.5 to 3 h). The mean time to epinephrine was 1.3 h (0.6 to 3.1 h). All participants received one dose of epinephrine, dexamethasone, and antihistamine simultaneously in the ED. Prednisolone and antihistamines were prescribed as home medications in almost all patients.

Conclusion: The present study showed that biphasic anaphylaxis is relatively rare with good outcomes in patients with uncomplicated anaphylaxis, indicating that a shorter observation period in EDs may suffice as a safe measure in this population.

Keywords: Anaphylaxis; Biphasic anaphylaxis; Incidence; Onset; observation period; Mortality

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The incidence of anaphylaxis is increasing worldwide, with a 0.5% to 1% mortality rate[1]. Anaphylaxis is an immediate systemic allergic reaction to allergens precipitated mainly by foods and medications. Manifestations of anaphylaxis include hives, throat tightness, breathing difficulty, shock, and death[2-4]. Several studies have demonstrated significant variation in biphasic anaphylaxis prevalence (0.5% to 21%) and onset (1 to 72 hour(s), h)[5]. A recent report showed that 7.2% of 430 patients with anaphylaxis developed biphasic anaphylaxis, with the median time from initial symptoms resolution to onset of the second reaction being 6 h (2 to 23 h) (range, 0.5 to 45 h)[6]. In Thailand, two studies conducted in 2011 and 2015 reported that 6.3% and 21.28% of patients with anaphylaxis experienced biphasic anaphylaxis, respectively[7,8]. Studies in Hong Kong and Korea reported that the incidence rates of biphasic anaphylaxis were 5.3% and 2.2%, respectively. Furthermore, they showed that biphasic reactions occurred at a mean time of 8 h (range, 1 to 23 h) and a median time of 15 h (range, 1 to 45 h)[9,10]. A far lower rate of biphasic anaphylaxis (0.4%) has been reported in the Canadian population[11]. A previous meta-analysis found that the median time to the onset of biphasic anaphylaxis was 11 h (range, 0.2 to 72 h)[12]. This inconsistency between studies may be due to the variations in definitions used in different settings.

Currently, the lack of strong evidence leads to various recommendations for the observation period after the resolution of the initial anaphylaxis[2-4,13,14]. Delayed discharge is a measure used to optimize patients' management in emergency departments (EDs).

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However, unnecessarily prolonged observation causes ED crowding, which in turn leads to adverse events, harm, and underperformance[15,16].

Biphasic anaphylaxis may occur in any individual with allergic reactions[11]. Therefore, observation in EDs after anaphylaxis resolution is recommended. However, one of the crucial issues is how long ED observation should be in patients with anaphylaxis because the time from initial resolution to biphasic reaction is considerably different, from 0.5 to the next few days[2,3,5]. The present study aimed to investigate the incidence and onset of biphasic anaphylaxis in urban emergency patients using the standard criteria defined by the World Allergy Organization (WAO[2] and the Australasian Society of Clinical Immunology and Allergy[4].

Materials and Methods

Study design and settings

This was a prospective cohort study conducted at a university ED in Bangkok, Thailand, with 60,000 emergency visits per year. The present study was approved by the Institutional Review Board (COA. 11/2560).

Study population

Patients aged ≥18 years diagnosed with anaphylaxis by the physicians in charge between July 1, 2022, and December 31, 2023, were prospectively enrolled in the present study. The exclusion criteria included patients with asthma or chronic obstructive pulmonary disease chronic obstructive pulmonary disease,, those transferred from other facilities, could not be reached via telephone follow-up, and those with low Thai literacy.

Patient involvement

Patients or their legal representatives were involved in the plan for result dissemination and reporting at the recruitment stage.

Sample size

A previous study showed that 2.3% of patients developed true biphasic anaphylaxis[17]. Therefore, 35 participants were required to provide the present study with 5% absolute precision and 95% confidence level. After adding 20% of patients for incomplete data, the minimum sample size required was 44.

Definitions and clinical diagnostic criteria

Participants were diagnosed with anaphylaxis when either of the following WAO criteria[2] was fulfilled:

(1) Acute onset of an illness (minutes to several hours) with simultaneous involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, and swollen lips/tongue/uvula) and at least one of the following symptoms:

(a) Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow rate, and hypoxemia).

(b) Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, and incontinence).

(c) Severe gastrointestinal symptoms (e.g., severe crampy abdominal pain and repetitive vomiting), especially after exposure to non-food allergens.

(2) Acute onset of hypotension, bronchospasm, or laryngeal involvement after exposure to a known or highly probable allergen for that patient (minutes to several hours), even in the absence of typical skin involvement.

Patients who simultaneously experienced skin manifestation and other systemic responses described by the Australasian Society of Clinical Immunology and Allergy[4] were also diagnosed with anaphylaxis. The mentioned signs and symptoms indicating anaphylaxis include the following:

Difficult or noisy breathing; swelling of tongue; swelling or tightness in throat; difficulty talking or hoarse voice; wheeze or persistent cough (unlike the cough in asthma, the onset of coughing during anaphylaxis is usually sudden; persistent dizziness or collapse; pale and floppy (young children); abdominal pain or vomiting.

Biphasic anaphylaxis was identified when patients met the diagnostic criteria for anaphylaxis after initial symptoms and examination findings have completely resolved without further exposure to an allergen.

Mild anaphylaxis or uncomplicated anaphylaxis was defined as an anaphylaxis without hemodynamic compromised (syncope, hypotension, signs of shock, or cardiac arrest) or respiratory distress (cyanosis, desaturation, or respiratory failure). Mild anaphylaxis needs only 1 dose of epinephrine and is well responded to treatment.

Patient management and follow-up

All patients with anaphylaxis at the study site were treated according to standard practice by physicians in charge. Epinephrine 0.5 mg. intramuscular, chlorpheniramine 10 mg. intravenous, and dexamethasone 8 mg. intravenous were the core treatment at the study site. After the stabilization process, written informed consent was obtained from the participants or their relatives.

The patients who were discharged from the ED after 6 h of observation received phone follow-ups at 12, 24, 48, and 72 h with prespecified dialog and questions to identify the recurrence of biphasic anaphylaxis by researchers or research assistants.

Outcomes

The primary outcome was the incidence of biphasic

anaphylaxis diagnosed according to the criteria. The secondary outcome was the period between recovery from anaphylaxis and the onset of subsequent biphasic anaphylaxis.

Data collection

All baseline demographic data; including age, sex, allergic history, and clinical characteristics, including signs and symptoms, vital signs, time to epinephrine administration, were collected. The onset of biphasic anaphylaxis, since the patient developed signs and symptoms that aligned with the definition, was also prospectively collected by phone. All data were obtained from the patients and/or medical records by the researchers, or trained research assistants.

Statistical analysis

Data analysis was performed using IBM SPSS Statistics for Windows, version 25.0 (Released 2013, IBM Corp., Armonk, NY, USA). Quantitative variables were presented as mean and standard deviation or median and interquartile. Categorical variables, such as gender, signs and symptoms, and allergen type, were presented as numbers and percentages.

Results

Of the 102 patients with anaphylaxis, 26 were excluded because they could not be reached by telephone follow-up (n=24) and had a history of asthma (n=2). Finally, 76 patients met the inclusion criteria and were included in this study (Figure 1).

Of the 76 eligible patients, 64.5% were females with a median age of 32 (20 to 50) years. Furthermore, 43% of the patients had an allergic history. However, only three patients experienced anaphylaxis before. Food was the most common trigger of anaphylaxis in the present study. The likely trigger could not be identified in 30.3% of the patients. Almost all patients developed skin reactions, with urticaria being the dominant manifestation. Breathing difficulty, represented by throat tightness, was the second most common symptom. Most patients demonstrated a normal range of vital signs on arrival. However, some patients had tachycardia and/or tachypnea (Table 1).

The median time from anaphylaxis onset to ED arrival was 1.25 h (range, 0.5 to 3 h). Only one dose of epinephrine 0.5 mg was intramuscularly administered to each patient within a short period after arrival without any complications such as chest pain or arrhythmia. Antihistamines (chlorpheniramine 10 mg) and corticosteroids (dexamethasone 8 mg) were also administered to all patients. One patient was admitted because of the slow resolution of angioedema, and airway compromise was a concern. Nonetheless, the patient did not develop recurrent anaphylaxis. Prednisolone was not prescribed as home medication in two patients; however, none of them developed biphasic anaphylaxis. Seven unscheduled returned visits occurred within 24 h after discharge from the ED. Two patients experienced biphasic anaphylaxis (2.63%; 95% confidence interval [CI], 0.17 to

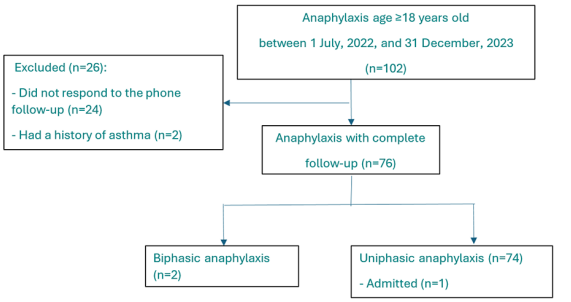

Figure 1. Flow diagram of the study.

Table 1. Demographic and clinical characteristics of anaphylactic patients (n=76)

Age (year)*	32 (20 to 50)
Female (%)	49 (64.5)
Allergic History (%)	33 (43.4)
Previous anaphylaxis (%)	3 (3.9)
Triggers (%)	
Food	39 (51.3)
Seafood	16 (41.0)
Medication	11 (14.5)
Insect	3 (3.9)
Unknown	23 (30.3)
Initial vital signs	
Systolic blood pressure⁺, mm Hg	130 (±25)
Respiratory rate⁺, bpm	20 (±4)
Heart rate⁺, bpm	96 (±23)
Body temperature*, Celsius	37.1 (36.8 to 37.2)
Oxygen saturation*, %	99 (98 to 100)
Skin manifestation (%)	73 (96.1)
Urticaria	70 (92.1)
Angioedema	2 (2.6)
Pruritic rash	1 (1.3)
Respiratory system (%)	51 (67.1)
Throat tightness	47 (61.8)
Wheezing	5 (6.6)
Gastrointestinal system (%)	24 (31.6)
Abdominal cramping	21 (27.6)
Vomiting	3 (3.9)
Cardiovascular system (%)	13 (17.1)
Lightheadedness/syncope	11 (14.5)
Palpitation	2 (2.6)

*Median with IQR; ⁺ Mean with SD

9.65) without hospitalization or resuscitation. Five patients presented with urticaria alone, which did not meet the diagnostic criteria for anaphylaxis (Table 2).

Both patients who developed biphasic anaphylactic reactions were female in their middle age, without previous anaphylaxis history. No biphasic reactions occurred within 6 h of observation. The onset of biphasic anaphylaxis was 10 and 14.5 h after the initial resolution. The manifestations of the second reaction were similar to those of the initial anaphylaxis. They were discharged home without the need for hospitalization or resuscitation (Table 3).

Discussion

To the best of our knowledge, this is one of the first few studies in Thailand to use a clear definition to examine biphasic anaphylaxis. In the present study, most patients had uncomplicated anaphylaxis, including skin reactions and breathing difficulty, without significant abnormal vital signs. Epinephrine and other medications were administered to all patients according to the standard practice. The result showed that the incidence rate of biphasic anaphylaxis among the study population was 2.63% (95% CI, 0.17 to 9.65 compared with the incidence rate of less than 1% to more than 20% reported in previous studies[5,12,18]. These conflicting results may be due to differences in diagnostic criteria, study settings, and populations.

A previous study with a similar setting to the present study showed that the incidence rate of biphasic anaphylaxis among Thai patients was as high as 21.28% (10 of 47 patients)[8]. However, nine patients had only one system involvement, and a skin reaction, such as urticaria, was the only reaction in most cases. This significant difference in the results between studies may be due to differences in diagnostic criteria for biphasic anaphylaxis. The reasonable incidence rate might be 2.1% when the WAO criteria were strictly applied. Furthermore, two other retrospective cohort studies in Thai EDs on 208 and 441 patients with anaphylaxis reported that the incidence rates of biphasic anaphylaxis were 6.25% and 1.4%, respectively, without mentioning the diagnostic criteria for biphasic reaction[7,19]. A previous study showed that 8.7% of Thai pediatric patients experienced biphasic reactions. However, this incidence rate might be falsely high because nonanaphylactic reactions were regarded as biphasic anaphylaxis[20].

Despite applying the diagnostic criteria used in the present study, Ellis et al. reported an incidence rate of biphasic anaphylaxis of 19.4%, which is much higher than that reported in this study[21]. In their study, epinephrine was administered to a few patients, especially in the biphasic group, whereas epinephrine was administered to all patients in the present study. This could be the reason for the discrepancy in the incidence rates. Conversely, only 0.4% of 496 anaphylaxis patients at two large EDs in Canada experienced biphasic anaphylaxis, and epinephrine was injected in only half of them[11]. Unreceiving epinephrine or delaying its administration has been reported to be significantly associated with biphasic anaphylaxis[7,22,23]. Other studies have shown no correlation between delayed epinephrine administration and the biphasic reaction[8,9,17].

Anaphylaxis with severe symptoms or required more than one dose of epinephrine were the risk factors of biphasic anaphylaxis[14]. A cohort study reported that patients who required more epinephrine tended to experience biphasic reactions, which occurred in 18% (6 of 34 patients) of cases[24]. However, none of 83 patients with severe anaphylaxis admitted to the intensive care units in

Table 2. Treatment received at the ED and outcomes

	Number of patients (%)
Onset to ED (hour)+	1.25 (0.5 to 3.0)
Onset to epinephrine (hour)+	1.3 (0.6 to 3.1)
Medication given during anaphylaxis (%)	
Epinephrine IM	76 (100)
Dexamethasone	76 (100)
Antihistamine(chlorpheniramine)	76 (100)
Salbutamol	5 (6.6)
Normal saline	7 (9.2)
ED disposition (%)	
Discharged home	75 (98.7)
Home medication (%)	
Prednisolone	74 (97.4)
Chlorpheniramine	71 (93.4)
Cetirizine	5 (6.58)
Return visit within 24 hours (%)	7 (9.2)
Biphasic anaphylaxis	2 (2.63)
Non-anaphylactic urticaria	5 (6.58)

+ Mean with SD

Table 3. Characteristics of biphasic anaphylactic patients

Gender	Age (year)	Allergic History	Trigger	Previous anaphylaxis	Onset to epinephrine	Time to biphasic anaphylaxis	Anaphylaxis symptoms	Biphasic anaphylaxis symptoms	ED Disposition
Female	50	Doxycycline	Unknown	None	60 minutes	14.5 hours	Urticaria & lightheadedness	Urticaria & syncope	Discharged
Female	45	Yeast	Bread	None	30 minutes	10 hours	Urticaria & throat tightness	Urticaria & wheezing	Discharged

Denmark's capital region between 2011 and 2014, developed biphasic anaphylaxis[25]. Unlike our study, in most cases, anaphylaxis was mild and required only one standard dose of epinephrine.

Studies using similar criteria revealed an incidence rate of biphasic anaphylaxis comparable to that in the present study. Ko et al. reported an incidence rate of 2.2%[10], a 13-year retrospective review showed an incidence rate of 2.3%[17], and a slightly higher incidence was reported at 5%[6,26].

Biphasic anaphylaxis may occur in any individual with allergic reactions[11]. Therefore, observation in EDs after anaphylaxis resolution is recommended. However, one of the crucial issues is how long ED observation should be in patients with anaphylaxis because the time from initial resolution to biphasic reaction is considerably different, from 0.5 to the next few days[2,3,5], which leads to controversy on the observation period. Currently, no consensus has been reached on the optimal observation period because of the wide range of biphasic reaction onset[6,12]. The Australian guidelines recommend at least 4 h of observation[4], whereas the United Kingdom and European guidelines recommend a longer observation period of up to 24 h[3,13]. Notably, the observation period is not stated in the 2023 updated American Joint Task Force or the 2020 WAO guidelines[2,27].

In the present study, both cases of biphasic anaphylaxis occurred outside the traditional 6 h observation period, consistent with the median onset time reported in Thailand[7,8], Asia[9,10], and internationally[6,17,21,22,24-26]. Moreover, a systematic review and meta-analysis including 4,165 patients with anaphylaxis, with 193 (4.6%) having biphasic reactions, concluded that the median time to biphasic anaphylaxis was 11 h[12], which is comparable to another study[18].

Nonetheless, biphasic anaphylaxis could occur within the first few hours of ED observation. Grunau et al. reported that one patient developed biphasic reaction around 3 h, and another had recurrent symptoms 16 min after ED arrival[11]. According to the American guidelines, the latter is probably not biphasic anaphylaxis[27]. In a recent prospective cohort study, approximately half of the biphasic reactions (16 of 31) occurred within 6 h. However, at least seven of them did not meet the criteria of biphasic anaphylaxis due to having only mucocutaneous reactions[6]. In a study of 872 patients with anaphylaxis (one-fourth were children) with 4.1% subsequent biphasic reactions, the median onset was 3 h (range, 0.5 to 44 h). Notably, only half of the biphasic anaphylaxis patients received epinephrine[22].

An older study reported fatality in two biphasic anaphylaxis cases who were not treated with epinephrine[28]. Conversely, zero mortality was reported in a contemporary study in which all 59 patients with anaphylaxis received epinephrine with four biphasic reactions[26]. More recent studies have shown that mortality is rare in biphasic anaphylaxis cases[5,6,11,12,19]. A previous study showed no statistically significant difference in biphasic episodes between ≥8 h of observation and a lower observation period. Furthermore, none of the 532 patients, including those who experienced biphasic episodes, had any mortality after a 10-day follow-up[17]. These findings are similar to those of a large cohort study, which reported five cases of biphasic anaphylaxis in 496 patients with anaphylaxis with a 7-day follow-up (95% CI, 0 to 0.17)[11]. Another prospective study on 430 patients with anaphylactic reactions with 31 cases of subsequent episodes showed zero mortality rate within 7 days[6]. Moreover, no fatal outcomes were reported among 49 biphasic reactions following 696 anaphylactic reactions in the Thai population[7,8,19]. According to systematic reviews, severe biphasic reactions or death is rare[2,5,12-14,23,27]. Most fatal anaphylaxis and biphasic reactions occur in suboptimal treatment groups or individuals with significant underlying diseases[3,13,27].

Fatal anaphylaxis is rare, with an incidence rate of 0.25% to 0.33% among ED and hospitalized populations. Suboptimal treatment, older age, adolescence, poorly controlled asthma, and other respiratory diseases are risk factors associated with fatal anaphylaxis[23]. In the present study, almost all patients were not older adults without airway diseases. This could be the reason for the mild biphasic reactions.

One patient among 23 unknown allergen anaphylaxis episodes (4.3%) experienced a biphasic reaction, compared with 1.8% in which triggers were identified. Previous studies demonstrated that undetermined precipitant relates to biphasic anaphylaxis occurrence[12,22].

Delayed discharge is a measure that helps delineate unwanted outcomes. However, prolonged observation, especially over 4 h, leads to high ED occupancy and crowding. Crowded ED has been identified as a cause of ED underperformance and harmful events[15,16]. The findings of the present study indicate that an early discharge may be appropriate for patients with uncomplicated anaphylaxis who have the following characteristics: nonolder adult, without asthma or COPD, normal vital signs on presentation, and rapid improvement with one dose of epinephrine. This practice may help minimize ED crowding and avoid its negative consequences.

A meta-analysis of 2,890 patients with anaphylactic episodes with an incidence rate of recurrent reactions of 4.9%, 95% of the patients did not have biphasic reactions after 1 h of observation (95% CI, 90.9% to 97.3%)[18]. They also found that the negative predictive value increased gradually with a longer observation period; however, the incidence rate did not accordingly increase.

Individualized anaphylaxis observation planning based on multiple factors is a current suggested strategy[2,3,5,13,14]. Early discharge in a selected group of patients is supported by the Resuscitation Council UK. They recommend a 2 h observation period in patients with mild anaphylaxis who require only one dose of epinephrine with a rapid response and complete resolution[23]. These characteristics were found in almost all patients in the present study, except receiving epinephrine within 30 min of anaphylaxis onset. However, time to epinephrine administration as a predictor of biphasic anaphylaxis is still controversial, and both biphasic reactions in the present study occurred in patients who were injected with epinephrine in that reference range[5,6,22,27].

Biphasic anaphylaxis possibly occurs outside a healthcare facility, health literacy, and giving a patient autoinjector epinephrine could be beneficial in fatal biphasic anaphylaxis prevention.

Limitations

The present study has several limitations. First, the sample size of patients with anaphylaxis was small, which might have led to a low incidence of biphasic anaphylaxis. Therefore, the authors could not perform a robust comparative statistical analysis. Second, this was a single urban center study. Thus, the results should be verified in other settings. Third, none of the participants had unstable or severe anaphylaxis. Therefore, the results do not represent all ranges of allergic reactions. Fourth, biphasic reactions may occur after the 72-hour phone follow-up. Furthermore, the participants' memory might have an impact on the accuracy of biphasic anaphylaxis onset. Fifth, selection bias must be considered along with other limitations. Although a clear definition was used for inclusion, this clinical diagnosis alone is not sufficient to differentiate anaphylaxis from other conditions. Finally, unaware re-exposure to an allergen could be the cause of biphasic reactions in the present study.

Conclusion

The present study, which included a limited number of patients with uncomplicated anaphylaxis, showed that biphasic anaphylaxis was relatively rare and mild and occurred outside the traditional ED observation period. This study extends the evidence on the observation period in the mild anaphylaxis group in which a shorter ED observation period with early discharge would be considered for this specific population.

What is already known on this topic?

The incidence and onset of biphasic anaphylaxis varies greatly. Accordingly, the observation period after anaphylaxis is controversial, leading to an unnecessarily prolonged observation period in EDs.

What this study adds?

The incidence of biphasic anaphylaxis is relatively rare when the diagnostic criteria for anaphylaxis and subsequent biphasic reactions are strictly applied in healthy nonolder adults who have a good response to epinephrine. This study expands the evidence of a short observation period in healthy, nonolder patients with anaphylaxis who have a good response to epinephrine.

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Conflicts of interest

The authors declare no conflict of interest.

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