



# A multicenter anaphylaxis registry in Korea: Clinical characteristics and acute treatment details from infants to older adults

Kyunguk Jeong<sup>a</sup>, Young-Min Ye<sup>b</sup>, Sang-Ha Kim<sup>c</sup>, Kyung Won Kim<sup>d</sup>, Jeong Hee Kim<sup>e</sup>, Ji-Won Kwon<sup>f</sup>, Song-I. Yang<sup>g</sup>, So-Yeon Lee<sup>g,†</sup>, Eun Hee Chung<sup>h</sup>, Mi-Ae Kim<sup>i</sup>, Yoon Hee Kim<sup>d</sup>, Hye-Young Kim<sup>j</sup>, Gwang Cheon Jang<sup>k</sup>, Joo-Hee Kim<sup>l</sup>, Eunjoo Lee<sup>a,‡</sup>, Jihyun Kim<sup>m</sup>, Kangmo Ahn<sup>m</sup>, Yoon-Seok Chang<sup>n</sup>, Gyu-Young Hur<sup>o</sup>, Jeongmin Lee<sup>p</sup>, Taek Ki Min<sup>q</sup>, Bok-Yang Pyun<sup>q</sup>, Kyung Hee Park<sup>r</sup>, Jaechun Lee<sup>s</sup>, Tae Won Song<sup>t</sup>, Hye Mi Jee<sup>u</sup>, Yoo Seob Shin<sup>b</sup>, Dankyu Yoon<sup>v</sup>, Jeom-Kyu Lee<sup>v</sup> and Sooyoung Lee<sup>a\*</sup>

## ABSTRACT

**Background:** Although the prevalence of anaphylaxis is increasing worldwide, the large-scale studies in Asia evaluating anaphylaxis in all age groups are limited. We aimed to collect more precise and standardized data on anaphylaxis in Korea using the first multicenter web-based registry.

**Methods:** Twenty-two departments from 16 hospitals participated from November 2016 to December 2018. A web-based case report form, designed by allergy specialists, was used to collect anaphylaxis data.

**Results:** Within the 2-year period, 558 anaphylaxis cases were registered. The age of registered patients ranged from 2 months to 84 years, and 60% were aged <18 years. In children and adolescents, foods (84.8%) were the most common cause of anaphylaxis, followed by drugs (7.2%); in adults, drugs (58.3%) were the most common cause, followed by foods (28.3%) and insect venom (8.1%). The onset time was ≤10 min in 37.6% of patients. Among the 351 cases registered via the emergency department (ED) of participating hospitals, epinephrine was administered to 63.8% of patients. Among those receiving epinephrine in the ED, 13.8% required 2 or more epinephrine shots. Severe anaphylaxis accounted for 23.5% cases (38.1% in adults; 13.7% in children); patients with drug and insect venom-induced anaphylaxis had higher rates of severe anaphylaxis.

**Conclusion:** This multicenter registry provides data on anaphylaxis for all age groups for the first time in Asia. The major causes and severity of anaphylaxis were remarkably different according to age group, and the acute treatment features of anaphylaxis in the EDs were examined in detail.

**Keywords:** Anaphylaxis, Registry, Severity, Trigger, Epinephrine

<sup>a</sup>Department of Pediatrics, Ajou University School of Medicine, Suwon, South Korea

\*Corresponding author. Department of Pediatrics, Ajou University School of Medicine, Worldcup-ro 164, Yeongtong-gu, Suwon 16499, South Korea. E-mail: [jsjs87@ajou.ac.kr](mailto:jsjs87@ajou.ac.kr)

<sup>†</sup>The current affiliation of So-Yeon Lee is "Department of Pediatrics, Childhood Asthma Atopy Center, Environmental Health Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea".

<sup>‡</sup>The current affiliation of Eunjoo Lee is "Department of Pediatrics, Haeundae Paik Hospital, Inje University College of Medicine, Busan, South Korea".

Full list of author information is available at the end of the article

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## INTRODUCTION

Anaphylaxis, a severe and life-threatening systemic hypersensitivity reaction, is mostly triggered by food, drugs, or insect venom.<sup>1,2</sup> The expected lifetime prevalence of anaphylaxis is 0.05%–2%;<sup>3,4</sup> recent studies show a profoundly rising trend.<sup>5–8</sup> Food is the most common trigger of anaphylaxis in children, whereas drugs and insect venom are more common causes in adults.<sup>9</sup> However, anaphylaxis patterns according to different age groups have not been adequately studied in a large population. Through the European Anaphylaxis Registry, established in 2007, valuable information regarding the clinical features of anaphylaxis have been collected and published.<sup>9–11</sup> The use of intramuscular epinephrine to treat anaphylaxis is still suboptimal,<sup>9</sup> despite being the first-line treatment recommended by international guidelines. In Korea, previous anaphylaxis studies were mostly retrospective medical chart reviews focusing on specific age groups, either children or adults.<sup>12,13</sup> Recent big data analyses on anaphylaxis are useful in investigating the epidemiology or trends over a period of time;<sup>14,15</sup> however, limitations exist as some factors such as eliciting triggers, severity, or treatment cannot be identified through the national big data. Hence, we developed a multicenter web-based registry to investigate the triggers, clinical features, and treatment details of anaphylaxis in Korean patients, including all age groups.

## METHODS

### Study design and participants

Allergy specialists from 22 departments in 16 tertiary or secondary hospitals in Korea took part in this registry from November 2016 to December 2018. Participation of allergy centers was voluntary; this study was approved by the institutional review board of each hospital. Patient recruitment involved identification of anaphylaxis cases by participating allergists at the time of admission from the emergency department (ED) or at the follow-up outpatient department (OPD) visit. In the case of anaphylaxis patients who had been treated at another hospital for acute anaphylactic symptoms and visited the OPD of a participating hospital for further workup or long-term management, cases managed within the last 3 months from the visit day with an identifiable date of anaphylaxis

were included. After obtaining written consent, the allergist completed a standardized case report form (CRF). The diagnosis of anaphylaxis was based on the criteria published in 2006 by the National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network.<sup>2</sup>

### Web-based registry and variables

The data assessed by the web-based systematic CRF developed by allergy specialists in this registry were date of anaphylactic reaction, date of hospital visit, route of visit to participating hospitals (ED, OPD, or ward), demographic profiles, medical history, family history of allergic diseases, triggers of current anaphylactic reaction, time of symptom onset after exposure to the trigger, place of occurrence, symptom profile, presence of cofactors, acute treatment details, and laboratory tests performed. In the analysis, adult participants were divided into age groups with 10-year intervals; pediatric and adolescent participants were categorized as infants (<24 months), preschool children (2–6 years), schoolchildren (7–12 years), and adolescents (13–17 years) to illustrate the age-specific pattern according to developmental and social stages. Anaphylaxis severity was classified according to the modified grading system published by Brown.<sup>16</sup>

### Statistics

All analyses were conducted using SPSS 20.0 for Windows (SPSS, Inc., Chicago, IL, USA). This study mainly contains raw, stratified description of variables. Categorical variables were expressed as a percentage or ratio. Comparison between groups was performed using Fisher's exact test. *P* values < 0.05 were considered significant. Missing data were minimized by configuring the final save of the web-based CRF only when essential variables were completed.

## RESULTS

### Participating centers and participants' demographic data

The data of 558 participants from 16 centers in Korea were obtained. Of these, 351 (62.9%) patients visited the EDs of participating hospitals during acute anaphylaxis episodes; 35.1% visited the OPDs of participating centers after acute anaphylaxis episodes; and 2.0% experienced

anaphylaxis in the wards. Women accounted for 45.2%; female sex was predominant in adults (56.5%) compared to in children (37.6%). Children aged <18 years accounted for 60% of the registered patients. Among children and adolescents, the proportion of preschool children (2-6 years) was the highest, followed by infants (<24 months) and schoolchildren (7-12 years). Among adults, the proportion of middle-aged patients aged 40-49 years was the highest (Table 1). Known food

allergy was the most common comorbidity in children, followed by atopic dermatitis, allergic rhinitis, previous anaphylaxis, and asthma. The percentages of food allergy and atopic dermatitis were remarkably lower in adults than in children, while the percentage of drug allergy was higher in adults than in children. Family history of allergic diseases was present in 76.1% of children and 31.8% of adults.

Sex	n (%)	
Female	252 (45.2)	
Male	306 (54.8)	
Age	n (%)	
Children and adolescents (<18 years)	335 (60.0)	
Adults (≥18 years)	223 (40.0)	
Age sub-groups		
<24 months	93 (16.7)	
2-6 years	143 (25.6)	
7-12 years	67 (12.0)	
13-17 years	32 (5.7)	
18-29 years	45 (8.1)	
30-39 years	34 (6.1)	
40-49 years	54 (9.7)	
50-59 years	48 (8.6)	
60-69 years	30 (5.4)	
≥70 years	12 (2.2)	
Comorbidities <sup>a</sup>	n (%)	
	<18 years	≥18 years
Asthma	36 (10.7)	11 (4.9)
Allergic rhinitis	98 (29.3)	62 (27.8)
Atopic dermatitis	159 (47.5)	9 (4.0)
Chronic urticaria	12 (3.6)	5 (2.2)
Anaphylaxis (previous)	72 (21.5)	37 (16.6)
Food allergy	203 (60.6)	41 (18.4)
Drug allergy	16 (4.8)	24 (10.8)
Diabetes mellitus	0 (0.0)	14 (6.3)
Hypertension	0 (0.0)	33 (14.8)
Other cardiovascular diseases	0 (0.0)	6 (2.7)
Family history of allergic diseases	n (%)	
	<18 years	≥18 years
	255 (76.1)	71 (31.8)

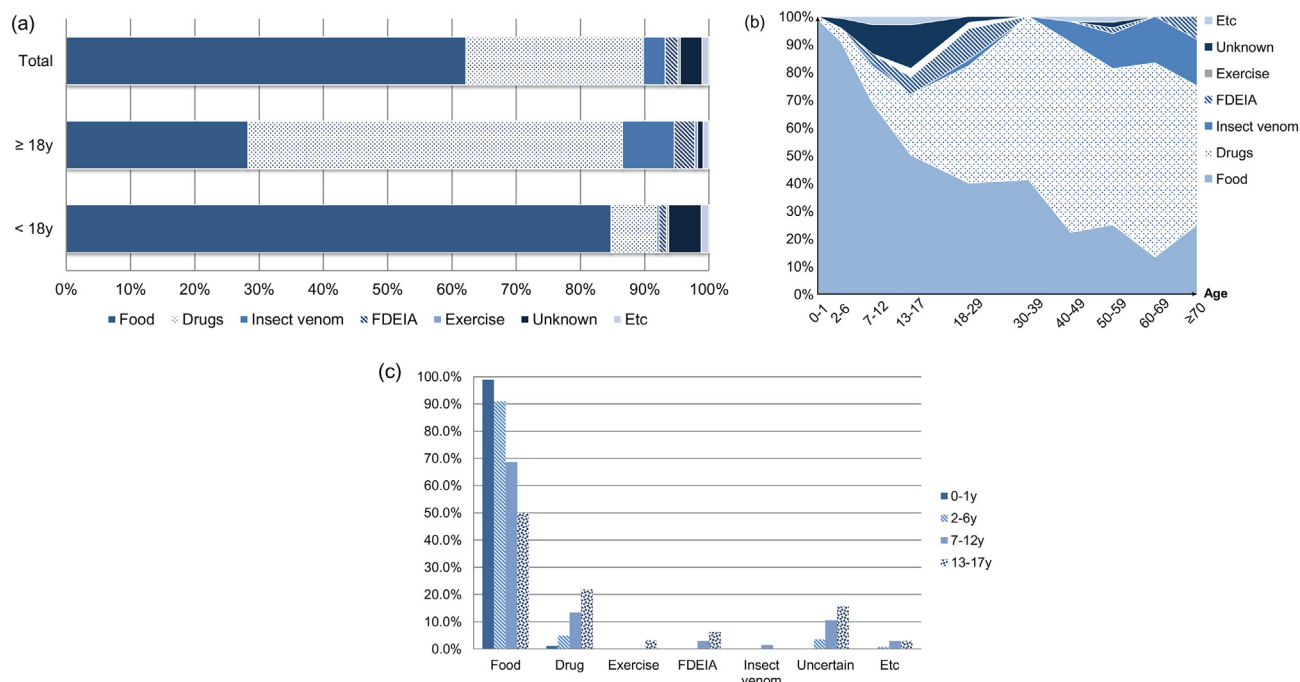
**Table 1.** Participants' demographic profile. *a.* Most of the participants had more than one comorbidity

## Triggers of anaphylaxis

Of the 558 cases, food (62.2%) was the most common cause of anaphylaxis, followed by drugs (27.6%), insect venom (3.4%), food-dependent exercise-induced anaphylaxis (FDEIA, 2.0%), and exercise (0.4%). Other triggers such as cat fur, feather of unknown bird, hair dye, and bee pollen accounted for 1.1%. Specific anaphylaxis triggers were not identified in 3.4% of patients. Patterns of anaphylaxis triggers were remarkably different in children and adults (Fig. 1 A). In children (age <18 years, n = 335), food accounted for 84.8%, followed by drugs (7.2%); in adults (n = 223), drugs (58.3%) were a more common trigger than food (28.3). Insect venom-induced anaphylaxis was observed only in 0.3% of children, but the percentage was relatively high (8.1%) in adults. Exercised-induced anaphylaxis was observed in 0.3% of children and 0.4% of adults. On sub-analysis, the pattern of anaphylaxis trigger was distinct in every age group (Fig. 1 B and C). Food was the most common cause of anaphylaxis in infants (98.9%), and the proportion of food-induced anaphylaxis decreased as age increased. The proportion of drug-induced anaphylaxis increased as age increased (Fig. 1 C). The percentage of idiopathic anaphylaxis was higher

in older children than in younger children. In adults, the proportion of food-induced anaphylaxis was higher in young adults, and the percentage of drug-induced anaphylaxis was higher in patients in their 40s (68.5%) and 60s (70%). The percentage of insect venom-induced anaphylaxis was higher in older patients than in young adults.

Of the 284 cases of food-induced anaphylaxis in children, hen's egg was the most common cause, followed by cow's milk, walnuts, wheat, and peanut (Table 2). Other food triggers, which accounted for more than 5 cases each, in children were kiwi (n = 12), pine nuts (n = 11), buckwheat (n = 9), and soybean (n = 5). Minor food triggers included cashew nuts (n = 4), shrimp (n = 4), unspecified tree nuts (n = 3), fish (n = 3), vegetables (n = 3), pistachio, hazelnuts, mango, almonds, peach, apple (2 cases each), macadamia nuts, mulberry, banana, strawberry, grape, melon, crab, unspecified crustaceans, and shellfish (1 case each). Other uncategorized food triggers included multiple foods taken at the same time or consumption of processed food products. Of the 24 cases of drug-induced anaphylaxis in children, analgesics accounted for 54.2%, followed by antibiotics (16.7%). The detailed individual drug list of causative analgesics



**Fig. 1** Triggers of anaphylaxis. (a) In overall. (b) By age groups. (c) In children and adolescents by age sub-groups. FDEIA: food-dependent exercise-induced anaphylaxis

		Triggers	n (% <sup>b</sup> )		
<b>Children and adolescents (&lt;18 years)</b>	<b>Food</b>	Hen's egg	72 (25.4)		
		Cow's milk	51 (18.0)		
		Walnut	27 (9.5)		
		Wheat	23 (8.1)		
		Peanut	14 (4.9)		
		Kiwi	12 (4.2)		
		Pine nut	11 (3.9)		
		Buckwheat	9 (3.2)		
		Soybean	5 (1.8)		
		Other foods	60 (21.1)		
	<b>Drugs</b>	Analgesics	13 (54.2)		
		Antibiotics	4 (16.7)		
		Other drugs	7 (29.1)		
<b>Adults (≥18 years)</b>	<b>Food</b>	Shrimp	14 (22.2)		
		Wheat	12 (19.0)		
		Crab	4 (6.3)		
		Soybean	2 (3.2)		
		Peanut	2 (3.2)		
		Beef	2 (3.2)		
		Pork	2 (3.2)		
		Other foods	25 (39.7)		
			<b>Drugs</b>	Antibiotics	65 (50.0)
				Analgesics	24 (18.5)
H <sub>2</sub> blockers	23 (17.7)				
Radiocontrast media	2 (1.5)				
Other drugs	16 (12.3)				

**Table 2.** Specific food triggers and drug triggers of anaphylaxis. *b.* Refers to the percentage within the same category

and antibiotics in children is described in the [Supplemental Table 1](#). Other drug triggers included H<sub>2</sub> histamine receptor antagonist, vaccines, and traditional medicine.

The patterns of food- and drug-induced anaphylaxis differed between children and adults. In 63 adult cases of food-induced anaphylaxis, shrimp was the most common cause, followed by

wheat and crab. Two cases of anaphylaxis induced by soybean, peanuts, beef, and pork, respectively, were reported. The food triggers in adults were mango, melon, plum, cow's milk, almonds, macadamia nuts, unspecified vegetable, buckwheat, unspecified crustaceans, cuttlefish, and pupa, with 1 case for each trigger. Among the 130 cases of drug-induced anaphylaxis in adults, antibiotics accounted for 50%, among which cefaclor was the most common culprit. Analgesics, H<sub>2</sub> histamine receptor antagonist, and radiocontrast media were among the drugs that trigger anaphylaxis in adults, while minor drug triggers in adults included anesthetics and chemotherapeutic agents. The detailed individual drug list of causative antibiotics, analgesics, and H<sub>2</sub> histamine receptor antagonists in adults is described in the [Supplemental Table 1](#).

The percentages of patients in whom serum tryptase levels, total immunoglobulin E, and tests for anaphylaxis cause were performed were 23.8%, 81.4%, and 81.4%, respectively. The proportion of patients who were tested to determine the cause of anaphylaxis was 84.2% in children and 77.1% in adults (results not described in this paper).

### Symptom profile, onset time, places of occurrence, and cofactors

Cutaneous symptom was observed in >90% of patients in both children and adults ([Table 3](#)), followed by respiratory (83.2%), gastrointestinal (48.9%), neurologic (30.3%), and cardiovascular (28.1%) symptoms. Compared with children, cardiovascular and neurologic symptoms were significantly higher in adults. Among detailed symptom profiles, there was a higher percentage of itching symptom in adults, whereas oral mucosal symptoms were more common in children. The percentage of respiratory symptoms was similar in children and adults; the proportion of rhinorrhea, stridor, cough, wheezing, and cyanosis was significantly higher in children, while that of dyspnea was higher in adults. Among gastrointestinal symptoms, the proportion of nausea, diarrhea, and abdominal pain was significantly higher in adults. Most of the cardiovascular symptoms were more commonly observed in adults, except pallor. Among neurologic symptoms, the proportion of dizziness

and loss of consciousness was significantly higher in adults.

Information on symptom onset time was available for 507 of 558 cases (311 children and 196 adults). Among these, symptom onset time was ≤10 minutes in 41.4%, 10–30 minutes in 30.6%, between 30 minutes and 2 hours in 21.3%, and >2 hours in 6.7%. In both children and adults, the most common place of anaphylaxis occurrence was the patient's own home ([Table 4](#)). Other major places of occurrence included restaurants, childcare centers, schools, workplaces, outdoors, and other people's homes. The anaphylaxis cases reported in hospitals occurred during oral food challenge tests.

Cofactors were present in 16.8% of the participants, absent in 64.8%, and the presence of cofactors was not definite in 18.5%. In children, cofactors were present in 18.8%, with acute infectious illness (n = 26) as the most common cofactor. The other cofactors in children included exercise (n = 17), major change in lifecycle such as travel (n = 5), and menstruation (n = 2). In adults, cofactors were present in 13.9%, with exercise (n = 9) being the most common cofactor. The other cofactors in adults included alcohol intake (n = 5), sleep deprivation (n = 4), acute infectious illness (n = 2), and mental stress (n = 2). Other minor cofactors both in adults and children included extreme temperatures, vaccination, and excessive physical activities.

### Emergency treatment of anaphylaxis and progress

We analyzed the treatment details of the 351 patients (190 children and 161 adults) who visited the ED of participating hospitals at the time of acute anaphylaxis event. The epinephrine administration rates were 66.7% and 61.3% in children and adults, respectively; the administration rates of intravenous fluids, systemic steroids, or H<sub>1</sub> antihistamine were higher than that of epinephrine ([Fig. 2](#)). Among the 224 patients (124 children and 98 adults) receiving epinephrine in the ED, epinephrine was administered within 1 hour of ED arrival in 91.2% of children and 81.6% of adults ([Table 5](#)). The route of epinephrine administration was intramuscular in 90.5% of children and 79.6% of adults. The number of



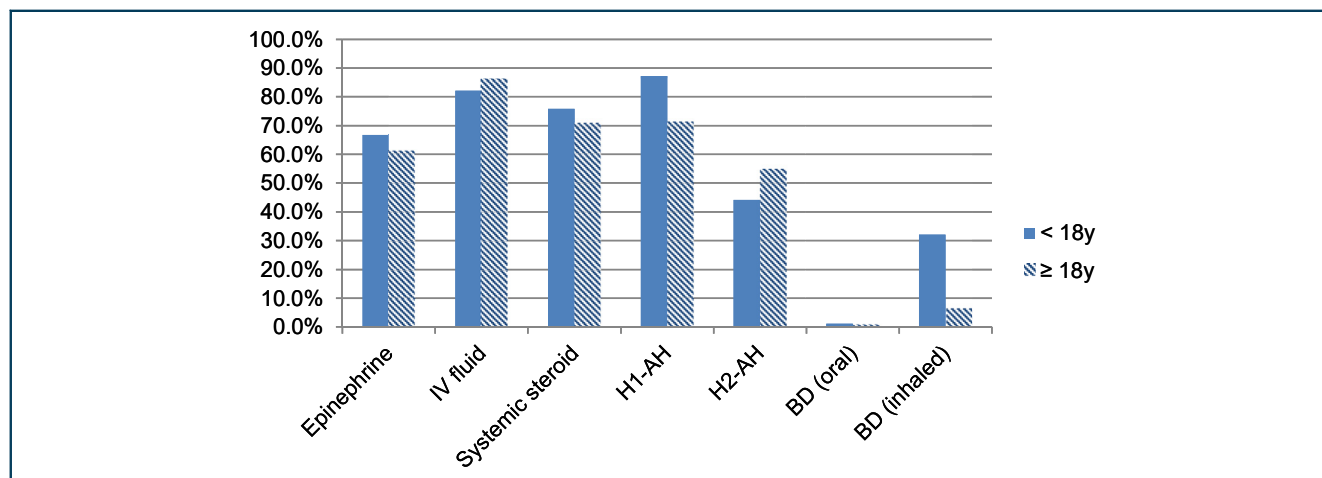
Symptoms <sup>c</sup>	n (%)		P value <sup>d</sup>
	<18 years	≥18 years	
<b>Cutaneous</b>	<b>317 (94.6)</b>	<b>207 (92.8)</b>	<b>0.636</b>
Itching	135 (40.3)	133 (59.6)	<0.001
Urticaria	235 (70.1)	148 (66.4)	0.353
Erythema	112 (33.4)	63 (28.3)	0.226
Angioedema	168 (50.1)	116 (52.0)	0.667
Pruritus and swelling of lips-tongue-uvula	66 (19.7)	23 (10.3)	0.003
<b>Respiratory</b>	<b>279 (83.3)</b>	<b>185 (83.0)</b>	<b>0.294</b>
Rhinorrhea	30 (9.0)	7 (3.1)	0.008
Stridor	15 (4.5)	0 (0.0)	0.001
Dyspnea	168 (50.1)	182 (81.6)	<0.001
Cough	141 (42.1)	10 (4.5)	<0.001
Wheezing	95 (28.4)	8 (3.6)	<0.001
Cyanosis	24 (7.2)	4 (1.8)	0.005
<b>Gastrointestinal</b>	<b>163 (48.7)</b>	<b>110 (49.3)</b>	<b>0.410</b>
Nausea	36 (10.7)	67 (30.0)	<0.001
Vomiting	108 (32.2)	66 (29.6)	0.516
Diarrhea	9 (2.7)	31 (13.9)	<0.001
Abdominal pain	57 (17.0)	72 (32.3)	<0.001
<b>Cardiovascular</b>	<b>61 (18.2)</b>	<b>96 (43.0)</b>	<b>&lt;0.001</b>
Chest pain	16 (4.8)	22 (9.9)	0.025
Pallor	26 (7.8)	4 (1.8)	0.002
Collapse	4 (1.2)	12 (5.4)	0.007
Diaphoresis	4 (1.2)	12 (5.4)	0.007
Hypotension	22 (6.6)	64 (28.7)	<0.001
Arrest	0 (0.0)	0 (0.0)	N/A
<b>Neurologic</b>	<b>60 (17.9)</b>	<b>109 (48.9)</b>	<b>&lt;0.001</b>
Dizziness	23 (6.9)	75 (33.6)	<0.001
Anxiety	12 (3.6)	12 (5.4)	0.394
Paresthesia	1 (0.3)	1 (0.4)	1.000
Weakness	30 (9.0)	17 (7.6)	0.642
Confusion	0 (0.0)	2 (0.9)	0.159
Loss of consciousness	1 (0.3)	38 (17.0)	<0.001
<b>Death</b>	<b>0 (0.0)</b>	<b>0 (0.0)</b>	<b>N/A</b>

**Table 3.** Clinical manifestations of anaphylaxis. *c.* More than one symptom was recorded in each case. *d.* Fisher's exact test

epinephrine shots administered in the ED were as follows: 1, 84.9% children and 63.3% adults; 2, 10.3% children and 18.4% adults; and  $\geq 3$ , 3.2% children and 7.1% adults.

After acute anaphylaxis treatment in the ED, 43% patients were hospitalized (41%, general wards; 2%, intensive care unit) for further treatment

or close observation. A biphasic reaction was observed in 4.3% of patients, while a sustained reaction was observed in 2.3%. After acute anaphylaxis treatment in the ED, epinephrine autoinjector was prescribed to 59% of patients, with a higher percentage in adults (62.7%) than in children (55.8%).



**Fig. 2** Treatment details of anaphylaxis patients in the emergency departments of participating hospitals. IV: intravenous, H1-AH: H<sub>1</sub> antihistamine, H2-AH: H<sub>2</sub> antihistamine, BD: bronchodilator

### Severity of anaphylaxis

Severe anaphylaxis combined with hypoxia, hypotension, or neurologic compromise according

to Brown's classification<sup>16</sup> was observed in 23.5% of patients; the percentage of severe anaphylaxis increased with age (Fig. 3 A). The percentage of severe anaphylaxis in children was 13.7%: 9.7%,

Symptom onset time after exposure to trigger	n (%) <sup>e</sup>	
≤10 minutes	210 (41.4)	
10-30 minutes	155 (30.6)	
0.5-2 hours	108 (21.3)	
>2 hours	34 (6.7)	

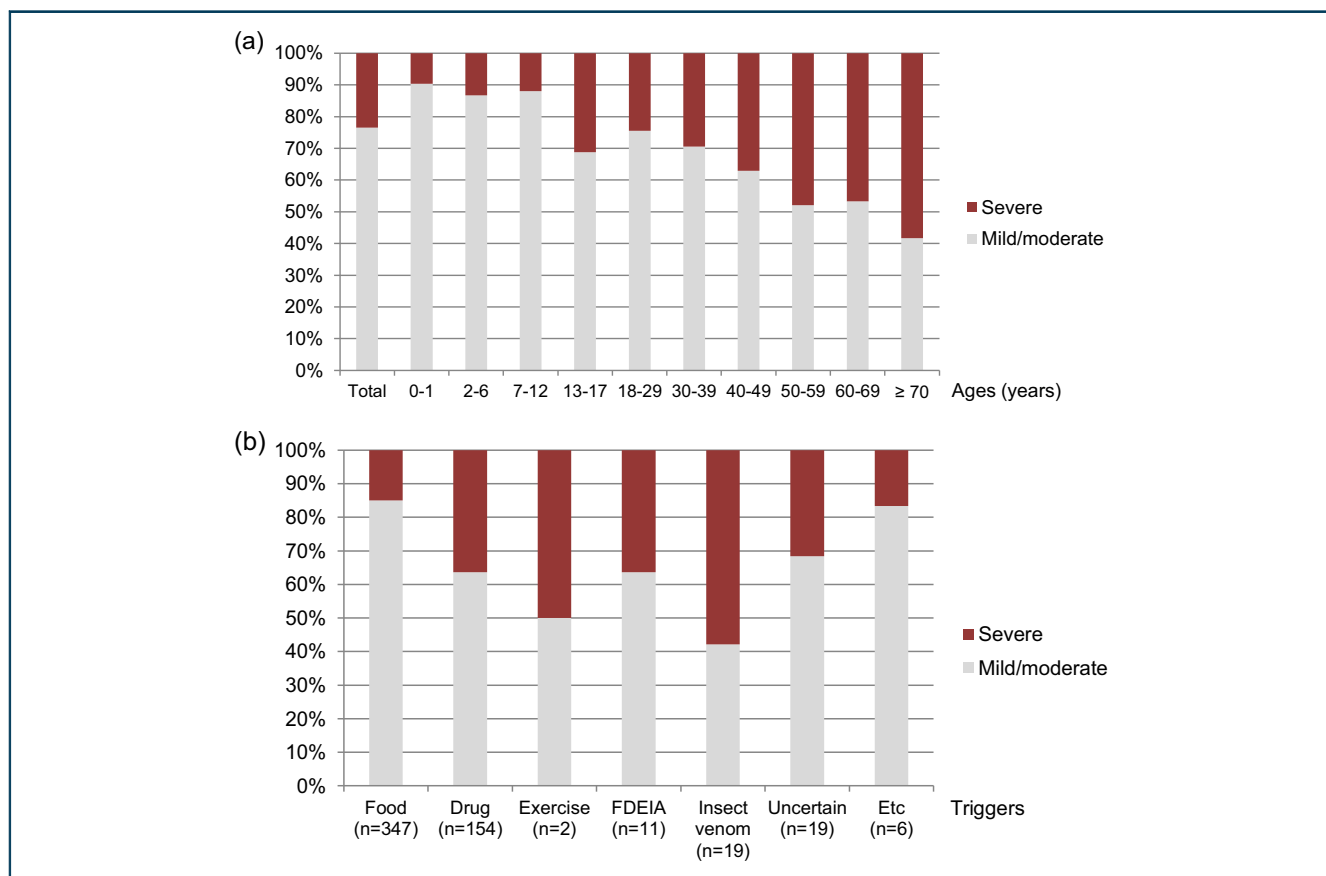
Places of occurrence of anaphylaxis	n (%)	
	<18 years	≥18 years
Own home	193 (57.6)	94 (42.2)
Others' home	11 (3.3)	5 (2.2)
Restaurants	30 (9.0)	11 (4.9)
Childcare centers	30 (9.0)	0 (0.0)
School	26 (7.8)	3 (1.3)
Workplace	0 (0.0)	7 (3.1)
Outdoor	16 (4.8)	20 (9.0)
Hospital <sup>f</sup>	17 (5.1)	20 (9.0)
Others	11 (3.3)	6 (2.7)
Uncertain	1 (0.3)	57 (25.6)

**Table 4.** Symptom onset time and places of occurrence of anaphylaxis. <sup>e</sup> Refers to the percentage of cases with records of symptom onset time. <sup>f</sup> Cases that were reported in hospitals occurred during oral food challenge tests



Details of epinephrine administration in ED	n (%)	
	<18 years	≥18 years
<b>Epinephrine administration time after arrival to ED</b>		
≤1 hour	115 (91.2)	80 (81.6)
>1 hour	7 (5.6)	8 (8.2)
Uncertain	4 (3.1)	10 (10.2)
<b>Route of epinephrine administration</b>		
Intramuscular	114 (90.5)	78 (79.6)
Intravenous	8 (6.3)	7 (7.1)
Subcutaneous	0 (0.0)	1 (1.0)
Others	2 (1.6)	2 (2.0)
Uncertain	2 (1.6)	10 (10.2)
<b>Number of epinephrine shots administered</b>		
1	107 (84.9)	62 (63.3)
2	13 (10.3)	18 (18.4)
≥3	4 (3.2)	7 (7.1)
Uncertain	2 (1.6)	11 (11.2)

**Table 5.** Details of epinephrine administration in the emergency department *g*. Refers to the percentage among cases in which epinephrine was administered in the emergency department (ED) of participating hospitals (total n=224, <18 years=124, ≥18 years=98)



**Fig. 3** Severity of anaphylaxis. (a) By age group. (b) By triggers. FDEIA: food-dependent exercise-induced anaphylaxis

infants aged <24 months; 13.3%, preschool children (2–6 years); 11.9%, schoolchildren (7–12 years); and 31.3%, adolescents (13–17 years). The percentage of severe anaphylaxis in adults was 38.1%: 24.4%, patients aged 18–29 years; 29.4%, patients in their 30s; 37%, patients in their 40s; 47.9%, patients in their 50s; 46.7%, patients in their 60s; and 58.3%, patients aged  $\geq 70$  years. The proportion of severe anaphylaxis according to the triggers is presented in Fig. 3 B. The percentage of severe anaphylaxis was the highest in insect venom-induced anaphylaxis (57.9%), followed by exercise-induced anaphylaxis (50%), drug-induced anaphylaxis (36.4%), FDEIA (36.4%), idiopathic anaphylaxis (31.6%), and food-induced anaphylaxis (15%).

## DISCUSSION

Through this first web-based multicenter registry in Asia, we were able to collect and present a broad and detailed understanding of the clinical features of anaphylaxis. Due to the large number of anaphylaxis cases at all ages, we could track the differences in clinical profiles according to age, especially the profoundly different triggers between infants and older patients. Additionally, assessing the concomitant comorbidities may allow future identification of severe allergic reactions.

The concomitant allergic history of patients in this study was similar to that reported in previous studies, with atopic dermatitis being the most common in children, and allergic rhinitis being the most common in adults.<sup>10,17</sup> The proportion of children with asthma was relatively higher in the European registry than that in our region, possibly due to the variance in the age distribution of patients registered in each study and the difference in the prevalence of asthma.<sup>18</sup> Unlike other studies, we classified that a previously known food allergy is a separate medical history and identified that >50% of children in this registry had a previously known food allergy.

Due to the relatively large data used, we were able to present the continuous shift from food-induced anaphylaxis toward drug-induced and insect venom-induced anaphylaxis with increasing age, consistent with previous studies.<sup>6,10,19,20</sup> The

insect venom-induced anaphylaxis was remarkably more common in older patients, as reported previously.<sup>11,20–22</sup> The percentage of insect venom-induced anaphylaxis was remarkably higher in Europe than in our region both in adults and children, although the reasons for the difference are not clear. The proportion of insect venom-induced anaphylaxis from a multicenter study in Singapore was quite compatible with that reported in our study both in adults and children.<sup>23</sup> Hen's egg and cow's milk were the top 2 food triggers in children, as reported previously studies; walnuts were identified as an unusually common food trigger in our region, while peanuts were a more common trigger in most Western studies.<sup>10,24</sup> Walnuts are consistently identified as a common food allergen in children in our region and ranked third or fourth in previous Korean studies.<sup>12,25,26</sup> As the distribution of food allergens reflects the distinctive eating habits in different regions, the relatively lower intake of peanuts and progressively increasing consumption of walnuts as an ingredient of various Korean cuisines may explain this result. By dividing children and adolescents into subgroups according to age, a progressive decrease in the proportion of patients reporting food as the trigger and a constant increase in the proportion of patients reporting drugs as the trigger was observed from infants to adolescents. This finding is consistent with those of previous studies,<sup>10,20</sup> but the differences in triggers among infants, preschoolers, schoolchildren, and adolescents are a fairly unique and significant finding. Hence, our results indicate that detailed distribution of triggers by age would be useful for age-specific management and anaphylaxis prevention along with patient education.

Cutaneous symptoms as the most common manifestation have been reported; the prevalence of respiratory and gastrointestinal symptoms was relatively higher in this study, while that of cardiovascular symptoms was low;<sup>6,9</sup> this may be because 60% of the registered patients were aged <18 years. The prevalence of cardiovascular and neurologic symptoms was higher in older patients, consistent with previous reports,<sup>11</sup> due to the higher proportion of preexisting cardiovascular comorbidities and more frequent use of cardiovascular drugs in older patients or the

differences in the prevalence of triggers between adults and children or in both age groups. In addition to the symptom outline according to organ system, the detailed symptom profiles within each system were compared between adults and children. Although the percentages of cutaneous, respiratory, and gastrointestinal symptoms were similar in children and adults, the symptom details were noticeably different. Significantly higher proportions of children had wheezing, consistent with previous reports, while remarkably higher proportions of adults had abdominal pain and diarrhea, inconsistent with previous reports.<sup>27</sup> The most common place of anaphylactic reaction occurrence was the patient's own home, consistent with previous reports.<sup>24</sup> The distribution of places of occurrence in children was comparable with those of previous studies, except that the rates of occurrence in schools, childcare centers, or restaurants were relatively higher in our study.<sup>10,24</sup> This is due to the fact that children in Korea eat school meals instead of bringing homemade food, and are spending more time outside their homes and consuming food prepared outside their homes.

The higher rates of severe anaphylaxis with increasing age were consistent with previous results.<sup>11,13</sup> In the analysis of the severity of anaphylaxis according to the trigger, the risk of severe anaphylaxis was particularly higher in patients with drug- or insect venom-induced anaphylaxis than in those with food-induced anaphylaxis. Moreover, the severity of anaphylaxis was higher in patients with drug-induced anaphylaxis than in those with food-induced anaphylaxis, which was also reported in other studies;<sup>13,28</sup> however, the number of studies evaluating the potential risk factors for severe anaphylaxis are limited. We identified increasing age, anaphylaxis history, and presence of cofactors (specific data not shown) as significant risk factors for severe anaphylaxis; further analysis will be conducted as more data are collected in this registry.

Acute infectious illness and physical exercise are the most frequently reported cofactors in children, which was compatible with those in the European registry, whereas the distribution of major cofactors in adults was rather diverse between studies. Physical exercise was the most common cofactor of anaphylaxis in adults in this study,

whereas drug intake or tiredness was a more common cofactor among adults in other studies.<sup>29,30</sup> To date, little is known about the cofactors affecting the induction and augmentation of severe allergic reactions. In future studies, cofactors related with anaphylaxis should be more thoroughly evaluated so that patients can be better informed about the risk factors amplifying severe allergic reactions.

Although the international guidelines for the acute management of anaphylaxis recommend the intramuscular administration of epinephrine as first-line treatment,<sup>31,32</sup> the proportion of acute anaphylactic patients receiving epinephrine is not high enough, with contrasting rates varying from study to study.<sup>9,33,34</sup> The proportion of patients who received epinephrine in the EDs of participating hospitals (66.7% in children and 61.3% in adults) was similar or slightly higher than those reported in previous studies, partly because the data were obtained from secondary or tertiary hospitals and due to the growing awareness of medical personnel on the acute management of anaphylaxis. A recent study has reported clinically and statistically significant increases in epinephrine administration, in concordance with epinephrine-related guidelines for food-induced anaphylaxis, in the past 15 years in the EDs in the United States and Canada.<sup>35</sup> One of our study strengths related to acute treatment was that the epinephrine administration time, route of administration, and number of epinephrine shots required were investigated and analyzed in detail. In a recent report from the European registry, 3.3% of anaphylaxis patients who did not receive epinephrine before the start of professional emergency management received more than 1 epinephrine dose.<sup>36</sup> The higher rates of adults requiring 2 or more shots of epinephrine are most probably related to the greater proportion of severe anaphylaxis in adults. This is an important data, which suggests that there may be a considerable proportion of patients with anaphylactic reactions who do not show improvements in symptoms after receiving a single shot of epinephrine. The proportion of epinephrine administered intramuscularly was higher in our study than that in the European registry, in which 36.3% patients received epinephrine intravenously.<sup>36</sup>

Our data do not reflect the general population, as the participating hospitals were mostly tertiary hospitals and were selected based on the clinicians' interest in establishing this registry. Only patients who provided written consent were included, and the reporting was voluntarily conducted by the participating clinicians. However, given that all registries of allergic diseases, including the largest existing anaphylaxis registry in Europe, are collecting information by voluntary reporting of healthcare professionals, the results of this study are meaningful as yielding an extensive and heterogeneous data covering all age groups. The ongoing operation of this registry will enable the collection of larger-scale data on anaphylaxis and thus will reveal more about the rare causes of anaphylaxis.

## CONCLUSION

This multicenter web-based anaphylaxis registry, the first registry established in Asia, has produced in-depth reporting on 558 anaphylaxis cases in the first 2 years and will be valuable for collection of systematic and standardized data on anaphylaxis in the future. Furthermore, noting trends over time will provide changes in the triggers, clinical manifestations, and treatment of anaphylaxis and therefore improve the overall management of the disease.

### Abbreviations

ED: emergency department; OPD: outpatient department; CRF: case report form; FDEIA: food-dependent exercise-induced anaphylaxis

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### Ethics approval and consent to participate

The study was approved by the institutional review board (IRB) of each participating hospital. The IRB approval number of the leading research institution (Ajou University School of Medicine) is MED-SMP-16-248.

### Ethics, consent and permissions

All study participants provided an informed consent.

### Author contributions

Sooyoung Lee and Kyunguk Jeong designed the study, obtained research funding, set up the backbone of the

web-based case report form (CRF), undertook recruitment of participating centers and patients, and managed the data, including quality control. Young-Min Ye, Sang-Ha Kim, Kyung Won Kim, Jeong Hee Kim, and Ji-Won Kwon participated in the development of the web-based CRF and actively contributed in the enrollment of patients and analysis of the collected data. Song-I Yang, So-Yeon Lee, Eun Hee Chung, Mi-Ae Kim, Yoon Hee Kim, Hye-Young Kim, Gwang Cheon Jang, Joo-Hee Kim, Eunjoon Lee, Jihyun Kim, Kangmo Ahn, Yoon-Seok Chang, Gyu-Young Hur, Jeongmin Lee, Taek Ki Min, Bok-Yang Pyun, Kyung Hee Park, Jaechun Lee, Tae Won Song, Hye Mi Jee, and Yoo Seob Shin developed the web-based CRF specified for anaphylaxis, simulated the CRF, applied the modifications to the final CRF, and enrolled patients. Dankyu Yoon and Jeom-Kyu Lee designed the study and contributed to the development of web-based registry. Kyunguk Jeong drafted the manuscript, and all authors discussed the results and contributed to the final manuscript. Sooyoung Lee takes responsibility for the paper as a whole.

### Consent for publication

All authors agreed to publication of the work.

### Availability of data and materials

The data that support the findings of this study are available from the corresponding author, Sooyoung Lee, upon reasonable request, and with the permission of Korea Centers for Disease Control and Prevention.

### Declaration of Competing Interest

The authors report no competing interests.

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### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.waojou.2020.100449>.

### Author details

<sup>a</sup>Department of Pediatrics, Ajou University School of Medicine, Suwon, South Korea. <sup>b</sup>Department of Allergy and Clinical Immunology, Ajou University School of Medicine, Suwon, South Korea. <sup>c</sup>Department of Internal Medicine, Yonsei University Wonju College of Medicine, Wonju, South Korea. <sup>d</sup>Department of Pediatrics, Severance Hospital, Institute of Allergy, Yonsei University College of Medicine, Seoul, South Korea. <sup>e</sup>Department of Pediatrics, Inha University Hospital, Incheon, South Korea. <sup>f</sup>Department of Pediatrics, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, South Korea. <sup>g</sup>Department of Pediatrics, Hallym University Sacred Heart Hospital, Hallym University College of Medicine, Anyang, South Korea. <sup>h</sup>Department of Pediatrics, Chungnam University College

of Medicine, Daejeon, South Korea. <sup>1</sup>Department of Pulmonary, Allergy, and Critical Care Medicine, CHA University School of Medicine, Seongnam, South Korea. <sup>2</sup>Department of Pediatrics, Pusan National Hospital, Pusan University College of Medicine, Busan, South Korea. <sup>3</sup>Department of Pediatrics, National Health Insurance Corporation Ilsan Hospital, Goyang, South Korea. <sup>4</sup>Division of Pulmonary, Allergy, and Critical Care Medicine, Hallym University College of Medicine, Anyang, South Korea. <sup>5</sup>Department of Pediatrics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea. <sup>6</sup>Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, South Korea. <sup>7</sup>Department of Internal Medicine, Korea University College of Medicine, Seoul, South Korea. <sup>8</sup>Department of Pediatrics, Yonsei University Wonju College of Medicine, Wonju, South Korea. <sup>9</sup>Department of Pediatrics, Soonchunhyang University Hospital, Seoul, South Korea. <sup>10</sup>Division of Allergy and Immunology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, South Korea. <sup>11</sup>Department of Internal Medicine, Jeju National University School of Medicine, Jeju, South Korea. <sup>12</sup>Department of Pediatrics, Ilsan Paik Hospital, Inje University College of Medicine, Goyang, South Korea. <sup>13</sup>Department of Pediatrics, CHA University School of Medicine, Seongnam, South Korea. <sup>14</sup>Division of Allergy and Chronic Respiratory Diseases, Center for Biomedical Sciences, National Institute of Health, Korea Centers for Disease Control and Prevention, Osong, South Korea.

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