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ORIGINAL ARTICLE

Drug Allergy, Insect Sting Allergy and Anaphylaxis

Disparities in pediatric anaphylaxis triggers and management across Asia

Agnes Sze Yin Leung[1] | Elizabeth Huiwen Tham[2] | Punchama Pacharn[3] | Yuhan Xing[4] | Hoang Kim Tu Trinh[5] | Sooyoung Lee[6] | Kangmo Ahn[7] | Pantipa Chatchatee[8] | Sakura Sato[9] | Motohiro Ebisawa[9] | Bee Wah Lee[2] | Gary Wing Kin Wong[4] | on behalf of the Asia-Pacific Research Network for Anaphylaxis (APRA)

[1]Department of Paediatrics, Prince of Wales Hospital, Hong Kong Hub of Paediatric Excellence, The Chinese University of Hong Kong, Shatin, Hong Kong

[2]Department of Paediatrics, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore

[3]Department of Pediatrics, Siriraj Hospital, Mahidol University, Bangkok, Thailand

[4]Department of Paediatrics, Faculty of Medicine, Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, Hong Kong

[5]Center for Molecular Biomedicine, University of Medicine and Pharmacy at Ho Chi Minh City, Ho Chi Minh City, Vietnam

[6]Department of Pediatrics, Ajou University School of Medicine, Suwon, Republic of Korea

[7]Department of Pediatrics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

[8]Department of Pediatrics, Division of Allergy and Immunology, Faculty of Medicine, HAUS IAQ Research Unit, King Chulalongkorn Memorial Hospital, Chulalongkorn University, The Thai Red Cross Society, Bangkok, Thailand

[9]Clinical Research Center for Allergy and Rheumatology, NHO Sagamihara National Hospital, Kanagawa, Japan

Correspondence
Gary Wing Kin Wong, Department of Paediatrics, Faculty of Medicine, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong.
Email: wingkinwong@cuhk.edu.hk

Abstract

Background: The epidemiology and management of anaphylaxis are not well-reported in Asia.

Methods: A regional pediatric anaphylaxis registry was established by the Asia-Pacific Research Network for Anaphylaxis (APRA), using standardized protocols for prospective data collection, to evaluate the triggers and management of anaphylaxis in the Asia-Pacific region. Pediatric patients below 18 years presenting with anaphylaxis across four Asian countries/cities (Thailand, Singapore, Hong Kong (HK), and Qingdao) were included. Allergen triggers, symptoms, anaphylaxis severity, and management were compared.

Results: Between 2019 and 2022, 721 anaphylaxis episodes in 689 patients from 16 centers were identified. The mean age at anaphylaxis presentation was 7.0 years (SD = 5.2) and 60% were male. Food was the most common trigger (62%), particularly eggs and cow's milk in children aged 3 years and below. In school-age children, nut anaphylaxis was most common in HK and Singapore, but was rare in the other

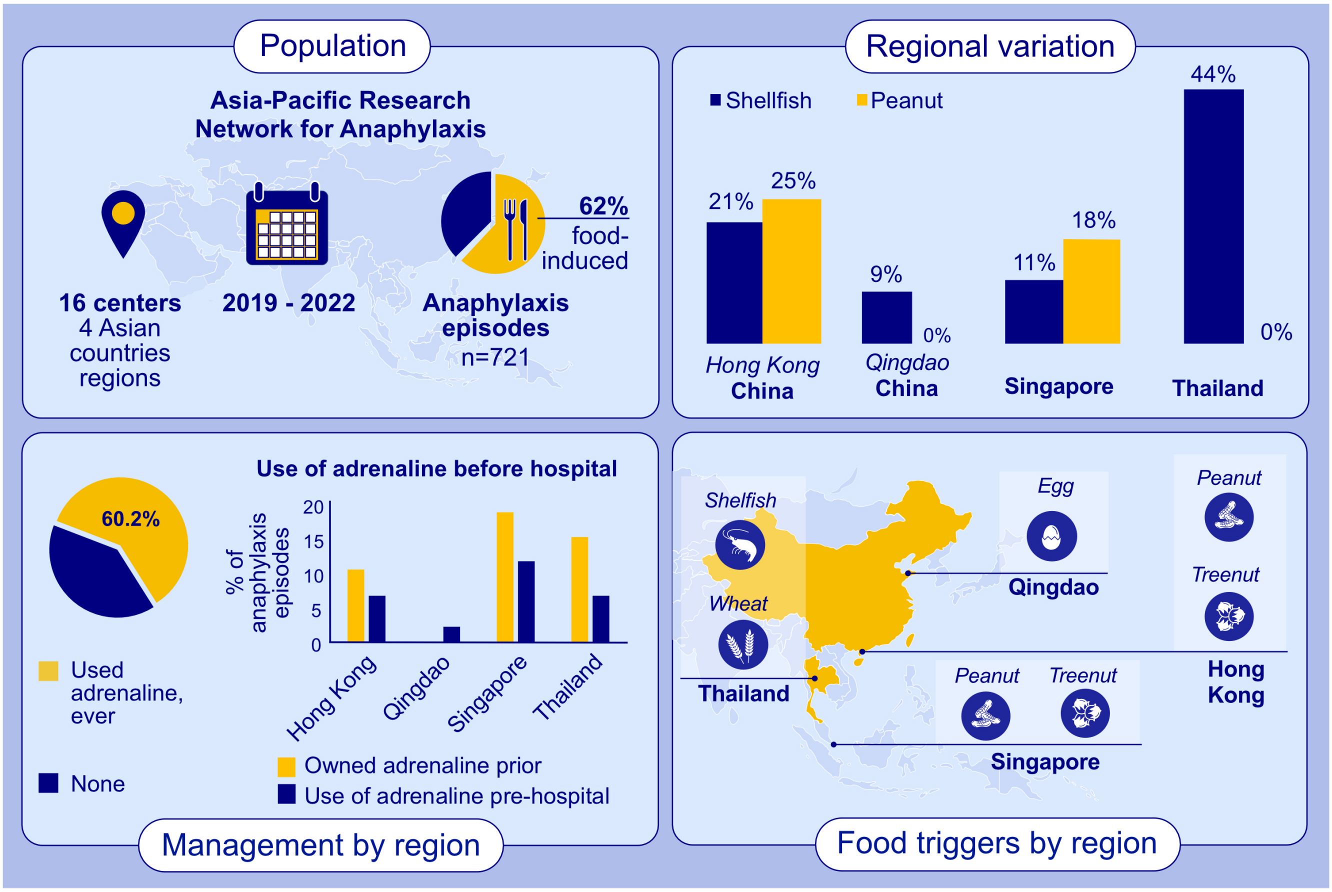
Abbreviations: APRA, Asia-Pacific Research Network for Anaphylaxis; ED, emergency department; FA, food allergy; HK, Hong Kong; IQR, interquartile range; IR, incidence rate; NIAID/FAAN, National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network criteria; oFASS-5, ordinal Food Allergy Severity Score 5; PA, peanut allergy; SD, standard deviation; WAO, World Allergy Organization.

Agnes Leung, Elizabeth Tham, and Punchama Pacharn contributed equally to this article.

countries, and wheat was the top allergen in Bangkok. Shellfish anaphylaxis was most common in children aged 7–17. Adrenaline was administered in 60% of cases, with 9% given adrenaline before hospital arrival. Adrenaline devices were prescribed in up to 82% of cases in Thailand but none in Qingdao.

Conclusions: The APRA identified food as the main trigger of anaphylaxis in children, but causative allergens differed even across Asian countries. Fewer than two-thirds of cases received adrenaline treatment, pre-hospital adrenaline usage was low, and adrenaline device prescription remained suboptimal. The registry recognizes an unmet need to strengthen anaphylaxis care and research in Asia-Pacific.

KEYWORDS
adrenaline, anaphylaxis, Asia, nuts, prospective, registry, shellfish, wheat



GRAPHICAL ABSTRACT

The APRA identified food as the primary trigger of anaphylaxis in children, but causative allergens differed across Asian countries. Shellfish was a common trigger, more so in Thailand, while nuts were common anaphylaxis elicitors in Singapore and Hong Kong. Fewer than two-thirds of cases received adrenaline treatment, with low pre-hospital usage and suboptimal device prescriptions.

1 | BACKGROUND

Anaphylaxis is a severe, potentially life-threatening, systemic allergic reaction that occurs immediately after contact with an allergen.[1] The delayed onset of anaphylaxis might occur in patients allergic to mammalian meat products, a condition known as Alpha-gal syndrome.[2] Over the past decade, studies have reported a significant increase in anaphylaxis presentation among children in developed countries, particularly food-induced anaphylaxis.[3,4] The review of published studies suggests that anaphylaxis is not uncommon in Asia,[5] although it is commonly believed that the prevalence of allergic disorders is lower. However, the heterogeneity in study design and anaphylaxis incidence reporting hindered spatial and temporal comparison of anaphylaxis burden, trends, and management across Asian countries and the rest of the world. Prospective anaphylaxis registries, such as the European Anaphylaxis Registry,[6] provide important epidemiological data that can inform clinical practice and target areas for education and research.

The Asia-Pacific Research Network for Anaphylaxis (APRA), established by the Asia Pacific Academy of Pediatric Allergy, Respirology and Immunology (APAPARI), is a prospective pediatric anaphylaxis registry that employs a standardized methodology for data collection across all participating Asian countries. The current study includes data from East and Southeast Asia with the aim of highlighting the patterns and elicitors of pediatric anaphylaxis in this region, in comparison with the rest of the world, and to identify the adequacy of anaphylaxis management such that gaps in infrastructure, education, and research can be addressed.

2 | PATIENTS AND METHODS

2.1 | Database

The APRA collected clinical data on anaphylactic reactions in pediatric patients using a standardized protocol. De-identified data of pediatric patients under the age of 18 presenting to hospitals for acute presentation of anaphylaxis or to the allergy centers for the workup of recent anaphylaxis were captured from 2019 to 2022. APRA comprises 16 tertiary centers across four regions of Asia, including five from Bangkok and one from Nakhon Nayok, Thailand; seven from Hong Kong (HK) and one from Qingdao, China; and two from Singapore. The registry aimed to include 200 anaphylactic episodes from each region or collect data in each country for at least 18 months. The local ethics committees in all participating centers approved the study, and informed consent was obtained as required. The diagnosis of anaphylaxis was based on consensus expert criteria set out by the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network criteria.[1] Cases were recruited prospectively by the local centers, and reviewed by the central team to confirm that they met the defining anaphylaxis criteria.

The standardized Case Report Form was collectively developed a priori by APRA over rounds of discussions, with training provided for all site investigators and data extractors. Anaphylaxis episodes were classified according to the modified World Allergy Organization (WAO) Grading System for severe allergic reactions[7]; and severity of food anaphylaxis according to the ordinal Food Allergy Severity Score 5 (oFASS-5).[8]

2.2 | Statistical analysis

Statistical analyses were conducted with SPSS 25.0 for Windows software (SPSS Inc, Chicago, IL, USA). The Shapiro–Wilk's test was used to determine the normality of distribution of interval variables. Age was expressed as mean ± standard deviation (SD), time intervals were expressed as median ± interquartile range (IQR), and the distribution of categorical variables reported as percentage. Comparison of categorical variables was performed by using either the chi-square test or Fisher exact test (if there were <10 observations). In the comparisons with two or more independent variables, we used factorial ANOVA or Kruskal–Wallis test for parametric and non-parametric data, respectively. Association analysis of therapeutic interventions and symptoms was performed with Spearman's Rank Correlation. Cramer's V association was used to analyze the association between food triggers and allergic symptoms, and the network analysis was by Gephi 0.10 software. Statistical significance was defined as $p < .05$. Anaphylaxis incidence was defined as the frequency of new cases of anaphylaxis among the pediatric populations within the selected geographical districts (per 100,000 persons). The incidence rate (IR) was calculated by using the cases that met inclusion criteria as the numerator and the population counts as the denominator (Data S1).

3 | RESULTS

A total of 721 anaphylactic reactions in 689 patients were reported, which comprised 219 (30%) cases from HK collected between January 2020 and October 2021, 130 (18%) cases from Qingdao between July 2019 and October 2022, 254 (35%) cases from Singapore between January 2019 and June 2020, and 118 (16%) cases from Thailand between June 2019 and May 2021. The estimated anaphylaxis incidence was the lowest in Qingdao (1 per 100,000 person-years) followed by HK (11 per 100,000 person-years), Singapore (21 per 100,000 person-years), and Thailand (25 and 21 per 100,000 person-years in Bangkok and Nakhon Nayok, respectively) (Table S1A). The IR was similar between Singapore and Thailand ($p = .25$), but was significantly higher compared to HK and Qingdao ($p < .001$) (Table S1B).

3.1 | Ethnicity, age, co-morbidities and triggers

The ethnicity, age distribution and co-morbidities of our subjects are outlined in Table 1 and the online supplement. Overall, the top 3 triggers of anaphylaxis were food (62%), idiopathic causes (22%), and drugs (10%) (Figure 1A). Insect venom-induced anaphylaxis was uncommon in Asia, with only eight cases reported in Bangkok and one in Singapore. Among food-induced anaphylaxis, in children younger than 3 years, eggs (38%) and cow's milk (27%) were the most common food triggers of anaphylaxis, followed by tree nuts (31%) in children aged 4–6 years, and shellfish in those aged 7–11 years (37%) and 12–17 years (44%) (Figure 2; Table S2). The most common triggers in children below age 3 years were eggs (38%) and cow's milk (27%); however, this was mainly in HK and Singapore, whereas in Thailand, wheat was the most common trigger (Figure 1B; Table S3A). In children aged 4–6 and 7–12 years, tree nuts (31% and 15%) and peanuts

TABLE 1 Baseline data, co-morbidities, reaction circumstances and co-factors by age group.

	0–3 years		4–6 years		7–11 years		12–17 years		All[a]		
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*p*-value
Total	255	35.4	118	16.4	152	21.1	176	24.4	721	100	**<.001**
Country											
Singapore	108	42.4	44	37.3	50	32.9	52	29.5	254	35.2	**<.001**
Thailand	26	10.2	13	11.0	33	21.7	26	14.8	118	16.4	**.036**
Hong Kong, China	89	34.9	15	12.7	31	20.4	84	47.7	219	30.4	**<.001**
Qingdao, China	32	12.5	46	39.0	38	25.0	14	8.0	130	18.0	**<.001**
Males	167	65.5	66	55.9	91	59.9	93	52.8	432	59.9	.053
Ethnicities											
Chinese	175	68.6	83	70.3	103	67.8	112	63.6	473	65.6	.619
Malay	21	8.2	9	7.6	5	3.3	11	6.3	46	6.4	.254
Indian	6	2.4	5	4.2	2	1.3	8	4.5	21	2.9	.270
Caucasian	8	3.1	3	2.5	3	2.0	11	6.3	25	3.5	.151
Japanese	4	1.6	2	1.7	1	0.7	1	0.6	8	1.1	.668
Thai	25	9.8	13	11.0	33	21.7	26	14.8	117	16.2	.022
Vietnamese	0	0.0	0	0.0	0	0.0	1	0.6	1	0.1	.394
Mixed	9	3.5	2	1.7	3	2.0	1	0.6	15	2.1	.207
Others	7	2.7	1	0.8	2	1.3	5	2.8	15	2.1	.514
Comorbidities											
Allergic rhinitis	32	12.6	39	33.1	61	40.4	67	39.2	204	28.3	**<.001**
Asthma	13	5.1	35	29.7	33	21.9	36	21.1	118	16.2	**<.001**
Atopic dermatitis	132	52.0	34	28.8	39	25.8	36	21.1	247	34.3	**<.001**
Chronic urticaria	5	2.0	6	5.1	10	6.6	19	11.1	40	5.5	**.001**
Known food allergies	105	41.2	41	34.7	50	32.9	88	50.0	292	40.5	**.008**
History of anaphylaxis	23	9.0	17	14.4	22	14.5	59	33.7	122	16.9	**<.001**
Family history of atopy	132	64.7	38	52.8	51	47.2	61	45.2	290	40.2	**.003**
Place of occurrence											
Own home	220	86.3	83	70.3	114	75.0	117	66.5	541	75.0	**<.001**
Known food allergy	87	39.5	25	30.1	37	32.5	60	51.3	210	38.8	
Others' home	3	1.2	1	0.8	2	1.3	2	1.1	8	1.1	
Restaurant/café/diner	6	2.4	6	5.1	4	2.6	8	4.5	26	3.6	
Kindergarten/nursery/school	15	5.9	7	5.9	7	4.6	14	8.0	45	6.2	
Yard/field	1	0.4	1	0.8	6	3.9	10	5.7	19	2.6	
Hospital	8	3.1	13	11.0	13	8.6	10	5.7	52	7.2	
Others	2	0.8	7	5.9	6	3.9	15	8.5	30	4.2	
Co-factor											
None	224	90.0	83	70.3	118	77.6	134	77.9	569	78.9	**<.001**
Exercise	1	0.4	3	2.5	5	3.3	24	4.0	35	4.9	
Acute infection	24	9.6	31	26.3	29	19.1	13	7.6	102	14.1	
Menstruation	0	0.0	0	0	0	0.0	1	0.6	1	0.1	
Abrupt temperature change	0	0.0	0	0	0	0.0	2	1.2	2	0.3	
Others	0	0.0	1	0.8	0	0.0	0	0.0	4	0.6	

Note: The significant values are in bold.

Abbreviations: KG,Kindergarten; temp, temperature.

[a]Includes subjects with missing information on age.

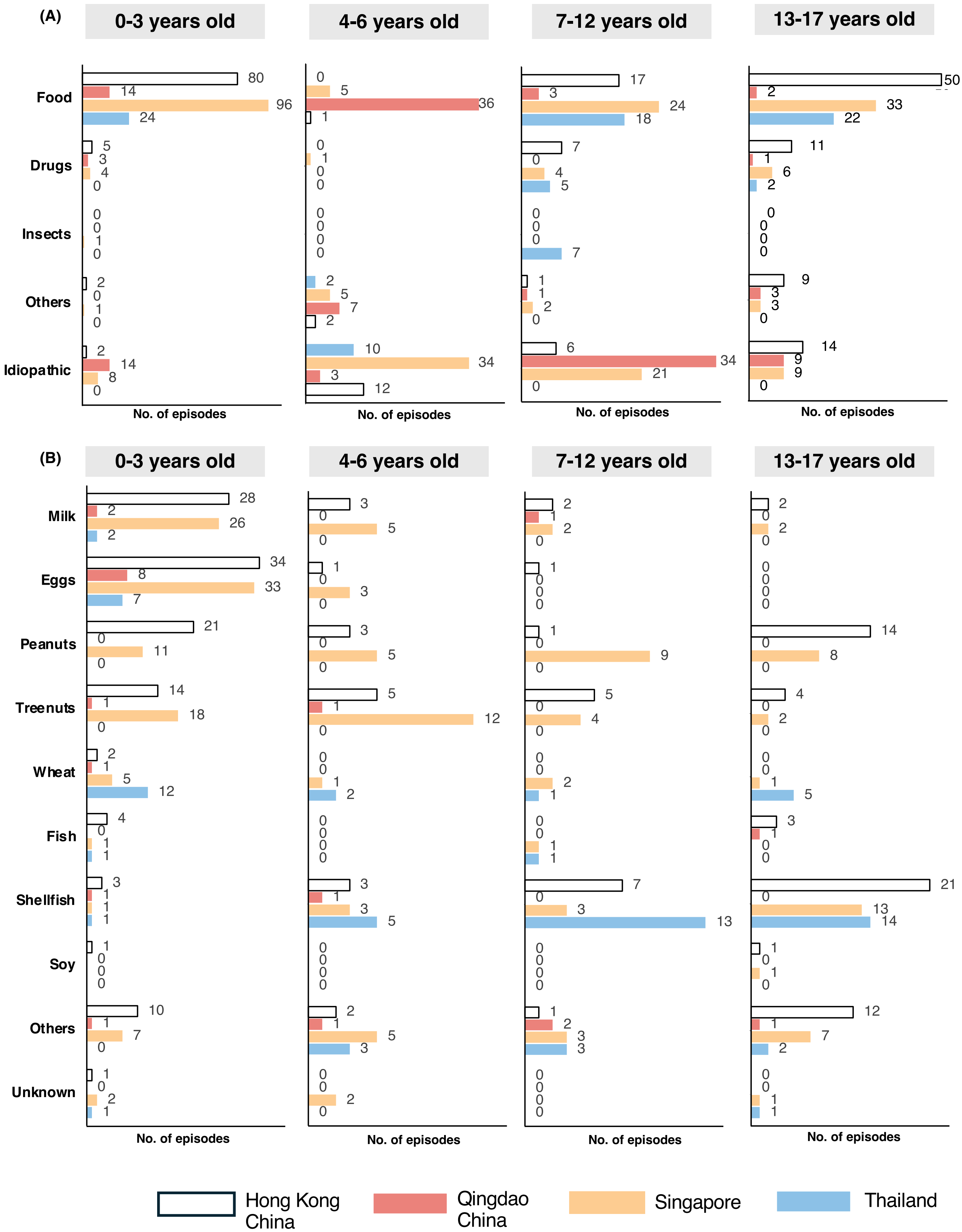


FIGURE 1 (A, B) Figure displaying the distribution of food triggers for anaphylaxis by age groups across the different Asian regions.

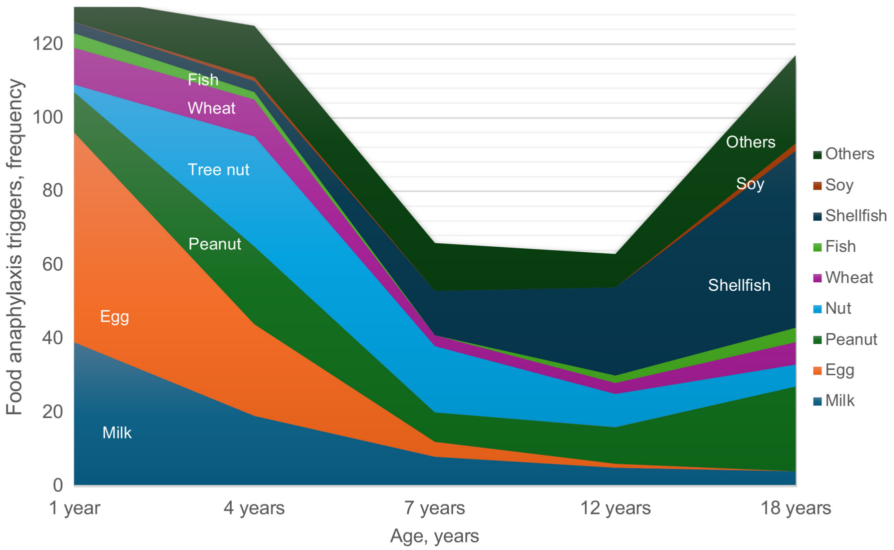


FIGURE 2 Figure displaying the distribution of food triggers for anaphylaxis across the different age groups.

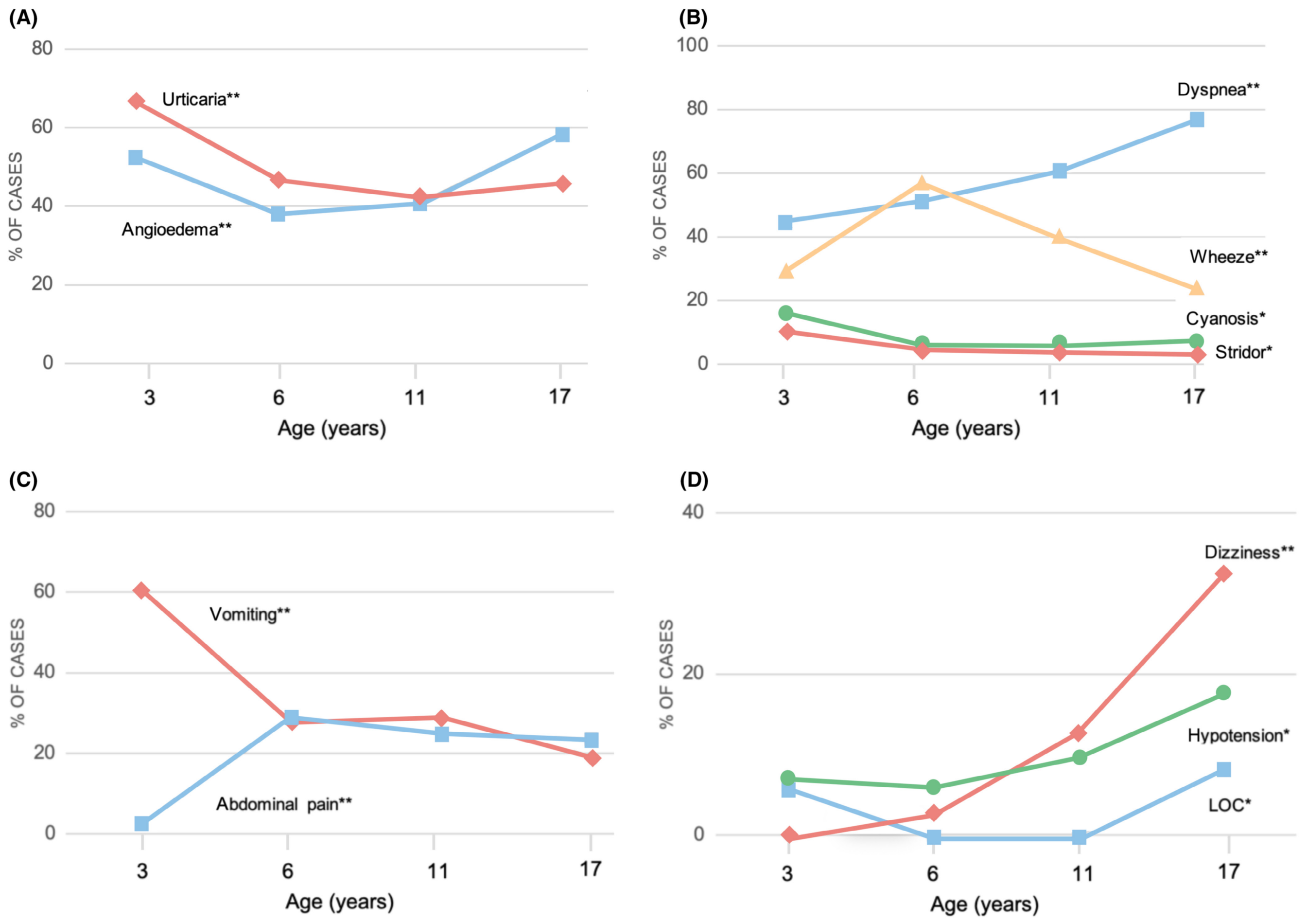


FIGURE 3 (A-D): Figure showing the frequency of mucocutaneous, respiratory, gastrointestinal, and cardiovascular symptoms across the different age groups. ** Denotes significant difference between age groups, $P<.001$; * Denotes significant difference between age groups, $P<.05$.

(14% and 16%) were the most common triggers; again this was only seen in HK and Singapore, whereas in Thailand, shellfish (20% and 37%) became the major cause of anaphylaxis. Among children aged 13–17 years, shellfish was the predominant cause of anaphylaxis in HK, Singapore, and Thailand. Peanuts and tree nuts remained as common triggers only in HK and Singapore. Compared to other regions, Qingdao had a higher proportion of episodes labeled as idiopathic (72% in Qingdao vs. 22% total, $p<.001$).

3.2 | Clinical symptoms, co-factors and severity

The locations and co-factors of anaphylactic episodes are detailed in Table 1 and the online supplement. Skin manifestations were mostly commonly reported, including angioedema in 337 (47%) and urticaria in 365 (51%) (Table S4; Figure S1). Respiratory involvement was reported in 574 (80%) cases. Dyspnea was more commonly reported in adolescents (12–17 years: 77%) compared to other age groups (45%–61%, $p<.001$), while wheezing was most notable in school-age children (4–11 years: 40%–57%) compared to others (24%–30%, $p<.001$). Cyanosis (0–3 years: 16%) and stridor (0–3 years: 10%) were mostly commonly observed in young children under four ($p<.05$) (Figure 3A,B). Gastrointestinal symptoms accompanied around half of the anaphylaxis cases (44%). Younger children were more likely to vomit (0–3 years: 61%) compared to older children (4–17 years: 19%–29%, $p<.001$), while abdominal pain was more common in older children (4–17 years: 23%–29%) than in young children (0–3 years: 2.5%, $p<.001$) (Figure 3C). Hypotension, dizziness, and syncope were experienced in 8%, 7% and 3% of cases, respectively, and mainly in older children (Figure 3D). The Cramer's V association between food triggers and symptoms was weak (Table S7).

According to the 5-stage WAO severity scores, 573 (82%) cases were classified as Grade 3, while 53 (8%) and 66 (9%) were classified as Grade 4 and 5 in severity, respectively (Table S5). The distribution of anaphylaxis severity was similar across different age groups and food allergens, but there was an increase in the proportion of Grade 5 symptoms in adolescents ($p<.001$) (Figure S2). When food anaphylaxis was analyzed independently, most reactions were classified as Grade 4 (61%) in severity by the oFASS-5 scores, followed by Grade 3 (21%) and Grade 5 (18%). Among adolescents aged 12 and above, the frequency of Grade 5 symptoms (35%) was higher compared to the other age groups (7%–15% $p<.001$), while the frequency of Grade 3 symptoms was higher in infants and toddlers aged below 4 years (33% vs other age groups: 11%–19%, $p<.001$).

3.3 | Emergency treatment & disposition

Adrenaline, given both pre-hospital and in-hospital, was administered in 434 (60%) anaphylaxis cases, of which only 9% of cases received adrenaline prior to hospital arrival (Table 2). A total of 89 (12%) children owned adrenaline before the anaphylaxis episodes, including 17 (2%) with a prefilled syringe and 72 (10%) with a commercial autoinjector, of which 86/292 (29%) children with known food allergies and 66/124 (53%) with prior anaphylaxis. The rate of prehospital use of an adrenaline device was lower than the rate of owning an adrenaline device prior to an anaphylactic event, most apparent in Thailand (use 6.8% vs. own 15.3%) (Table S3B). Before their anaphylactic events, no individuals in Qingdao possessed an adrenaline device, resulting in a longer time lapse between the onset of symptom and adrenaline administration in Qingdao (median 60 min, IQR 50, 240 min), compared to other regions ($p=.011$). Of the individuals who owned an adrenaline device before the current anaphylaxis episode, 46/89 (52%) administered their devices before hospital arrival. The use of adrenaline ever was similar across age groups, but pre-hospital administration of adrenaline was more common in children aged 12–17 years (15%) and 4–6 years (13%), compared to other groups (5%, $p<.001$) (Figure 4).

Adrenaline was administered intramuscularly in 389 (54%) cases (ampules & syringes 52%; autoinjector 5%), and 403 cases (56%) only required one dose of adrenaline (Table 2). Antihistamines were prescribed in 510 cases (71%), more so than adrenaline (60%). Steroids were given in 430 (60%) cases, more commonly in adolescents (72%) compared to younger children (51%–59%, $p<.001$). Table 2 and the online supplement outline other treatments and dispositions of subjects.

Biphasic reactions occurred in 16 (2.2%) cases. Upon discharge, 229 (32%) cases were given follow-up appointments at specialist allergy clinics, and 296 (41%) were prescribed adrenaline autoinjectors or prefilled syringes upon discharge. No adrenaline devices were prescribed upon discharge in Qingdao, while in Thailand, the prescription rate was as high as 82% ($p<.001$). After excluding cases from Qingdao, the overall percentage of prescriptions for adrenaline devices was 50%.

4 | DISCUSSION

A multicenter prospective pediatric anaphylaxis registry (APRA), conducted in 16 centers across China, Singapore, and Thailand using standardized methodology, provides the first comprehensive set of data showing the distinct patterns of anaphylaxis profiles, triggers, and management practices in Asia and highlights the unmet needs in research and education in this region.

Within Asia, there have been observed changes in anaphylaxis triggers over time. In HK, we have observed a shift in the presentation of anaphylaxis cases in pediatric emergency departments (EDs) in HK from drug-induced to food-induced cases between 2001 and 2015.[9] In this study, we confirm that food was the predominant trigger, accounting for more than 60% of anaphylaxis cases in our registry, similar to that reported in Western countries,[6,10] and other parts of Asia (66%–90%).[11–14] Bird's nest was the most common food anaphylaxis trigger in Singapore in the 1990s,[15] but peanut and seafood have surpassed it in the last decade. Wheat remained a specific food trigger in parts of Asia including Thailand and Japan.[16]

The disparity of anaphylaxis triggers across Asia is apparent across age groups and regions in Asia. The incidence of anaphylaxis among school-age children decreased due to the natural outgrowth of egg and milk allergies,[17,18] but increased in adolescents as shellfish allergies developed in late childhood. The pattern observed in HK and Singapore exhibited similarities with the Western countries,[19] in which egg and milk anaphylaxis was more frequently observed in young children, while peanuts and tree nuts were commonly observed in older children in HK and Singapore. After 12 years of age, shellfish emerged as the primary trigger in Asia, in contrast to Western countries where peanuts

TABLE 2 Emergency treatment of anaphylaxis by age group.

	0–3 years		4–6 years		7–11 years		12–17 years		All[a]		
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*p*-value
Adrenaline use, ever	156	61.4	62	52.5	92	60.9	105	59.7	434	60.2	.411
Adrenaline use, pre-hospital	14	5.5	15	12.7	8	5.3	27	15.3	64	8.9	**<.001**
Owned adrenaline prior to episode	16	6.3	18	15.3	20	13.2	33	18.9	89	12.3	**.003**
Autoinjector	13	34.2	17	56.7	18	35.3	24	48.0	72	10.0	
Prefilled syringe	3	7.9	1	3.3	1	2.0	9	18.0	17	2.4	
Route of adrenaline administered											
Autoinjector	3	1.2	0	0.0	1	0.7	8	4.8	12	1.7	**.122**
Intramuscular	146	60.1	52	48.6	86	61.9	86	51.8	389	54.0	
Subcutaneous	1	0.4	0	0.0	0	0.0	2	1.2	3	0.4	
Intravenous bolus	1	0.4	0	0.0	2	1.4	5	3.0	8	1.1	
Intravenous infusion	1	0.4	0	0.0	1	0.7	3	1.8	5	0.7	
Nebulized	2	0.8	1	0.9	0	0.0	0	0.0	3	0.4	
Total number of adrenaline doses required											
1 dose	149	58.7	56	47.5	85	56.3	95	54.0	403	55.9	.374
2 doses	6	2.4	3	2.5	5	3.3	8	4.5	23	3.2	
3 doses	1	0.4	3	2.5	1	0.7	2	1.1	7	1.0	
4 doses	0	0.0	0	0.0	1	0.7	0	0.0	1	0.1	
Other treatment											
CPR	1	0.4	1	0.8	0	0	0	0	2	0.3	.503
Intravenous fluid	49	19.2	28	23.7	39	25.7	42	23.9	171	23.7	.435
Salbutamol	49	19.2	62	52.5	59	38.8	42	23.9	216	30.0	**<.001**
Antihistamines	175	67.8	78	66.1	110	72.4	129	73.3	510	70.7	.393
Steroids	136	53.3	60	50.8	89	58.6	127	72.2	430	59.6	**<.001**
Oxygen	21	8.2	9	7.6	17	11.2	32	18.2	88	12.2	.006
Intubation	1	0.4	0	0.0	1	0.7	2	1.1	5	0.7	.608
Others	24	19.8	33	54.1	27	39.1	8	8.2	92	12.8	**<.001**
Time in minutes, median, IQR											
Exposure to symptom onset	15	5, 30	30	10, 60	30	10, 64	30	5, 86	30	5, 60	**<.001**
Onset to medical attention arrival	82	51, 133	70	49, 120	77.5	37, 149	68	30, 120	95	50, 190	**<.001**
Onset to 1st dose of adrenaline	90	60, 136	83	45, 120	85	55, 139	66	20, 120	81	46, 132	**.009**

Note: The significant values are in bold.

Abbreviations: CPR, cardiopulmonary resuscitation; IQR, interquartile range; IVF, intravenous fluid; 1st, first.

[a]Includes subjects with missing information on age.

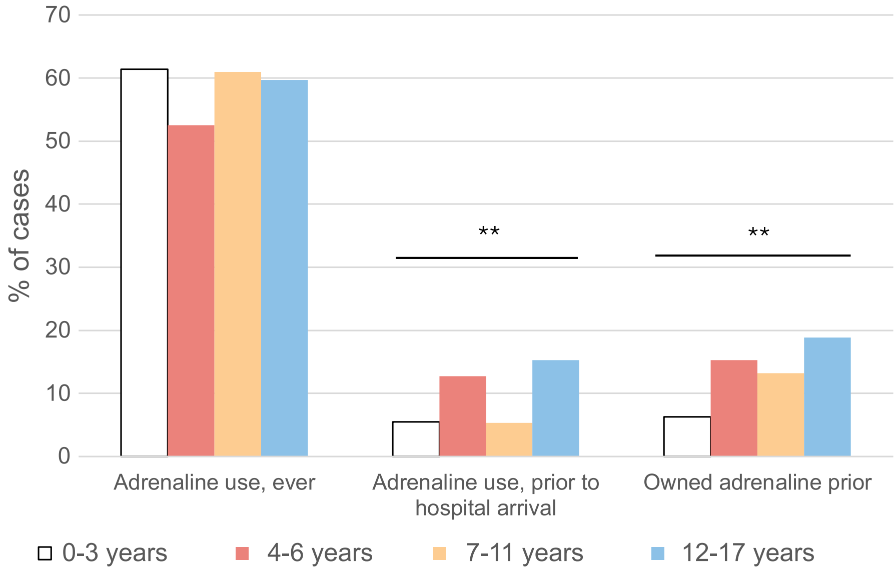


FIGURE 4 Figure displaying the proportion of cases receiving adrenaline ever and before arrival to hospital, and those who owned an adrenaline device prior to the anaphylactic episode. ** Denotes significant difference between age groups, $P < .001$.

remained the predominant trigger.[6,20,10] This study also reveals that wheat was more common than milk as a cause of anaphylaxis in young Thai children.

The differences in anaphylaxis triggers between Asia and Western countries may be partly related to dietary exposures. Seafood is abundant in Southeast Asia, which makes shrimp a common food item and a common trigger of food-induced anaphylaxis in this region. In Asia, shrimp-induced anaphylaxis becomes apparent in children aged 4–6 years. In contrast, shrimp only accounted for 1.6% of all anaphylaxis elicitors in European children,[6] and was rare in children less than 6 years old in Europe (median age of 36 years).[21] A US survey also found a four times higher seafood allergy prevalence in adults (2.8%) compared with children (0.6%). Regional variations within Asia were observed, with a significantly higher percentage of cases in Thailand (44%), compared to other Asian regions (9%–21%). Intriguingly, shellfish-induced anaphylaxis was less severe (Ring and Messmer Grade II > III) in Europe,[21] but it accounted for most grade 5 reactions among food allergens that elicited severe allergic reactions in our registry. It will be intriguing to evaluate allergens other than tropomyosin that may contribute to these severe allergic reactions,[22] and further research is necessary to understand the mechanism underlying shellfish anaphylaxis in Asia, where a high prevalence of HDM allergies is reported.[23,24] On the other hand, peanut is not a common weaning food in Asian infants, in contrast with infants in Israel,[25] However, peanuts are ubiquitous in Asian cuisines, such as Thai and Chinese dishes, where peanuts are often used in the form of oil, crumbs or flour to add flavor, texture, and nutrition to dishes. While Asian parents may not intentionally feed plain peanuts to young infants, feeding table food from adults' plates is a common practice in many Asian cultures. Hence, exposure to small amounts of peanut allergens from a young age, particularly in multigenerational families living under the same roof, may be more common than documented. Despite the similarities in culture and cuisine between HK and Qingdao, there was a significant difference in the rate of peanut-induced anaphylaxis. It is also unclear why wheat allergy is more common in Thailand compared to other parts of Asia even though there are no significant differences in wheat introduction in young infants.

It is important to highlight that anaphylaxis patterns do not necessarily correspond to food allergy (FA) prevalence in this region. Despite peanuts being one of the top food anaphylaxis triggers in Singapore and HK in this study, the overall prevalence of peanut allergy (PA) remained low in these regions.[26,27] The difference in PA prevalence between the East and West may be due to environmental exposure. The striking difference in the estimated incidence of anaphylaxis between HK and Qingdao is intriguing as these patients share a common Han Chinese ethnic background. Our earlier studies documented that children from HK had a higher prevalence of asthma when compared with children from mainland China.[28,29] The Europrevall-INCO survey also documented a 2 to 7-fold higher prevalence of probable FA in children from HK than in children from mainland China.[27] Compelling epidemiologic studies suggest that children who grow up on traditional farms are strongly protected against asthma and allergies compared to nonfarm children,[30] in line with the hygiene and biodiversity hypotheses.[31,32] First-generation migrants, especially those moving from developing to developed countries, have a lower risk of developing allergic diseases than second-generation migrants.[33] Moving to a new country may lower the risk of developing allergic diseases, but this effect may decrease over time.[34] These studies have also shown that children of Asian descent possess a genetic predisposition to allergic diseases, which is unmasked in the absence of crucial environmental factors during migration.

Our research has revealed that there are differences in the anaphylaxis symptoms across different age groups. Younger children were more likely to present with vomiting, stridor, cyanosis, and pallor, as seen in Figure 2, whereas adolescents had more symptoms of dyspnea, dizziness, and hypotension. This difference may be explained by young children having difficulty describing sensations like dizziness and dyspnea, and they were usually held lying flat, unlike adolescents who are more likely to suddenly sit or stand, resulting in cardiovascular compromise.[35,36] Moreover, the time from symptom onset to arriving at medical care was the shortest among adolescents, as with the time from symptom onset to adrenaline administration, as shown in Table 2, suggesting that the higher occurrences of circulatory and neurological symptoms in adolescents were not caused by their later presentation to the ED. Similar characteristics were reported in the European anaphylaxis registry,[6] with higher frequency of dizziness, hypotension and collapse with increasing age, whereas vomiting was more commonly reported in young children. Comparable patterns were also observed in the United States,[37] Singapore,[11] and Korea.[12] It is critical to educate teenagers who are at high risk of adverse anaphylactic outcomes due to the intensity of their symptoms, increased risk-taking behaviors, and less adult supervision.

The current management of anaphylaxis in Asia still presents areas for improvement. Despite having a history of FA or anaphylaxis, only a subset of these patients owned an adrenaline device before the current anaphylaxis episode. Prescription of adrenaline devices often depends on the availability of adrenaline autoinjectors and variability in prescribing recommendations in each region. At the time of data collection, the supply of self-injectable adrenaline devices was very limited in mainland China and Thailand. None of the subjects in Qingdao owned an adrenaline device before and after the current anaphylaxis episodes. In Bangkok, subjects were given pre-filled syringes with adrenaline due to the limited supply and high cost of adrenaline autoinjectors (Figure E3), while commercial adrenaline autoinjectors were more readily available in HK and Singapore. Kerddonfak et al. reported that pre-filled adrenaline syringes remain stable and sterile for up to 3 months when stored at a temperature of 26 ± 3°C.[38] However, the stability may drop to less than 3 months in tropical regions with temperatures exceeding 30°C. A previous study showed a 50% decrease in adrenaline concentration after being stored at 37°C for 6 months.[39] Thus, the effectiveness of adrenaline syringes may be reduced due to global warming. These syringes are widely prescribed in Thailand (82%) due to their low cost, but our study has shown that the actual usage rate was low at 6.8% compared to other regions. The low rate of prehospital adrenaline administration may stem from difficulty recognizing the condition early, and fear of needle use, particularly for non-healthcare providers. In contrast, there was generally an over-reliance on the use of antihistamines (70%), particularly first-generation antihistamines, across all age groups as well as corticosteroids (60%), particularly in older children with anaphylaxis. Previous studies have also reported a high rate of corticosteroid use,[40,41] likely attributed to the unavailability of adrenaline devices and lack of standardized protocol in anaphylaxis management.[42] As a result, there is an urgent imperative to address barriers hindering the availability and affordability of adrenaline autoinjectors on a global scale, particularly in developing countries.

4.1 | Strength and limitations

The strengths of the APRA registry are its prospective nature, the sizeable cohort of children with anaphylaxis from East and Southeast Asia, and the use of a single standardized data collection protocol and reporting structure. Knowledge about the geographical-specific and age-specific triggers of anaphylaxis enables a better understanding of the prevalence and characteristics of food allergies in different regions of Asia. This can facilitate the development of improved diagnostic tools and targeted strategies for the prevention of accidental reactions.

In this study, although most of the data was sourced from developed urban centers in Singapore, HK, and Bangkok, we also collected data from developing regions like Qingdao, and Nakhon Nayok (a province in Thailand). The estimated anaphylaxis incidence was, however, similar across these regions, except for Qingdao. The incidence rates of anaphylaxis enable comparison of its burden across regions, but these remain to be estimations and may not accurately reflect the true frequency of anaphylaxis cases. Cases admitted to the private hospitals in HK and Singapore were not included, although they accounted for less than 10% of the region's healthcare services. In Bangkok, data was collected from five out of the top 10 largest institutions out of a total of 127 hospitals. The pediatric population served in Thailand and Qingdao was calculated based on the assumption that patients are equally distributed among these hospitals. However, it's crucial to note that patients may visit larger hospitals rather than regional ones, impacting how data on anaphylaxis cases are distributed across healthcare facilities. In spite of the limitations, the incidence rates give valuable insights into the impact of anaphylaxis in Asia and do not limit the interpretation of patterns of allergen triggers and anaphylaxis management in these regions. In our study, a high rate of "idiopathic" anaphylaxis in Qingdao was noted. Identifying allergen triggers in Chinese cuisine can be challenging due to the diversity of ingredients, herbs, spices, and condiments used. However, the limited diagnostic capabilities in identifying the underlying triggers may have contributed. A mere 18% of anaphylaxis cases in Qingdao were referred to specialists for further evaluation, suggesting that allergy testing might not have been widely available or sufficiently extensive to identify the specific trigger for a significant number of cases. Other risk factors, such as severe asthma and mastocytosis, may not be fully captured in our registry due to the limited availability of tryptase assay in some centers and the low number of cases included. Furthermore, the study was carried out amidst the COVID-19 pandemic, which may have caused changes in healthcare usage and allergen exposure patterns due to lockdowns, travel restrictions, and school closures. These changes, however, would have affected all Asian cities equally, and the overall incidence of anaphylaxis should not have been severely impacted, as patients with anaphylaxis would require urgent medical attention despite the ongoing pandemic.

Overall, with diseases in which targeted studies are difficult, a regional prospective registry is valuable in evaluating the anaphylaxis patterns and the adequacy of anaphylaxis management in this region. Our data showcased the disparity in anaphylaxis triggers between the East and the West, and even between the different Asian cities. In particular, PA was rare in Thailand and Qingdao compared to HK and Singapore. Although peanuts are not formally introduced to infants' diets until later in Asian culture, the prevalence of PA remains low. This suggests that there are other influential factors that provide protection against peanut allergies. Comparative studies on early feeding practices are crucial to understanding the protective factors for low incidence of food-induced anaphylaxis in certain regions in Asia. Singapore and HK are developed countries with Westernized lifestyles. It is conceivable that the patterns of FA in these countries are gradually evolving towards that of the Western world with rising FA rates, especially PA; while the rates of FA in Thailand and Qingdao may merely be a few decades behind this trend. Pre-hospital adrenaline use was very low and rates of the prescription of adrenaline devices were variable across Asia. Pre-filled syringes with adrenaline were feasible alternatives to adrenaline autoinjectors in countries where the latter are not commercially available, but continued endeavors to increase the global availability and maintenance of supply chains of adrenaline autoinjectors are much needed. Initiatives to establish guidelines for evidence-based best practices in anaphylaxis management and continued education to improve anaphylaxis care are warranted.

Expansion of this ongoing prospective registry, which collects anaphylaxis information with standardized working definitions and methodology, to other populations, including other developing nations, will allow more accurate estimates of the true anaphylaxis burden worldwide. A clearer understanding of the reasons explaining the differences in the patterns of anaphylaxis between Asia and countries in Europe and North America may provide insights into the etiologies and pathogenesis of anaphylaxis around the world.

AUTHOR CONTRIBUTIONS

ASYL, EHT and PP had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. ASYL, EHT and PP contributed to the study concept, data collection, data analysis and interpretation, all aspects of the study, and manuscript preparation and revision; YX and HKTT contributed to data collection; SYL, KMA, PC, SS, ME, BWL and GWKW contributed to the study design and critical review. All authors made substantial contributions for important intellectual and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Agnes Sze Yin Leung https://orcid.org/0000-0001-8249-4478
Yuhan Xing https://orcid.org/0000-0002-2373-5101
Kangmo Ahn https://orcid.org/0000-0001-7751-9829
Motohiro Ebisawa https://orcid.org/0000-0003-4117-558X
Gary Wing Kin Wong https://orcid.org/0000-0001-5939-812X

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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