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Predictors of serious outcomes among patients with anaphylaxis seen in the Philippine national tertiary hospital

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Conflict of Interest
The authors have no financial conflicts of interest.

ABSTRACT

Background: Anaphylaxis is a severe and life-threatening systemic hypersensitivity reaction. The incidence of anaphylaxis has increased significantly in recent years.
Objective: To identify predictors of serious outcomes among patients with anaphylaxis seen in the national tertiary hospital of the Philippines from 2015 to 2019.
Methods: Data was collected retrospectively through search of the medical records section and census reports on all patients diagnosed with anaphylaxis seen at the national tertiary hospital from 2015 to 2019. The patients' clinical profile, management, and outcome were extracted. Multiple logistic regression analysis was used to determine the association of clinical characteristics and physicians' management with the development of serious outcomes. Variable selection procedure through backward elimination method was used to determine significant predictors of serious outcomes of anaphylaxis. Data analysis was done using Stata 14 software.
Results: There were 300 patients with anaphylaxis seen at the Philippine national tertiary hospital from 2015 to 2019. Of the 300 patients, 179 were female (57.9%). The median age of the patients was 26 years old, with an interquartile range of 33 years. Only 75 patients (25%) had a past history of allergic disease. Majority of the patients (70%) had comorbidities. Drugs were the most common trigger of anaphylaxis (81.3%). Antibiotics were the most common type of drugs implicated (27%). Serious outcomes were noted in a total of 31 patients (10.3%). The significant predictors of serious outcomes in anaphylaxis are age ($p = 0.034$) and cofactors including use of beta-blockers and presence of acute infection ($p < 0.001$).
Conclusion: In the Philippine national tertiary hospital, the incidence of anaphylaxis increased by 240% in the past decade. Predictors of serious outcome in anaphylaxis include increased age and presence of cofactors such as beta-blocker use and presence of acute infection.

Keywords: Anaphylaxis; Hypersensitivity; Risk factors

INTRODUCTION

Anaphylaxis is defined as a severe and life-threatening systemic hypersensitivity reaction. It has a rapid onset, causes severe systemic manifestations, and can potentially lead to significant morbidity and mortality [1].

Author Contributions

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The incidence of anaphylaxis, similar to other allergic conditions, has increased significantly in recent years. The lifetime risk of the general population for developing anaphylaxis is 1.6% [2]. In the United States, the incidence increased from 153 per 100,000 in 2004 to 218 per 100,000 in 2016 [3]. A study in Australia reported an increase of 350% in food-induced anaphylaxis and a 230% increase in nonfood anaphylaxis from 1994 to 2005 [4]. In Europe, the incidence rate for anaphylaxis ranges from 1.5 to 7.9 per 100,000 person-years [5]. In Thailand, the incidence of anaphylaxis is 42.2 per 100,000 per year [6].

The diagnosis of anaphylaxis is made when any one of the following 3 criteria is fulfilled—(1) acute onset of illness with involvement of the skin or mucosal tissue and respiratory compromise or reduced blood pressure; (2) acute onset of at least 2 organ system manifestations (skin or mucosal manifestation, respiratory compromise, reduced blood pressure, gastrointestinal symptoms) after exposure to a likely allergen; or (3) reduced blood pressure after exposure to a known allergen. Cutaneous symptoms include flushing, pruritus, urticaria, angioedema, and conjunctival erythema. Respiratory symptoms include nasal pruritus, congestion, rhinorrhea, sneezing, hoarseness, cough, dyspnea, wheezing, and cyanosis. Gastrointestinal symptoms include abdominal pain, nausea, vomiting, and diarrhea. Cardiovascular symptoms include chest pain, tachycardia or bradycardia, palpitations, hypotension, and cardiac arrest. Neurologic symptoms include aura of impending doom, irritability, altered mental status, throbbing headache, dizziness, confusion, and tunnel vision.

Biphasic anaphylaxis refers to the recurrence of anaphylaxis symptoms within 1 to 72 hours. Refractory anaphylaxis refers to cases that do not respond to first-line treatment with intramuscular epinephrine, with need for vasopressors or intubation [1].

Common triggers for anaphylaxis include food, insect stings, and medications. A study conducted among pediatric patients in Singapore found that food was the most common trigger, accounting for 63% of the cases. This was followed by drugs at 30%, with ibuprofen as the most common drug causing anaphylaxis. The remaining 7% were idiopathic [7]. A study in Thailand involving adults and children reported food as the most common trigger (56.3%), followed by drugs (28.1%), insect stings (9.4%), and unknown trigger (6.2%) [6]. A study in Korea involving adults reported drugs as the most common trigger (46.5%), followed by food (24.2%), insect stings (16.4%), exercise (5.9%), and unknown etiology (7%). The most common implicated drugs were nonsteroidal anti-inflammatory drugs, antibiotics and radiocontrast media [8].

Patient risk factors for poor outcomes in anaphylaxis include age-related factors particularly infants, adolescents, women in labor, and elderly patients; and concomitant diseases such as asthma, respiratory disease, cardiovascular disease, mastocytosis, allergic rhinitis, atopic dermatitis, and psychiatric illness. Cofactors that can potentially amplify anaphylaxis include use of ethanol, sedatives, antidepressants, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, and recreational drugs; exercise; acute infection; emotional stress; disruption of routine; and premenstrual status [1]. A study in the United States found that women were 1.19 times more likely to develop anaphylaxis [3]. A study in Korea had different results, with more males developing anaphylaxis. In this study, predictors of serious outcomes included drug-associated anaphylaxis (odds ratio [OR], 2.11; 95% confidence interval [CI], 1.30–3.43), history of allergic disease (OR, 0.72; 95% CI, 0.53–0.98), multiorgan involvement (OR 2.31; 95% CI, 1.73–3.1), and older age group (OR, 1.02; 95% CI, 1.01–1.03). Serious outcomes were defined as need for hospital admission from the emergency room consult or prolonged admission

[8]. In a Singapore study, the only predictor of severe anaphylaxis was a previous drug allergy. Severe anaphylaxis was defined as respiratory compromise resulting in cyanosis or hypoxia, hypotension, or neurologic compromise [9].

The most common clinical symptoms of anaphylaxis in several studies were cutaneous manifestations, followed by respiratory symptoms [6-8].

The first-line treatment for anaphylaxis is intramuscular epinephrine. Other medications include H1 and H2 antihistamines, beta-agonists, and corticosteroids. Supportive management includes proper positioning of the patient, oxygen support, fluid boluses, and removal of trigger, as appropriate [1].

This study provides data on the clinical profile, triggers, risk factors, and outcomes of adult and pediatric patients with anaphylaxis seen in the national tertiary hospital of the Philippines from 2015 to 2019. Significant predictors for serious outcomes were determined. Serious outcomes include mortality and refractory anaphylaxis as defined by the need for vasopressor drip or intubation.

MATERIALS AND METHODS

Study design

This is a retrospective cohort study of all patients with anaphylaxis seen at the Philippine General Hospital from the years 2015 to 2019. The study protocol was approved by the University of the Philippines Manila Research Ethics Board. Data were collected retrospectively on all patients diagnosed with anaphylaxis seen at the Philippine General Hospital from January 1, 2015 to December 31, 2019. The records of patients were retrieved from the medical records section and from the monthly census reports of the Division of Allergy and Immunology – Philippine General Hospital. Only patients that fulfilled the clinical criteria of anaphylaxis were included. The patients' age, sex, trigger, clinical manifestation, risk factors, laboratory work-up, treatment, and outcome were tabulated by the principal investigator and analyzed using appropriate statistical methods. Serious outcomes were defined as the need for vasopressor drips or intubation, and death of the patient with anaphylaxis as an immediate or underlying cause.

Sample size

Sample size calculation for logistic regression to identify prognostic factors was based on the work of Peduzzi et al. [10] Let **p** be the smallest of the proportions of negative or positive cases in the population and **k** the number of covariates (the number of independent variables), then the minimum number of cases to include is N = 10 k/p.

For this study, 9 covariates will be included. A proportion of 38.9% (690 of 1,776) was used for prevalence of serious outcomes among those with anaphylaxis based on the study Ye et al. [8] The minimum number of cases required is N = 10 × 9/0.389 = 231.

Data analysis

Demographic and clinical data were presented using descriptive statistics. Quantitative variables were expressed using means and standard deviations for normally distributed data and median and interquartile range (IQR) for nonnormally distributed data. Qualitative

variables were expressed using frequencies and percentages. Normality of distribution for continuous variables was tested using the Shapiro-Wilks test. Multiple logistic regression analysis was used to determine the association of clinical characteristics and physicians' management with the development of serious outcomes of anaphylaxis. Variable selection procedure through backward elimination method was used to determine significant predictors of serious outcomes of anaphylaxis. Data analysis was done using Stata 14 (StataCorp LP., College Station, TX, USA).

Appropriate tables and graphs were used for data presentation. The number of anaphylaxis cases per year was presented in a graph to identify the trend over the past 5 years.

RESULTS

A total of 300 patients with anaphylaxis were seen at the Philippine General Hospital from 2015 to 2019. Of the 300 patients, 130 were pediatric patients (43.3%) and 170 were adult patients (56.7%). **Fig. 1** shows the incidence of cases of anaphylaxis per year. There was a 193% increase in the number of cases of anaphylaxis from 2015 to 2019.

Of the 300 patients, 121 were male and 179 were female. **Fig. 2** shows the age and sex distribution of the patients. Among patients less than 10 years old, there were slightly more male than female patients who developed anaphylaxis. Beyond the age of 10, there were more females who developed anaphylaxis. There were more patients who developed anaphylaxis in the 10 to 19 year old age group, with a total of 71 patients (23.7%). This is followed by the 1- to 9-year-old age group, with 50 patients (16.7%). The median age of the patients was 26 years, with an IQR of 33 years.

Only 75 patients (25%) had a past history of allergy. Thirteen patients had more than 1 allergic diagnosis. One patient had 4 allergic disease entities, namely drug allergy, food allergy, asthma, and allergic rhinitis. Three patients had 3 allergic disease entities (2 patients had drug allergy, asthma, and allergic rhinitis; 1 patient had food allergy, drug allergy, and allergic rhinitis). Nine patients had 2 allergic disease entities (5 patients had asthma and allergic rhinitis; 1 had allergic rhinitis and atopic dermatitis, 1 had food allergy and asthma; 1

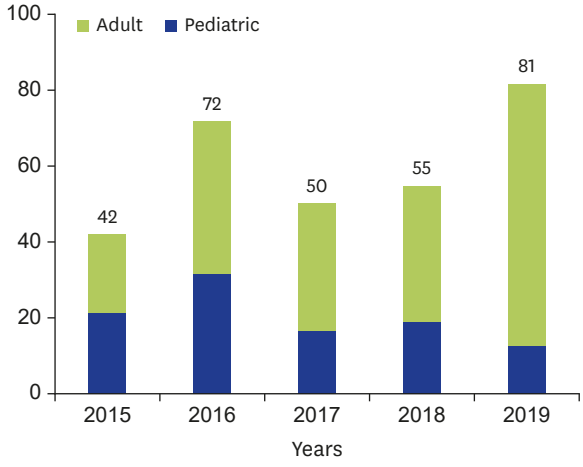

Fig. 1. Incidence of anaphylaxis in the Philippine national tertiary hospital from 2015 to 2019.

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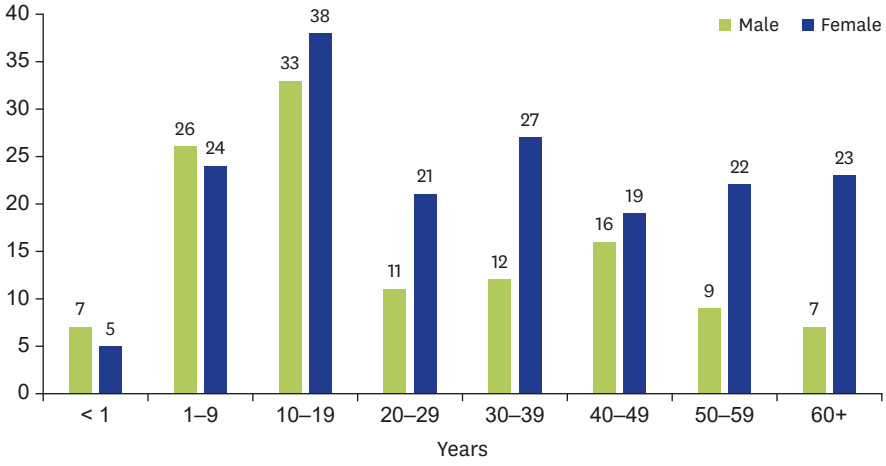

Fig. 2. Age and sex distribution of patients with anaphylaxis in the Philippine national tertiary hospital from 2015 to 2019.

had drug allergy and urticaria; 1 had asthma and urticaria). The number of patients for each allergic disease entity is summarized in **Table 1**.

A total of 210 patients (70%) had comorbidities. There were 24 patients who had multiple comorbidities. The most common type of comorbidity among the patients who developed anaphylaxis is malignancy (32.7%). The number of patients for each comorbidity is summarized in **Table 1**.

The most common trigger of anaphylaxis was drugs, with 244 patients developing drug-induced anaphylaxis (81.3%). This was followed by blood products in 23 patients (7.7%), food in 12 patients (4%), insect sting in 7 patients (2.3%), immunotherapy shots in 2 patients (0.7%), and cosmetics in the form of hair dye in 1 patient (0.3%). The cause of anaphylaxis was unknown in 11 patients (3.7%).

Among the drugs, the most common implicated drugs were antibiotics in 66 patients (27%). This was followed by chemotherapeutic drugs in 48 patients (19.7%), radiocontrast media in 24 patients (8%), and vitamins in 19 patients (8%), of which 17 out of these 19 patients had anaphylaxis to vitamin K. Other implicated drugs include anesthetics (19 patients, 7.8%), paracetamol (10 patients, 4.1%), antituberculosis medications (8 patients, 3.3%), nonsteroidal anti-inflammatory drugs (7 patients, 2.9%), opioids (6 patients, 2.5%), antifungal medications (6 patients, 2.5%), N-acetylcysteine (5 patients, 2%), and over-the-counter cough and colds medications (5 patients, 2%). The most common route of administration was intravenous (190 patients, 78%), followed by oral (49 patients, 20%), and intramuscular (5 patients, 2%). Out of the 244 patients with drug triggers, 219 patients (89.8%) developed anaphylaxis while admitted in the hospital and 25 patients (10.2%) developed anaphylaxis outside the hospital.

Among the blood products, 11 patients developed anaphylaxis to packed red blood cell (47.8%), 7 to platelet concentrate (30.5%), and 5 to fresh frozen plasma (21.7%).

For the food triggers, there were 2 cases each for peanut, shrimp, and flour mites. The other implicated food with 1 case each include crab, soy, chicken, egg, milkfish, and eggplant. The implicated food was identified through history of the patients.

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Table 1. Clinical characteristics of patients with anaphylaxis

Characteristic	Value
Age (yr), median (IQR)	26 (33)
Male sex	121 (40.3)
Past history of allergy	
History of drug allergy	39 (13.0)
Bronchial asthma	23 (7.7)
Allergic rhinitis	12 (4.0)
History of food allergy	9 (3.0)
Chronic urticaria	8 (2.7)
Atopic dermatitis	2 (0.7)
Concomitant diseases	
Malignancy	98 (32.7)
Cardiovascular disease	39 (13.0)
Gastrointestinal disease	21 (7.0)
Neurologic disease	18 (6.0)
Endocrinologic disease	18 (6.0)
Immunodeficiency	13 (4.3)
Renal disease	11 (3.7)
Autoimmune disease	7 (2.3)
Psychiatric disease	4 (1.3)
Hematologic disease	4 (1.3)
Respiratory disease	3 (1.0)
Genetic disease	3 (1.0)
Trigger	
Drug	244 (81.3)
Blood products	23 (7.7)
Food	12 (4)
Animal sting	7 (2.3)
Immunotherapy	2 (0.7)
Cosmetics	1 (0.3)
Unknown	11 (3.7)
Cofactors	
Acute infection	122 (40.7)
Use of ACE inhibitors	11 (3.7)
Use of beta-blockers	9 (3.0)
Setting of anaphylaxis	
Hospital	244 (81.3)
Outside the hospital	56 (18.7)

Values are presented as number (%) unless otherwise indicated.
IQR, interquartile range.

The most common animal sting was from jellyfish in 4 cases. There was 1 case of scorpion, 1 from triatoma, and 1 case where the stinging insect was unknown.

Cofactors that can potentially cause more severe anaphylaxis were present in 138 patients (46%). Nine patients had more than 1 cofactor. The most common cofactor was acute infection in 122 patients (40.7%). There were 11 patients on ACE inhibitors (3.7%) and 9 patients on beta-blockers (3%). There was no patient with documented ethanol or recreational drug use antecedent to the development of anaphylaxis.

The most common clinical manifestation of anaphylaxis was cutaneous, with 165 patients (55%) developing cutaneous symptoms. This was followed by respiratory symptoms in 160 patients (53.3%), cardiovascular symptoms in 98 patients (32.7%), and gastrointestinal symptoms in 55 patients (18.3%). Neurologic symptoms were least common, with only 18 patients (6%) manifesting with these symptoms. The most common combination of organ systems involved was cutaneous with respiratory organ system involvement, affecting

30.4% of patients. This was followed by the combination of cutaneous, respiratory, and cardiovascular organ system involvement, affecting 14% of patients.

Majority of the patients (244 patients, 81.3%) developed anaphylaxis while admitted at the Philippine General Hospital. Only 56 patients (18.7%) developed symptoms of anaphylaxis outside the hospital and were subsequently brought to the Philippine General Hospital Emergency Department for treatment.

There were 183 patients who were given intramuscular epinephrine (61%). The median number of dose of epinephrine administered was 1, with an IQR of 1. Steroids were given in 260 patients (86.7%), antihistamines in 272 patients (90.7%), and beta-agonist nebulization in 45 patients (15%). Noninvasive oxygen support was administered for 40 patients (13.3%). There were 23 patients who were intubated (7.7%) and 25 patients who were started on vasopressor drip (8.3%). There were 20 patients who died with anaphylaxis as an immediate or underlying cause (6.7%).

Serious outcomes were noted in 31 patients (10.3%); 10 were pediatric patients and 21 were adult patients. Of the 31 patients, 25 (80.6%) had comorbidities, the most common type is still malignancy. Cofactors were present in 25 patients (80.6%), namely acute infection in 23 patients, beta-blocker use in 3 patients, and ACE-inhibitor use in 1 patient. Three patients had 2 cofactors present. Out of the 31 patients with serious outcomes, 23 patients (74.2%) were given intramuscular epinephrine. **Table 2** summarizes the management and outcomes of patients.

The crude associations of the various factors with serious outcomes in anaphylaxis are shown in **Table 3**. Using the backward elimination approach, it was determined that age and cofactors are significant predictors of serious outcomes in anaphylaxis. Controlling for other variables in the model, each year increase in age increases the odds of developing a serious outcome in anaphylaxis by 1.9%. The odds of developing a serious outcome in anaphylaxis is 6.1 times higher among patients with cofactors compared to those without cofactors. In particular, the odds of serious outcome are 29.96 times higher among patients taking beta-blockers, 6.5 times higher among patients with acute infection, and 11.6 times higher among patients with multiple cofactors. The adjusted odds ratios are shown in **Table 4**.

Table 2. Management and outcomes of patients with anaphylaxis

Parameter	No. (%)
Epinephrine	
Use of epinephrine	183 (61.0)
No. of intramuscular doses, median (IQR)	1 (1.0)
Other medications	
Use of steroids	260 (86.7)
Use of antihistamines	272 (90.7)
Beta-agonist nebulization	45 (15.0)
Supportive treatment	
Oxygen support (noninvasive)	40 (13.3)
Intubation	23 (7.7)
Vasopressor drip	25 (8.3)
Mortality	20 (6.7)
Serious outcome	31 (10.3)

Values are presented as number (%) unless otherwise indicated.
IQR, interquartile range.

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Table 3. Crude association of factors with serious outcome in anaphylaxis

Factor	Crude OR	95% CI	*p* value
Age	1.02	0.99–1.03	0.06
Sex	1.74	0.77–3.93	0.18
History of allergy	0.55	0.20–1.48	0.23
Food allergy	1.53	0.17–13.62	0.70
Drug allergy	0.23	0.03–1.77	0.16
Asthma	1.39	0.29–6.63	0.68
Multiple allergy	0.64	0.09–5.11	0.67
Concomitant disease	1.89	0.75–4.78	0.18
Cardiovascular disease	1.91	0.44–8.25	0.39
Neurologic disease	1.00	0.11–8.95	1.00
Gastrointestinal disease	1.00	0.11–8.95	1.00
Malignancy	1.23	0.39–3.80	0.73
Autoimmune disease	2.80	0.28–27.96	0.38
Immunodeficiency	1.27	0.14–11.58	0.83
Endocrinologic disease	6.00	1.23–29.30	0.027
Renal disease	2.33	0.24–22.66	0.47
Multiple comorbidities	5.76	1.72–19.30	0.005
Cofactors	5.75	2.28–14.48	<0.001
Beta-blocker	27.17	1.51–488.36	0.025
Acute infection	6.01	2.34–15.40	<0.001
Multiple cofactors	13.58	2.72–67.80	0.001
Epinephrine use	0.45	0.18–1.15	0.095
Steroids use	0.39	0.05–3.01	0.37
Antihistamine use	1.01	0.65–1.85	0.726
Beta-agonist nebulization	1.77	0.71–4.40	0.22

OR, odds ratio; CI, confidence interval.

Table 4. Predictors of serious outcome in anaphylaxis

Factor	Adjusted OR	95% CI	*p* value
Age	1.019	1.001–1.036	0.034
Presence of cofactors	6.098	2.407–15.453	<0.001
Beta-blocker	29.959	1.557–576.620	0.024
Acute infection	6.513	2.517–16.860	<0.001
Multiple cofactors	11.597	2.280–58.993	0.003

OR, odds ratio; CI, confidence interval.

DISCUSSION

Consistent with the global trend of increasing incidence of anaphylaxis, the Philippine General Hospital experience similarly showed a significant increase in anaphylaxis cases in recent years. A previous unpublished study on anaphylaxis cases in the Philippine General Hospital from 2010 to 2014 reported 125 cases [11]. This study showed a 240% increase from this previous study, with 300 cases in 5 years from 2015 to 2019.

Similar to the study in Korea, the most common trigger in this study were drugs, in particular antibiotics. This is consistent with the high incidence of acute infection as a cofactor among the patients. Acute infection is an important cofactor for anaphylaxis since bacterial components such as lipopolysaccharide and lipotechoic acid can directly activate mast cells through Toll-like receptors [12]. The bacteria-derived peptide N-formyl-methionyl-leucyl-phenylalanine can also cause release of histamine from basophils [13]. In addition, infectious microorganisms activate the complement system, leading to the formation of anaphylatoxins C3a and C5a. Anaphylatoxins are potent inflammatory mediators that trigger the release of histamine from basophils and mast cells [14]. The massive histamine release from these immune cells amplifies anaphylaxis.

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Although 244 of the cases of anaphylaxis were due to drugs, only 39 patients had a previous history of drug allergy. This highlights the importance of careful monitoring of patients receiving medications, even those who do not have a history of drug allergy. The ability to recognize anaphylaxis among front-line health care providers, including nurses and doctors, is also crucial so that timely management may be given.

Furthermore, only 25% of patients had a previous history of allergic disease. This is consistent with the previous reports that atopy is not a risk factor for drug-induced anaphylaxis. Epigenetics plays an important role in allergic drug reactions, and certain alleles have been identified to be significantly associated with drug allergies. For example, HLA B*5702 is associated with abacavir drug allergy; interleukin (IL)-13 and IL-4RA polymorphisms are associated with beta-lactam allergy; E237G variant of FcεR1b gene, IL-4RaQ576R polymorphism, and IL-4 IL-13-SNP polymorphisms are associated with penicillin allergy. These genes are postulated to cause formation of reactive metabolites, produce specific antibodies, and produce pharmacologically active mediators [15].

The most common comorbidity among the patients in this study was malignancy. Chronic low-grade inflammation has been found to be a common feature of almost all noncommunicable diseases, including cancer, allergy, obesity, diabetes, and cardiovascular diseases. These noncommunicable diseases have common environmental risk factors that affect systemic inflammation through Toll-like receptors, leading to downstream effects on the immune system. The resulting changes in the immune system, particularly the higher levels of inflammatory cytokines, may predispose individuals with cancer to a more severe allergic response [16].

Moreover, patients with cancer are treated with toxic chemotherapeutic agents and monoclonal antibodies which may result in IgE or IgG-mediated anaphylaxis [1, 17]. These patients also often receive several concurrent medications such as analgesics, sedatives, and antiemetics that increase their risk for anaphylaxis. In particular, opioids may cause direct mast cell activation, while nonsteroidal anti-inflammatory drugs can cause IgE-mediated anaphylaxis and COX-1 inhibition leading to increased synthesis of leukotrienes [1, 18].

There were 2 predictors for developing serious outcomes in anaphylaxis from this study—age and cofactors. This is similar to the study in Korea which also reported increased risk for serious outcomes among the older age group. This may be due to the reduced ability of the older age group to cope with the systemic effect of anaphylaxis given their pre-existing health status. The presence of cofactors is also significantly associated with developing serious outcomes. Patients who are on beta-blockers had higher odds of serious outcome, which is likely due to the antagonistic effect of beta-blockers on epinephrine, the first-line medication for anaphylaxis.

An important limitation of this research is the retrospective study design. The exact timing of recognition of anaphylaxis and institution of management is not readily available. Early injection of epinephrine as a first-line intervention significantly improves outcome among patients with anaphylaxis [2]. In this study, the timing of epinephrine administration in relation to the diagnosis of anaphylaxis and the administration of other interventions such as antihistamines and steroids were not factored into the logistic regression. Among the 31 patients with serious outcomes, majority (74.2%) was given intramuscular epinephrine. A possible reason why these patients still developed serious outcomes despite receiving epinephrine is the delayed administration of the drug.

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Definite confirmation through skin testing or specific-IgE levels was also not done for all cases. Another limitation is the dependence of this study on the accuracy and completeness of the patient records. There is a possibility that some patient details may have not been accurately recorded which may affect the results of this study.

In conclusion, there was a 240% increase in the incidence of anaphylaxis in the Philippine national tertiary hospital from 2010 to 2019. Predictors of serious outcome include increased age and presence of cofactors such as use of beta-blockers and presence of acute infection.

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