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**EPIDEMIOLOGY OF ANAPHYLACTIC SHOCK AND ITS RELATED
MORTALITY IN HOSPITALPATIENTS IN TAIWAN: A NATIONWIDE
POPULATION-BASED STUDY**

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ABSTRACT

Anaphylactic shock is potentially life-threatening. However, there is a paucity of data about its incidence and associated mortality, particularly in Asian populations. We aimed to investigate the epidemiology of anaphylactic shock and its related mortality after the hospitalization of patients in the general population of Taiwan. The National Health Insurance Research Database was used to identify patients with anaphylactic shock and estimate its incidence for inpatients sampled from 2005 to 2012. The pattern of anaphylactic shock and anaphylactic shock-related mortality rate was also examined. Of 22,080,199 patients who were admitted to hospitals from 2005 to 2012, there were 2289 incident cases of anaphylactic shock and 2219 people were included. Incidence of hospitalizations due to anaphylactic shock ranged from 12.71 to 13.23 per million of the population between 2005 and 2012. The incidence of anaphylactic shock in our study was substantially lower than other western countries, including the United States. There were 24 deaths due to drug-induced anaphylactic shock among the hospitalizations; overall mortality rate was 1.08%. Eighteen (0.81%) patients died within 30 days; 22 (0.99%) died within two months following the anaphylactic shock. The highest incidence occurred in patients aged 70-79 years. Conversely, food-induced anaphylactic shock was not influenced by age. In conclusion, drug-induced anaphylactic shock was a major cause of deaths due to anaphylactic

shock in hospitalized patients. Most cases of anaphylactic shock occurred in the older population, and the mortality rate was lower in females than in males, though the difference was not significant.

Key words: Anaphylactic shock, epidemiology, mortality, hospitalization

INTRODUCTION

Anaphylactic shock is a rapid-onset systemic allergic reaction that is potentially life-threatening and can affect people of any sex or age(1,2). The diagnosis of anaphylactic shock is based on the recognition of clinical symptoms. It requires a detailed evaluation of the episode, including activities and events occurring within hours preceding the episode. Patients typically present with a combination of respiratory, dermatologic, gastrointestinal, and cardiovascular symptoms. The most common triggers for anaphylactic shock are medications, insect stings, and food(3). Medication-related anaphylactic shock accounts for most deaths as a result of anaphylaxis(4).

There was a wide variation in the reported prevalence and incidence of anaphylactic shock. The real incidence of anaphylaxis is difficult to estimate due to its varying definitions, the lack of confirmatory laboratory tests, as well as under-recognition and under-diagnosis by clinicians. It has an incidence of 3.2-20 episodes per 100,000 person-years(5-7), and the estimated prevalence is 0.3-5.1% depending on the rigor of the definitions used. Population-based studies in the United States, the United Kingdom, and other developed countries have estimated the incidence rate of anaphylactic shock to be 40-500 per million person-years(8). Based on previous studies, the lifetime prevalence of anaphylactic shock was 0.5%-2% and seems to be

increasing(8-10).Reported studies have estimated the anaphylactic shock-related mortality rate to be 0.5-5.5 per million population, with death occurring in 0.65%-2% of patients who encounter severe anaphylactic reactions(11,12). Tejedor Alonso et al. reported an increase in the incidence of anaphylaxis by about 5-7 fold in the last 10-15 years, but the number of deaths from anaphylaxis has not increased(13). Publications reported indicated that there had been a geographic gradient in the incidence of anaphylaxis. Higher frequencies of anaphylaxis were recorded in areas with fewer hours of sunlight(14).

A few studies of anaphylactic shock in the Asian population have been conducted, and most of those studies were limited by a regional focus or small populations. Buka et al. compared the incidence among the South Asian population (Indian) and the white population in Britain(15). The incidence rate of severe anaphylaxis in the South Asian population was 58.3 per 100,000 person-years compared to 31.5 in the white population.

Population-based epidemiologic data are valuable to assessing the risk of anaphylactic shock, and the information will be useful for informing patients and efforts to reduce the mortality associated with anaphylactic shock. However, studies analyzing fatal anaphylactic shock trends in a national registry for anaphylactic shock-related prevalence and deaths are rare. We sought to conduct a

large population-based epidemiologic study using current data from Taiwan's National Health Insurance Research Database (NHIRD) to estimate the case prevalence and mortality associated with food- and drug-induced anaphylactic shock, based on hospital records, and death certificates.

MATERIALS AND METHODS

This study was approved by the Institutional Review Board of the Chang Gung Memorial Hospital and the National Health Research Institute, the data holder of the National Health Insurance (NHI) research database.

Data sources and study population

Our primary data source was the NHI research database, which records the routinely collected health data for all individuals eligible for NHI, which has been operated as a single-payer program in Taiwan since March 1, 1995. By law, all citizens are required to enroll in the program, resulting in an exceptionally high coverage rate of over 99%. Approximately 28 million (living and deceased) beneficiaries were registered in the database between March 1995 and the end of 2012.

Denominator data were based on the Registry of Beneficiaries, a part of the NHI research database containing records of the demographics, insurance status, residence,

and socioeconomic data of all beneficiaries. The diagnostic coding system in the NHI follows the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). The validity, representativeness and clinical consistency of this database have been reported.

Case definition of anaphylactic shock

The identification of patients with anaphylactic shock was based on hospital records. We further classified patients with anaphylactic shock into drug-related and food-related cases. Drug-related anaphylactic shock was ascertained by using ICD-9-CM codes 995.4 and 995.0. Patients with the ICD-9-CM code 995.0 needed to have at least one of the external causes of injury codes (E930-E949) during admission to fulfill the case definition. The cases of food-related anaphylactic shock were ascertained by using the ICD-9-CM code 995.6.

Estimation of incidence and in-hospital mortality

The incidence was calculated by dividing the number of cases with anaphylactic shock by the number of person-years in the at-risk population in the same year. The patients had to have had at least a 1-year registration period prior to 1 January of each calendar year. We consider every episode of hospitalization as a single event. To

compare incidence rates between different calendar years, we standardized the incidence rates by age and sex using the population structure of 2012 as thereference. We also calculated the 30-, 60- and 90-days in-hospital mortality rates.

Trends in incidence

To determine the trends in incidence, we calculated the age- and sex-standardized incidence rates in each calendar year from 2005 to 2012 using the population structure in 2012 as thereference.

Statistical analysis

The 95% confidence intervals (CIs) for incidence were derived by the assumption of a Poisson distribution. We divided cases of anaphylaxis into two types, drug-related anaphylactic shock, and food-related anaphylactic shock, and calculated their incidence stratified by sex. We compared the in-hospital mortality rates of different age groups and sex by using the chi-square test. The Joinpoint Regression Program version 4.2.0.2 (National Cancer Institute, Bethesda, MD, USA) was used to estimate temporal trends in the standardized incidence of anaphylactic shock. Bayesian information criterion was used to generate different numbers of 'joinpoints' in time according to the trend of prevalence and incidence of anaphylactic shock changed

significantly to fit the data best, and it calculated the annual percentage changes (APCs) and 95%CI for each segment. All tests of statistical hypotheses were done on the 2-sided 5% level of significance. All analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Study population

The study population comprised 22,080,199 inpatients enrolled onto the NHI in Taiwan between March 1, 1995, and December 31, 2012 (Fig. 1). There were 2,289 anaphylactic shock episodes during 2005 to 2012. After excluding those who had multiple admissions due to anaphylactic shock ($n = 70$), the cohort consisted of 2,219 participants. The participants were classified either as admission due to food-related anaphylactic shock ($n = 418$) or drug anaphylactic shock ($n = 1,801$). In addition, there were 24 deaths as a result of drug-related anaphylactic shock.

Baseline characteristics of inpatients with anaphylactic shock

The data from 2,219 patients with first episodes of anaphylactic shock and relevant demographic information of the study group are reported in Table 1. Patients with anaphylactic shock were more likely to be older and to be female, and had with a significant difference in income levels and occupation ($P < 0.0001$).

Incidence and trend of anaphylactic shock in hospitalized patients

The incidences of anaphylactic shock in 2005 and 2012 during hospitalization were 12.71 and 13.23 per million population respectively, with a slight increase in the rate of hospitalization. The annual percentage changes were approximately 0.35% (95% CI, -1.94 to 2.69). The annual number of admissions due to drug-induced anaphylactic shock was 0.61 (95% CI, -2.13 to 3.43) and food-induced anaphylactic shock was -1.68% (95% CI, -5.49 to 2.29) from 2005 to 2012. However, while those due to food-related anaphylactic shock in females saw a significant decrease of approximately -6.02% (95% CI, -12.58 to 1.05) from 2005 to 2012. The results are shown in Table 2.

The incidence of drug-related anaphylactic shock in 2012 for in-patients was higher in all age groups, and especially high in older individuals (70-79 years) with a significant peak in incidence (Fig. 2). The incidence of drug-related anaphylactic shock from 2005 to 2012 was approximately 6 times higher than that due to food-related anaphylactic shock (Fig. 3).

Fatality of anaphylactic shock during hospitalization

As shown in Figure 4, 24 patients with drug-related anaphylactic shock died during hospitalization from 2005 to 2012. There were 17 males and 7 females, with more than half of the patients aged more than 60 years (Table 3). There was no

statistically significant difference between deaths by way of gender and the different age groups. No death was caused by food-induced anaphylactic shock during hospitalization from 2005 to 2012. The fatalities due to drug-induced anaphylactic shock by ICD-9 injury codes are shown in Figure 5.

DISCUSSION

The analysis of the National Health Insurance Research Database in Taiwan from 2005 to 2012 suggested that the incidence of admissions due to anaphylactic shock in Taiwan is lower than reported in other studies (1-6). The most common causes for admissions due to anaphylactic shock were a drug-related anaphylactic shock, followed by food-related anaphylactic shock. Drug-induced anaphylactic shock remains the major cause of deaths due to anaphylactic shock during hospitalization. Based on our data, most cases of anaphylactic shock occurred in the older population, and its mortality rate is lower in the female population, though not a statistically significant difference. There was a slight increase in the number of admissions due to anaphylactic shock from 2005 to 2012, though not statistically significant.

Anaphylaxis may cause problems that affect many body systems such as the skin, cardiovascular, respiratory, central nervous and gastrointestinal systems. Anaphylactic

shock is potentially life-threatening and should be handled seriously(3,7). However, the incidence of anaphylaxis is difficult to estimate. The diagnostic procedures and symptoms of anaphylaxis vary widely. Some patients may not seek medical assistance due to their lack of alertness or because their symptoms are not severe. Thus, the real incidence of anaphylaxis may be underestimated.

The incidence of anaphylactic shock in our study was substantially lower than previously reported in other studies. Reported incidences of anaphylactic shock ranged from 3.2 to 20 per 100,000 person-years. About 30% of patients get more than one attack(13). Australia and the United States have some of the highest incidence rates of severe anaphylaxis among developed countries. Decker et al. found a rate of 498 cases per million person-years in Rochester, Minnesota, between 1990 and 2000(16). Mullins et al. showed the admission rate due to anaphylaxis to be 10.6 per 100,000 population-years in 2011-2012 in Australia(17). The incidence differs in different geographical areas. The reasons for that may be the difference in the distribution of races, environmental conditions, socioeconomic status, medical resources, and the definition of anaphylaxis used.

The incidence of anaphylactic shock in Taiwan has increased slightly, but not statistically significantly so. Studies conducted in Australia, the United Kingdom, and the United States showed there had been an increase in hospitalizations due

to anaphylactic shock (17-19). Mullins et al. reported an increasing rate of anaphylactic shock in Australia (17), especially for food-related anaphylactic shock in children and teenagers. Decker et al. reported an increase from 469 per million persons in 1990 to 589 per million persons in 2000 in Rochester, Minnesota (16). In our study, incidence of anaphylaxis caused by food allergy was 6.53 per-million-person-year for age 0-9 years and 2.06 per-million-person-year for age 10-19 years (Table 4). Food allergy related anaphylactic shock is relatively lower in Taiwan than other studies (17-19). Similar result was reported in Singapore (20). Tham EH and his colleague surveyed the prescription incidence of adrenaline autoinjectors in Singapore. Adrenaline autoinjectors are beneficial for food-induced anaphylactic shock in prehospital system. They found a relatively low prescription frequency of adrenaline autoinjectors. In Taiwan, adrenaline autoinjectors are not standard equipments in prehospital system. The incidence of food-induced anaphylactic shock (peanut and shellfish) in Asian populations seemed to be different from that observed in Western populations.

The possible inciting allergens for anaphylactic shock are medications, insect stings, food, and other substances. In some cases, anaphylactic shock may take place without any obvious reason. In our study, the incidence rate of drug-related anaphylactic shock was about 6 times higher than that due to food-related anaphylactic shock. Hospitalization for insect sting-related anaphylactic shock was not presented in

the National Health Insurance Research Database in our study. Anaphylactic shock is due to insect stings is not an ordinary illness in Taiwan by clinical observation. However, this observation need further study to be confirmed.

Drugs were the leading cause of fatalities due to anaphylactic shock in Taiwan. Reports from the United States, Australia, the United Kingdom, and New Zealand also demonstrated similar results(4,21-23).In our study, there were 24 deaths out of 2,289 anaphylactic shock episodes from 2005 to 2012, giving an in-hospital mortality of 1.09%. Men had higher in-hospital mortality rates than women (0.75% and 1.39%), respectively; however, this is not a statistically significant difference. The most common inciting agents for drug-induced anaphylactic shock fatalities in the United Kingdom were general anesthetics(24), whereas antibiotics were the major inciting agents in France(2) and Australia(21). Other possible inciting agents for drug-related anaphylactic shock with fatalities were radiocontrast agents, chemotherapy, and other drugs(25). In our study, unspecified agents were the leading cause of hospitalization due to drug-related anaphylactic shock (n=663, 36%), followed by antibiotics. There were 314 (17%) hospitalizations due to drug-induced anaphylactic shock caused by antibiotics out of a total 1,801 drug-induced anaphylactic shock episodes. Two drug-related anaphylactic shock fatalities were caused by antibiotics and accounted for 9% of total drug-related anaphylactic shock fatalities. Based on our study, the

peak incidence of drug-related anaphylactic shock occurred in patients between the ages of 70 and 79, with equal sex distribution. Older persons are likely to receive more medications than younger ones, and so are more likely to be exposed to the trigger agents for anaphylactic shock. In the age under 19 years-old group, only 1 death was recorded and the trigger agent was medication.

There are potential limitations in our study. With the great variation in clinical manifestations and diagnostic definition, the diagnosis of anaphylactic shock is possibly disregarded by clinicians. Due to a lack of alertness to identify symptoms and seek medical assistance, patients may not seek treatment for anaphylaxis. Patients with anaphylactic symptoms treated without hospitalization were thus not included in our study. For the mortality cases, we collected the data from NHI research database based on the Registry. It is difficult to determine whether the late deaths within 2 months were caused by anaphylactic shock or related complications. This is a potential limitation in our study. Anaphylactic shock might not be the only cause responsible for the mortalities. The incidence rate of anaphylactic-shock-related mortalities might be overestimated.

CONCLUSION

Based on the NHIRD, the incidence rate of anaphylactic shock in Taiwan was lower than in most studies. Moreover, the incidence rate of anaphylactic shock had not

significantly changed each calendar year from 2005 to 2012 in Taiwan. Drug-induced anaphylactic shock remains the major cause of deaths due to anaphylactic shock in hospitalized patients. The incidence of food induced anaphylactic shock is relatively low in Taiwan. It seemed to be different from that observed in Western populations. Most cases of anaphylactic shock occurred in the older population, and the mortality rate was lower in females than in males, though not significantly.

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Figure 1.Flowchart showing people hospitalized for anaphylactic shock from 2005 to 2012

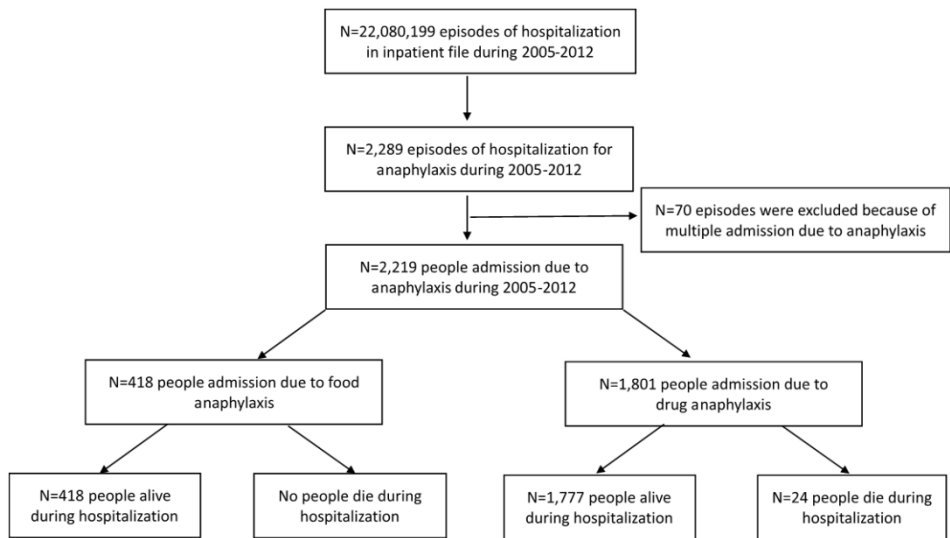


Figure 2. Age-specific anaphylactic shock rates according to the different types of anaphylaxis in 2012

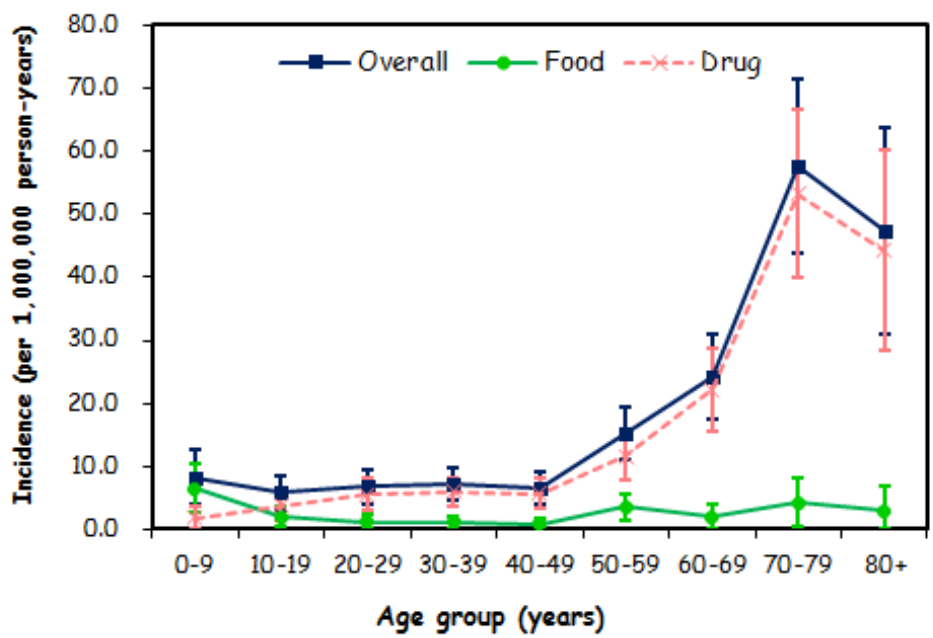


Figure 3. Trends in different types of anaphylactic shock

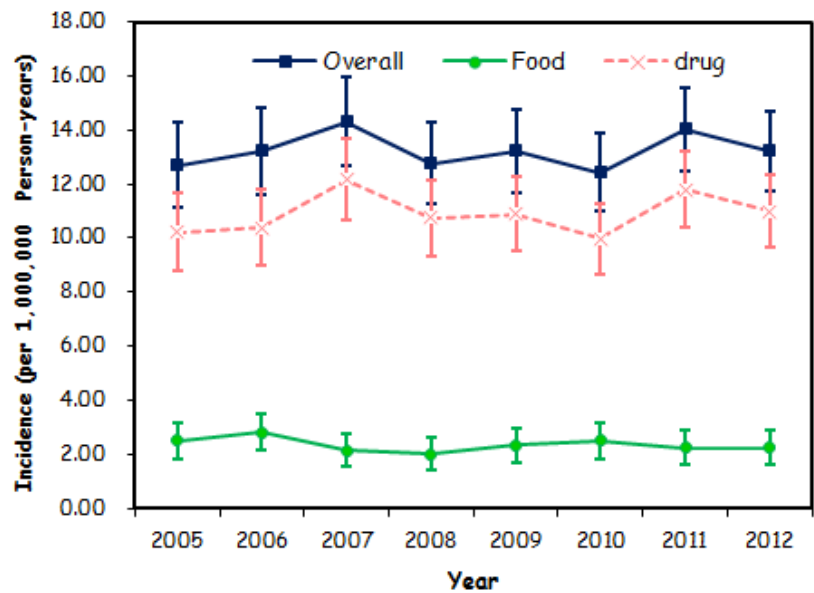


Figure 4. Patients with anaphylactic shock who died during hospitalization from 2005 to 2012. Data are shown according to sex (A) and age (B) and only include cases with the first episode of anaphylaxis.

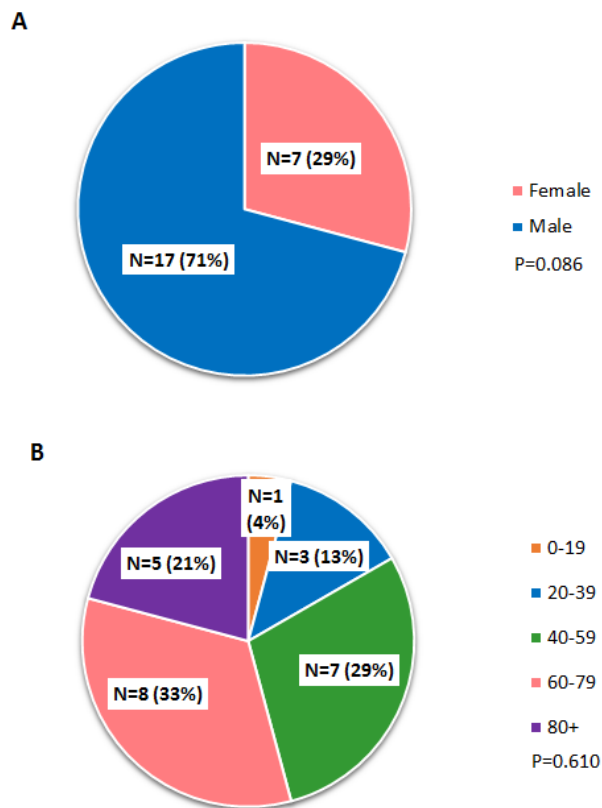


Figure 5. Drugs causing allergic drug reaction, by different external causes of injury

codes, data only include cases with the first episode of anaphylactic shock. Patients

hospitalized owing to drug-related anaphylaxis from 2005 to 2012, (A). Patients with

drug-related anaphylaxis who died during hospitalization from 2005 to 2012 (B).

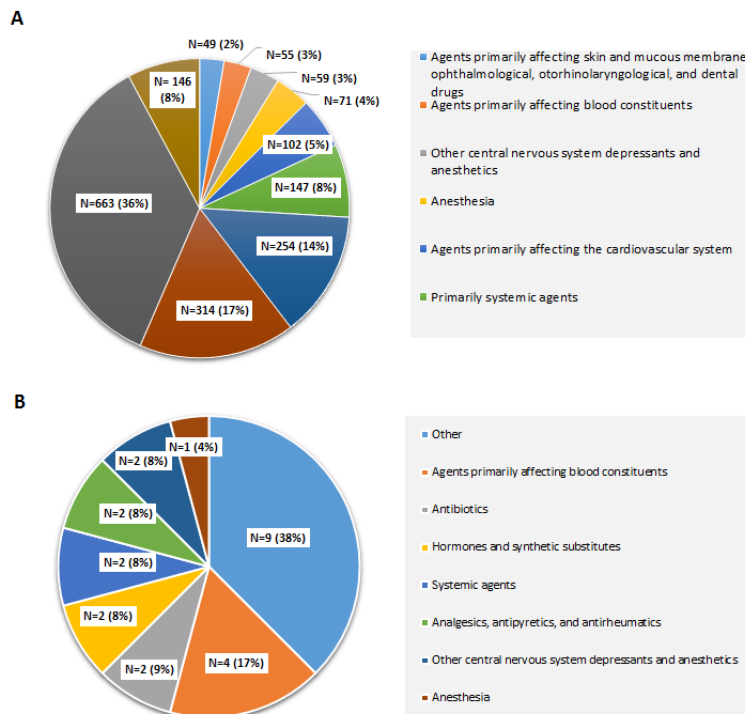


Table 1. Clinical characteristics of patients with anaphylactic shock from 2005 to 2012

Characteristics	Women	Men	P-value
	(n=1,033)	(n=1,186)	
Age (years) (mean $\pm$ standard deviation)	55.11y20.84	52.93y20.84	0.0154
0-9	22 (2.13)	41 (3.46)	0.4551
10-19	50 (4.84)	66 (5.56)	
20-29	74 (7.16)	90 (7.59)	
30-39	90 (8.71)	119 (10.03)	
40-49	126 (12.20)	144 (12.14)	
50-59	193 (18.68)	224 (18.89)	
60-69	180 (17.42)	194 (16.36)	
70-79	187 (18.10)	184 (15.51)	
≥ 80	111 (10.75)	124 (10.46)	
Place of residence, No. (%)			
Urban	215 (20.81)	219 (18.47)	0.0182
Suburban	271 (26.23)	261 (22.01)	
Rural	429 (41.53)	560 (47.22)	
Unknown	118 (11.42)	146 (12.31)	
Income levels, No. (%)			
Quintile 1	201 (19.46)	296 (24.96)	<.0001
Quintile 2	83 (8.03)	105 (8.85)	
Quintile 3	410 (39.69)	413 (34.82)	
Quintile 4	156 (15.10)	192 (16.19)	
Quintile 5	179 (17.33)	159 (13.41)	
Unknown	4 (0.39)	21 (1.77)	
Occupation, No. (%)			
Dependents of the insured individuals	388 (37.56)	316 (26.64)	<.0001
Civil servants, teachers, military personnel and veterans	38 (3.68)	116 (9.78)	
Non-manual workers and professionals	139 (13.46)	191 (16.10)	
Manual workers	394 (38.14)	391 (32.97)	
Other	74 (7.16)	172 (14.50)	
Charlson index (mean $\pm$ standard deviation)*	1.82lson	1.76lson	0.5662

Abbreviation: CCI, Charlson Comorbidity Index codes. *The Dartmouth-Manitoba's

Charlson Comorbidity Index code was used to calculate the CCI score.

Table 2. Joinpoint analysis of different types of anaphylactic shock by sex in Taiwan, 2005-2012

	Anaphylactic shock incidence (per 1,000,000 person-year)			Trend	P-value
	2005	2012	Years	APC (95%CI)	
Overall anaphylaxis incidence					
Total	12.71 (11.13 to 14.29)	13.23 (11.75 to 14.71)	2005-2012	0.35 (-1.94 to 2.69)	0.73
Male	12.53 (10.35 to 14.72)	13.30 (11.19 to 15.42)	2005-2012	1.59 (-2.54 to 5.89)	0.39
Female	12.89 (10.61 to 15.16)	13.16 (11.08 to 15.24)	2005-2012	-1.13 (-4.45 to 2.31)	0.45
Drug-related anaphylaxis incidence					
Total	10.22 (8.79 to 11.65)	10.98 (9.63 to 12.33)	2005-2012	0.61 (-2.13 to 3.43)	0.61
Male	9.92 (7.96 to 11.88)	10.15 (8.30 to 12.0)	2005-2012	1.70 (-3.22 to 6.87)	0.44
Female	10.51 (8.43 to 12.58)	11.79 (9.83 to 13.76)	2005-2012	-0.27 (-4.12 to 3.72)	0.87
Food-related anaphylaxis incidence					
Total	2.50 (1.82 to 3.17)	2.25 (1.64 to 2.86)	2005-2012	-1.68 (-5.49 to 2.29)	0.34
Male	2.61 (1.64 to 3.59)	3.15 (2.12 to 4.18)	2005-2012	1.14 (-4.25 to 6.83)	0.63
Female	2.38 (1.45 to 3.31)	1.37 (0.70 to 2.04)	2005-2012	-6.02 (-12.59 to 1.05)	0.08

Abbreviation: APC, annual percent change

Table 3. Patient with anaphylaxis hospitalization in-hospital mortality

	Anaphylaxis cases	In-hospital mortality	
	No	No	Death, % (95%CI)
Sex			
Male	1,186	17	1.43 (0.84-2.29)
Female	1,033	7	0.68 (0.27-0.14)
Age			
0-19	179	1	0.56 (0.01-3.07)
20-39	373	3	0.80 (0.17-2.33)
40-59	687	7	1.02 (0.41-2.09)
60-79	745	8	1.07 (0.46-2.10)
>=80	235	5	2.13 (0.69-4.90)
Overall	2,219	24	1.08 (0.69-1.61)
Days after admission			
1-30 days	2,219	18	0.81 (0.48-1.28)
1-60 days	2,219	22	0.99 (0.62-1.50)
1-90 days	2,219	22	0.99 (0.62-1.50)

Table 4. Age-specific anaphylaxis rate

Age specific anaphylaxis rate in 2012 (total anaphylaxis)				
year	person-year	cases	standardized incidence	CI
0-9	1,683,715	14	8.32	3.96-12.67
10-19	2,919,254	17	5.82	3.06-8.59
20-29	3,410,654	23	6.74	3.99-9.5
30-39	4,215,407	30	7.12	4.57-9.66
40-49	3,716,424	24	6.46	3.87-9.04
50-59	3,360,637	51	15.18	11.01-19.34
60-69	1,980,187	48	24.24	17.38-31.1
70-79	1,164,522	67	57.53	43.76-71.31
80+	677,818	32	47.21	30.85-63.57
Age specific anaphylaxis rate in 2012 (food anaphylaxis)				
year	person-year	cases	standardized incidence	CI
0-9	1,683,715	11	6.53	2.67-10.39
10-19	2,919,254	6	2.06	0.41-3.7
20-29	3,410,654	4	1.17	0.02-2.32
30-39	4,215,407	5	1.19	0.15-2.23
40-49	3,716,424	3	0.81	0-1.72
50-59	3,360,637	12	3.57	1.55-5.59
60-69	1,980,187	4	2.02	0.04-4
70-79	1,164,522	5	4.29	0.53-8.06
80+	677,818	2	2.95	0-7.04
Age specific anaphylaxis rate in 2012 (drug anaphylaxis)				
year	person-year	cases	standardized incidence	CI
0-9	1,683,715	3	1.78	0-3.8
10-19	2,919,254	11	3.77	1.54-5.99
20-29	3,410,654	19	5.57	3.07-8.08
30-39	4,215,407	25	5.93	3.61-8.26
40-49	3,716,424	21	5.65	3.23-8.07
50-59	3,360,637	39	11.60	7.96-15.25
60-69	1,980,187	44	22.22	15.65-28.79
70-79	1,164,522	62	53.24	39.99-66.49
80+	677,818	30	44.26	28.42-60.1