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Epidemiology of out-of-hospital cardiac arrests caused by anaphylaxis and factors associated with outcomes: an observational study

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ABSTRACT

Objectives Describe the epidemiologic features of out-of-hospital cardiac arrest (OHCA) caused by anaphylaxis and identify outcome-associated factors.

Design Observational study.

Setting Data from the Japanese Fire and Disaster Management Agency database.

Participants A total of 292 patients from 879 057 OHCA events between 2013 and 2019 with OHCA caused by anaphylaxis and for whom prehospital resuscitation was attempted were included in the analysis.

Outcome measures The incidence of anaphylaxis-induced OHCA, neurologically favourable 1-month survival, defined as cerebral performance category 1 or 2, and 1-month survival.

Results The proportion of OHCAs caused by anaphylaxis was high in non-elderly and male patients from July to September and during business hours. Bystander-witnessed (adjusted OR=4.43; 95% CI 1.84 to 10.7) and emergency medical service-witnessed events (adjusted OR=3.28; 95% CI 1.21 to 8.87) were associated with higher rates of neurologically favourable 1-month survival as well as better 1-month survival. Shockable initial ECG rhythms were recorded in only 19 patients (6.5%), and prehospital defibrillation was attempted in 16 such patients (84.2%). Neither shockable initial rhythms nor prehospital defibrillation was associated with better outcomes. Patients requiring advanced airway management had poor neurological outcomes (adjusted OR=0.17; 95% CI 0.07 to 0.42) and worse 1-month survival (adjusted OR=0.28; 95% CI 0.14 to 0.58).

Conclusions Few cases of OHCA were attributable to anaphylaxis. Witnessed OHCAs, particularly those witnessed by bystanders, were associated with better neurological outcomes. Airway complications requiring advanced airway management were likely associated with poor outcomes.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This study specifically examined out-of-hospital cardiac arrests caused by anaphylaxis using Japan's nationwide database.
- ⇒ Diagnosis of anaphylaxis depends on the clinician's experience based on allergen exposure and characteristic clinical symptoms.
- ⇒ Analyses were limited because of insufficient information gathered before the arrival of the emergency medical service.
- ⇒ The results may not be generalisable to other countries with different emergency medical services.

INTRODUCTION

The World Allergy Organization defines anaphylaxis as 'the most serious clinical manifestation of an acute systemic allergic reaction'.[1] Anaphylaxis begins with skin and mucosal symptoms, followed by life-threatening problems involving the airways (pharyngeal or laryngeal oedema), breathing (bronchospasm with tachypnea) and circulation (hypotension, tachycardia).[1–3] Drug exposure, insect bites and food consumption are common exposure pathways to allergens associated with anaphylaxis. Lethal anaphylaxis develops immediately after contact with the trigger,[3–5] followed by upper airway obstruction attributable to laryngeal oedema, circulatory insufficiency attributable to anaphylactic shock, bronchoconstriction leading to asthma-like respiratory insufficiency and hypoxemia attributable to pulmonary oedema, leading to cardiac arrest.[3]

A review of anaphylaxis revealed an annual incidence of 1.5–7.9/100 000 people, and estimates suggest that 0.05%–2% of the population will experience anaphylaxis in their lifetimes.[4 6 7] In recent years, a combination of genetic and environmental factors has led to greater sensitivity for detecting anaphylactic reactions.[8 9] However, the mortality rate of anaphylaxis has remained low and stable (0.3%).[9]

Anaphylaxis occurs in both in-hospital and out-of-hospital settings, and little information is available on factors related to epidemiology or outcomes. To our knowledge, few studies used a nationwide out-of-hospital cardiac arrest (OHCA) database to explore the incidence of anaphylaxis-induced OHCA. Of these, a representative study from South Korea reported 196 158 OHCA cases and attributed 233 cases (0.12%) to anaphylaxis.[10]

Correctable factors associated with outcomes should be identified to improve the clinical outcomes of patients with anaphylaxis-associated OHCA. This study examined the epidemiologic features of OHCA caused by anaphylaxis and the factors associated with outcomes using an extensive nationwide OHCA database in Japan.

METHODS

Population and setting

Japan features 47 prefectures, and the country is divided into eight regions from north to south. In 2015, Japan's population totalled 127 million, and 26.6% were ≥65 years.[11] 6184 ambulances were operating in 750 fire departments throughout the country,[12] and no termination of resuscitation rules exist for prehospital settings. Unless a patient with OHCA is obviously dead (such as decapitated) or has postmortem changes, emergency medical service (EMS) personnel continue resuscitation until arrival at the hospital. Paramedics are allowed to use advanced airway adjuncts and commence peripheral venous infusion of Ringer's lactate. Some paramedics are authorised to insert tracheal tubes and administer intravenous epinephrine, but they cannot administer other drugs. To care for patients with OHCA, EMS personnel used a protocol created by their regional medical control council based on Japan Resuscitation Council Guidelines.[13]

Data selection

Consent was obtained from the Japanese Fire and Disaster Management Agency (FDMA) to analyse nationwide OHCA data prospectively collected from 1 January 2013 to 31 December 2019. This population-based observational study was approved by the review board of the Ishikawa Medical Control Council.

The All-Japan Utstein Registry of FDMA contains Utstein-style data,[14] including patient sex, age, witness status, initial ECG rhythm, prehospital defibrillation, prehospital physician involvement, epinephrine administration, advanced airway management, recorded time of witness, bystander cardiopulmonary resuscitation (CPR) initiation, emergency call, time to EMS vehicle arrived at the scene and hospital, EMS contact with the patient, EMS CPR initiation and survival at 1 month with cerebral performance category (CPC).[15] There was no missing information in the final data used in this study.

According to the anaphylaxis guidelines of the Japanese Society of Allergology,[16] clinical diagnostic criteria for anaphylaxis include changes in vital signs, the skin or mucous membranes and symptoms of the respiratory, circulatory and gastrointestinal tracts. However, the onset of anaphylaxis or OHCA is rarely witnessed by healthcare personnel. The untrained public cannot be expected to correctly assess symptoms or measure vital signs. Therefore, clinicians collaborate with EMS personnel to comprehensively assess whether OHCA was caused by anaphylaxis based on allergen exposure and characteristic clinical symptoms. Biomarker measurements, such as tryptase,[17] may be used in hospitals delivering higher quality care but have not been included in this study. The clinicians provided information on 1-month survival and CPC to the fire department at the time of discharge, from the last hospital to care facilities or home.

Patient involvement

Patients were not involved in study design, data interpretation or report writing. The requirement for informed consent for patients was waived because the data were obtained from an existing anonymous database.

Outcome measures

First, we investigated the incidence of anaphylaxis-induced OHCA based on the population. Then, we investigated neurologically favourable 1-month survival, defined as a CPC score of 1 (good recovery) or 2 (moderate disability)[15] and 1-month survival.

Statistical analysis

We performed an epidemiological analysis by comparing the incidence by region, month (season), time of day (business time vs other time), day (weekend vs weekday), age (elderly (≥70 years) vs non-elderly) and sex. Considering monthly averages of ambient temperature and the rainy weather in June (commonly termed 'plum rain' in Japan), we defined the summer season as July to September. Differences across groups for nominal variables were assessed using the χ^2 test. We reported crude and adjusted ORs and 95% CIs. For each analysis, the null hypothesis was evaluated at a two-sided significance level of $p<0.05$. Multivariable logistic regression analysis was performed to identify major factors associated with neurologically favourable 1-month survival and 1-month survival. Multivariable logistic regression analysis included the following factors known to be associated with survival[14]: sex, age, witnessed status (unwitnessed, bystander-witnessed and EMS-witnessed), initial rhythm (shockable or not), prehospital defibrillation, prehospital epinephrine administration, advanced airway management (oesophageal obstructive or supraphayngeal airway and tracheal intubation), advanced life support by physicians and the intervals between contact to EMS arrival (EMS response time) and between EMS arrival and hospital arrival (EMS transportation time).

Information about dispatch locations and epinephrine auto-injection has been available for all emergency transport since 2015. This information was obtained in combination with the FDMA database covering 2015–2019. Therefore, we performed an additional analysis. All statistical analyses were performed using JMP Pro V.16 software (SAS Institute, Cary, North Carolina).

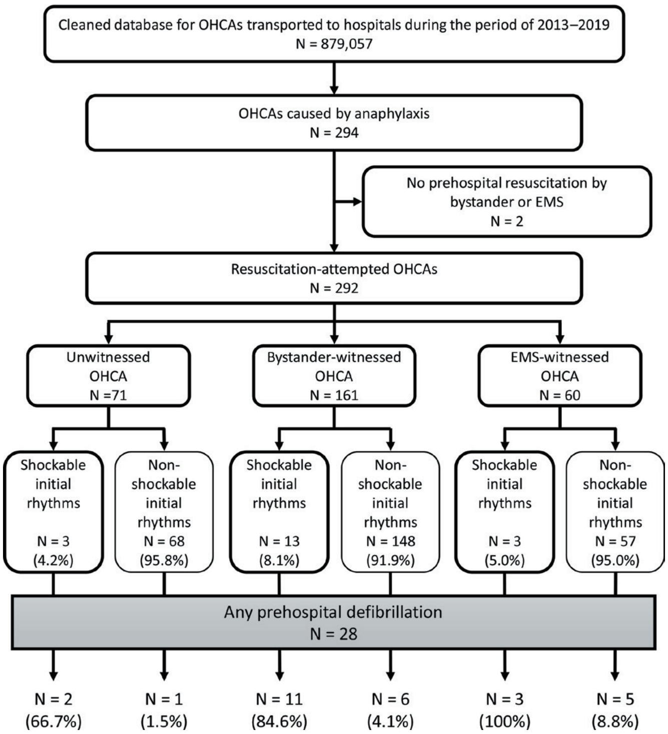

Figure 1 Data selection. EMS, emergency medical service; OHCA, out-of-hospital cardiac arrest.

RESULTS

Overview of case selection

From the cleaned nationwide database of 8 79 057 patients with OHCA recorded during the study period, we extracted 294 patients (0.03%) with anaphylaxis-associated OHCA. Two patients with no prehospital resuscitation attempts were excluded, and the remaining 292 patients were analysed. Of the 292 patients, the onset of OHCA was not witnessed in 71 (24.3%); was witnessed by bystanders, 161 (55.1%) and was witnessed by EMS personnel, 60 (20.6%). Shockable initial rhythms were recorded in 4.2% (3/71) of unwitnessed cases, 8.1% (13/161) of bystander-witnessed cases and 5.0% (3/60) of EMS-witnessed cases. Conversion from initially non-shockable rhythms to shockable rhythms was recorded in 1.5% (1/68) of unwitnessed cases, 4.1% (6/148) of bystander-witnessed OHCA and 8.8% (5/57) of EMS-witnessed OHCA. Shockable initial rhythms were recorded in 6.5 (19/292) and 7.2% (16/221) of all OHCAs and witnessed OHCAs, respectively, and conversions to shockable rhythms were recorded in 4.4 (12/273) and 5.4% (11/205) of these events, respectively. Prehospital defibrillation was performed in 66.7 (2/3), 84.6 (11/13) and 100% (3/3) of unwitnessed, bystander-witnessed and EMS-witnessed OHCAs, respectively. After conversion to shockable rhythms, prehospital defibrillation was performed in 12 of 273 patients with non-shockable initial rhythms (figure 1).

Epidemiologic analyses of OHCA cases caused by anaphylaxis

The annual incidence of OHCA was 115.4 per 100 000 in the Japanese population, and the proportion caused by anaphylaxis was 0.03%. The epidemiology of OHCA caused by anaphylaxis was analysed per 1000 cases (table 1). The proportion was 1.64 in the Shikoku region of Japan, which was significantly higher than the proportions of 0.20–0.65 in the other seven regions. The nationwide proportion was higher in July–September (0.78 vs 0.22 during other months), during business hours (0.43 vs 0.26 during other times) and among non-elderly patients (0.57 vs 0.24 in elderly patients) and male patients (0.39 vs 0.26 in female patients).

Table 1 Epidemiologic analysis of OHCA cases caused by anaphylaxis

Variable	Incidence rate (number/1000 OHCA cases)	Statistics (Yates' χ^2)
Region in Japan (north to south)		<0.01
Hokkaido	0.23 (9/38,832)	
Tohoku	0.32 (24/75,668)	
Kanto	0.20 (58/290,619)	
Chubu	0.36 (57/158,185)	
Kinki	0.34 (51/148,042)	
Chugoku	0.43 (21/49,032)	
Shikoku	1.64 (46/28,030)	
Kyushu	0.65 (59/90,649)	
Month (season)		<0.01
July–September (Summer)	0.78 (136/174,336)	
Other	0.22 (158/704,721)	
Time of day (emergency call)		<0.01
Business hours (9:00 –16:59)	0.43 (169/397,001)	
Other	0.26 (125/482,056)	
Weekday		0.80
Weekend	0.33 (84/256,620)	
Other	0.34 (210/622,437)	
Age		<0.01
Elderly (≥70 y)	0.24 (152/631,947)	
Other	0.57 (142/247,110)	
Sex		<0.01
Male	0.39 (197/502,059)	
Female	0.26 (97/376,998)	

OHCA, out-of-hospital cardiac arrest.

When detailed OHCA locations were analysed for 167 cases from 2015 to 2019, nearly half (74/167 (44.3%)) occurred at home. Medical institutions (42/167 (25.1%)) including medical offices and places for outdoor activities (39/167 (23.4%)) were other major locations of anaphylactic OHCA. Only one case was treated with epinephrine auto-injection before cardiac arrest (online supplemental table 1).

Table 2 Factors associated with neurologically favourable 1-month survival

Characteristics of OHCA	Neurological outcomes at 1M		Crude OR (95% CI) for favourable neurological outcomes or P value	Adjusted OR (95% CI) for favourable neurological outcomes or P value
	Favourable (N=78)	Unfavourable (N=214)		
Male patients, % (N)	56.4 (44)	71.5 (153)	0.52 (0.30 to 0.88)	0.76 (0.42 to 1.39)
Elderly patients, % (N)	55.1 (43)	50.9 (109)	1.18 (0.70 to 1.99)	1.35 (0.75 to 2.45)
Witness status, % (N)				
Unwitnessed	10.3 (8)	28.5 (61)	Reference	Reference
Bystander-witnessed	66.7 (52)	51.9 (111)	3.57 (1.59 to 8.01)	4.43 (1.84 to 10.7)
EMS-witnessed	23.1 (18)	19.6 (42)	3.27 (1.30 to 8.21)	3.28 (1.21 to 8.87)
Shockable initial rhythm, % (N)	6.4 (5)	6.5 (14)	0.98 (0.34 to 2.81)	1.53 (0.27 to 8.76)
Prehospital defibrillation, % (N)	7.7 (6)	10.3 (22)	0.73 (0.28 to 1.87)	0.57 (0.12 to 2.71)
Prehospital epinephrine administration, % (N)	11.5 (9)	27.6 (59)	0.34 (0.16 to 0.73)	0.51 (0.22 to 1.20)
Advanced airway management, % (N)	7.7 (6)	35.5 (76)	0.15 (0.06 to 0.36)	0.17 (0.07 to 0.42)
Advanced life support by physician, % (N)	14.1 (11)	28.5 (61)	0.41 (0.20 to 0.83)	0.52 (0.22 to 1.23)
Physician in ambulance, % (N)	6.4 (5)	13.1 (28)	0.45 (0.17 to 1.22)	0.44 (0.13 to 1.42)
Time intervals, min, median (IQR)				
EMS response time	8 (7–10)	9 (7–14)	p<0.01	0.94 (0.88 to 1.01) /1 min
EMS transportation time	25 (16–33)	26 (18–34)	p=0.06	1.03 (0.84 to 1.21) /10 min

EMS, emergency medical service; 1M, 1 month; OHCA, out-of-hospital cardiac arrest.

Factors associated with neurologically favourable 1-month survival

The neurologically favourable 1-month survival rate was 26.7% (78/292). In univariate analysis, bystander-witnessed and EMS-witnessed OHCA cases and shorter EMS response times were associated with better neurological outcomes. Poor neurological outcomes were associated with male sex, prehospital epinephrine administration, advanced airway management and advanced life support by physicians. After adjustment for confounding factors, bystander-witnessed (adjusted OR=4.33; 95% CI 1.84 to 10.7) and EMS-witnessed OHCA (adjusted OR=3.28; 95% CI 1.21 to 8.87) were found to be predominant factors associated with better neurological outcome, but the association between shorter EMS response times and favourable neurological outcome was not significant. In the multivariate-adjusted models, advanced airway management was the sole factor associated with poor neurological outcomes (adjusted OR=0.17; 95% CI 0.07 to 0.42). Neither shockable initial rhythms nor prehospital defibrillation was associated with neurological outcomes (table 2). OHCA caused by anaphylaxis requiring advanced life support by physicians likely occurred in medical institutions. Despite the higher rate of epinephrine administration (33.3%) and defibrillation (18.1%) in these cases, they were not associated with better outcomes.

Factors associated with 1-month survival

The 1-month survival rate was 35.3% (103/292). As shown in online supplemental table 2, both univariate and multivariable regression analyses revealed that bystander-witnessed and EMS-witnessed OHCA and shorter EMS response times were associated with better 1-month survival. In contrast, male sex, prehospital epinephrine administration and advanced airway management were associated with worse 1-month survival. Advanced life support by physicians was associated with lower survival rates in the univariate analysis, but the association was not significant after adjustment for confounding factors in the multivariate analysis. Notably, neither shockable initial rhythms nor prehospital defibrillation was associated with 1-month survival.

Timing of epinephrine administration

The median interval (IQR) between EMS contact and epinephrine administration was 15 (12–20) min. No patients received epinephrine within 6 min of EMS contact (online supplemental figure 1).

DISCUSSION

This study identified the epidemiological features of OHCA caused by anaphylaxis and outcome-associated factors using a nationwide database from Japan. Witnessed OHCAs were associated with better neurologically favourable outcomes than unwitnessed OHCAs. Airway complications requiring advanced airway management were associated with poor outcomes. Although the number of target cases was small, this study is meaningful because the analysis is based on extensive statistical data representing Japan.

Our findings showed that, of 1000 OHCA cases, approximately 0.3 were caused by anaphylaxis. This finding was much lower than previously reported in South Korea (1.2 of 1000 OHCA cases).[10] In this study, the proportion of all OHCA cases in the total population was 115.4 per 100 000 people per year, and OHCA caused by anaphylaxis was 0.039; the South Korean report was 49.0 and 0.058, respectively. In Japan, instances of OHCA caused by anaphylaxis were also low, about two-thirds of that reported in South Korea. Potential differences in incidence rates between countries and regions cannot be ruled out as a factor for low incidence in Japan. Nevertheless, the diagnosis of anaphylaxis relies on the clinician's assessment based on allergen exposure and characteristic clinical symptoms. Non-compliance with biomarker measurements may also reduce diagnostic ability. In addition, some patients with Kounis syndrome[18] may have been diagnosed and treated as pure cardiogenic events.

As reported in South Korea, our results indicate that the incidence of anaphylaxis-induced OHCA increased during the day and summer.[10] In addition, non-elderly and male patients had increased rates of anaphylaxis-induced OHCA. In Japan, anaphylaxis is reported to kill 50–80 people each year, and drugs and bee stings cause most cases.[19] The high number of insect bites and stings (especially bee stings) in the summer[20] might be one of the factors contributing to the increased rate of anaphylaxis-induced OHCA in this season. Physical and environmental factors, such as exercise and sunlight, were associated with the risk of anaphylaxis,[21] which may also explain the increased rate of anaphylaxis during summer.

OHCA caused by anaphylaxis has been associated with better outcomes than other types of non-cardiac OHCA.[22] In this study, witnessed OHCAs, particularly those witnessed by bystanders, were associated with better outcomes. Bystanders can witness the progression from the initial symptoms of anaphylaxis to worsening, and they were in a position to notice anomalies earlier than EMS and take necessary actions. Additionally, based on information from bystanders, EMS personnel potentially suspected anaphylaxis earlier after the onset of OHCA, which may explain why witnessed OHCA was associated with better outcomes.

The causes of death from anaphylaxis include upper airway obstruction, circulatory insufficiency, bronchoconstriction and hypoxemia.[3] Respiratory symptoms are more common than cardiovascular symptoms in anaphylaxis, and most cases of lethal anaphylaxis are caused by airway obstruction and severe asthma.[4 23] In this study, advanced airway management for airway obstruction was the most detrimental factor associated with outcomes. In Japan, advanced airway management is generally performed by authorised paramedics when normal bag-valve-mask ventilation is insufficient. It was reported that the autopsy findings of anaphylactic shock death were predominantly pulmonary congestion/pulmonary oedema, upper airway oedema and bronchial mucus plug/severe swelling.[24] Poor outcomes are, thus, likely to be associated with airway obstruction and bronchoconstriction requiring advanced airway management rather than with advanced airway management itself.

In general cases of OHCA, epinephrine administration is not associated with better neurological outcomes,[25] but administration within 10 min has been associated with better neurological outcomes.[26] In circulatory instability and cardiac arrest attributable to anaphylaxis during anaesthesia, rapid intravenous administration of epinephrine had been reported to be effective and associated with better neurological outcomes.[27] However, epinephrine administration was not associated with better outcomes in this study, which may be explained by the prolonged interval between onset and drug administration. In OHCA, immediate administration of epinephrine is difficult because of the time required for EMS personnel to arrive and the need to follow the resuscitation guidelines.[28] Although the effectiveness of intramuscular injections in anaphylaxis is known, the efficacy of intravenous epinephrine for anaphylactic symptoms is undetermined in the case of cardiac arrest. It has also been reported that intravenous administration of epinephrine has a significantly higher risk of adverse cardiovascular events and overdose than intramuscular injections.[29]

Shockable initial rhythms represent a known major factor associated with better outcomes for OHCA, particularly cardiogenic OHCA.[15] In this study, the rates of shockable initial rhythms and conversion to shockable rhythms were lower than reported previously for general OHCA.[30 31] Meanwhile, neither shockable initial rhythms nor prehospital defibrillation was associated with better outcomes for OHCA caused by anaphylaxis. These results suggest that respiratory insufficiency is the primary pathology of OHCA caused by anaphylaxis, whereas cardiogenic elements are minor factors. In addition, defibrillation may be less effective because shockable rhythm is of non-cardiac origin.[32]

OHCA caused by anaphylaxis requiring advanced life support by physicians is likely to have occurred in a medical institution (25.1% in 167 cases with detailed location information). Despite the higher rate of epinephrine administration and defibrillation in these cases, they were not associated with better outcomes. Although OHCA caused by anaphylaxis is a more serious and fatal situation, medical institutions may not be adequately responding to anaphylaxis. These findings emphasise the importance of prevention, early detection or notification and appropriate treatment of anaphylaxis. Anaphylaxis must be widely recognised by the general public and healthcare professionals and the risk of anaphylaxis should be recognised according to the patient's medical history. Persons at high risk of anaphylaxis should carry an epinephrine auto-injection kit[33] and avoid outdoor activities alone. Unfortunately, supplemental analysis in this study revealed that an auto-injection kit was applied only in one case in 5 years. In one report in Japan, only 449 (0.87%) were used in 7 years, despite the prescription of 51 447 auto-injection kits mainly for children with food allergies.[34] Caregivers inject more than half. Self-injection may be difficult in some situations.[34] In Japan, being used by anyone other than the prescribed person is legally prohibited; hence, it will not be used in patients who suffer anaphylaxis for the first time. It is necessary to increase the number of prescriptions and usage to prevent OHCA caused by anaphylaxis by disseminating information about auto-injection kits. It is also desirable that unassigned auto-injection kits be used for non-specific patients in the future.

Additional research is needed to improve the diagnosis of anaphylaxis through tests, such as biomarker measurements. We also hope that similar studies in regions other than East Asia would allow for accurate diagnosis.

LIMITATIONS

Although this study covered a 6-year period in the community population, the number of patients with OHCA caused by anaphylaxis was small. Information on in-hospital management and treatment and causes of anaphylaxis was not collected. Although EMS personnel were encouraged to interview the bystanders and identify bystander-related time factors and resuscitation efforts, the records before EMS contact with the patient may be inaccurate. Except in cases of obvious death or post-mortem change, resuscitation is mandated for OHCA, but careful decisions must be made to reduce its impact on outcomes.

Although all OHCA cases are registered in the FDMA database, the present results may not be generalisable to other countries with different EMS systems. Data in other countries will, thus, need to be analysed independently.

CONCLUSIONS

The proportion of cases of OHCA caused by anaphylaxis was extremely low in Japan. Witnessed OHCAs, particularly those witnessed by bystanders, were associated with better neurologically favourable outcomes. Compared with common OHCA, there were few examples of shockable initial rhythms and conversion to shockable rhythms. Shockable rhythms, prehospital defibrillation and epinephrine administration were not associated with better outcomes. Airway complications requiring advanced airway management appeared to be associated with poor outcomes.

The person at high risk of anaphylaxis should carry an epinephrine auto-injection kit and avoid outdoor activities alone; the general public and healthcare professionals must widely recognise first aid for anaphylaxis.

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Patient consent for publication Not applicable.

Ethics approval This study involved human participants and was approved by the institutional review board of Ishikawa Medical Control Council.

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Supplemental Table 1 Additional epidemiologic analysis of OHCA cases during the period of 2015 to 2019

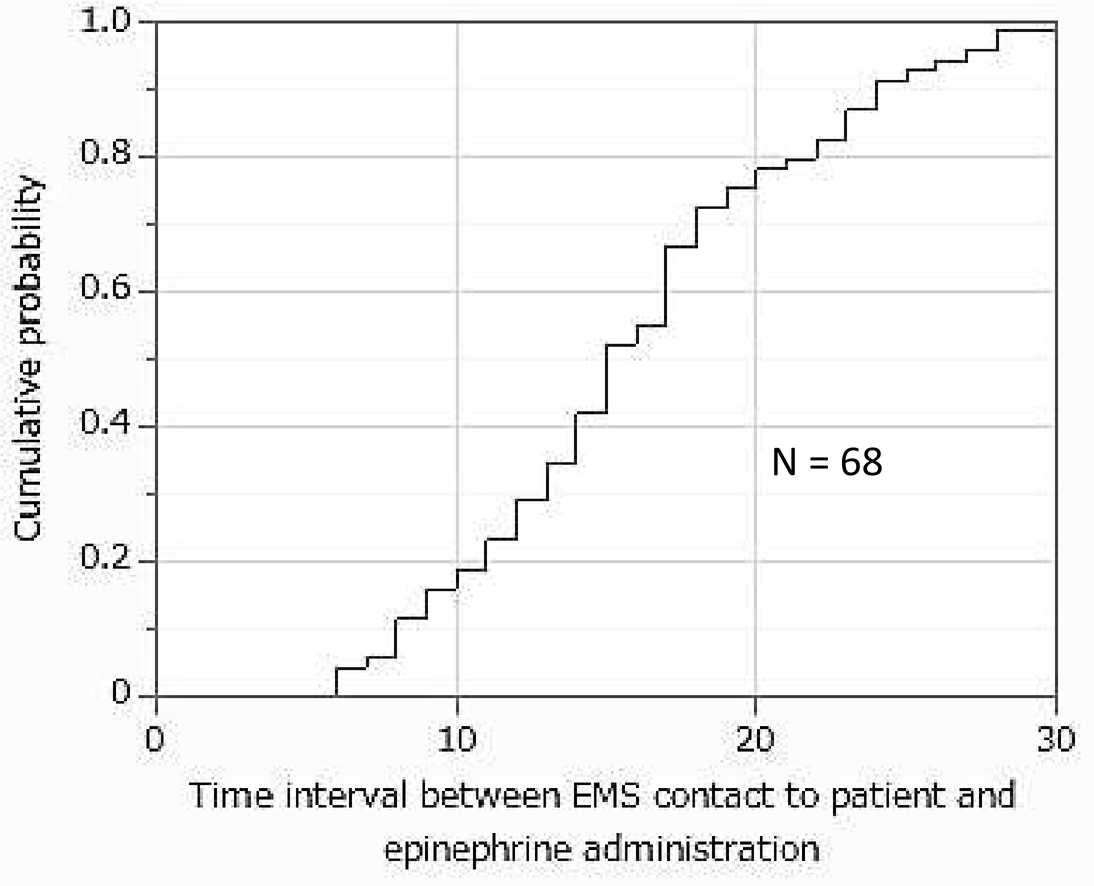
Location/incidence	**% (N) in OHCA caused by anaphylaxis (Total number = 167)**
Location	
Medical office	18.6 (31)
Hospital	1.2 (2)
Care facilities	5.4 (9)
Mountain, forest, field, park, and garden	11.4 (19)
Sidewalk, river, pond, and others for outdoor activities	12.0 (20)
Home	44.3 (74)
Public	4.8 (8)
Workplace	2.4 (4)
Incidence	
Epinephrine auto-injection	0.6 (1)

OHCA, out-of-hospital cardiac arrest.

Supplemental Table 2 Factors associated with 1-month survival

Characteristics of OHCA	**1M survival**		**Crude OR (95% CI) for 1M survival or P value**	**Adjusted OR (95% CI) for 1M survival**
	Survivors (N = 103)	**Non-survivors (N = 189)**		
Male patients, % (N)	57.3 (59)	73.0 (138)	0.50 (0.30 to 0.82)	0.48 (0.27 to 0.88)
Elderly patients, % (N)	46.6 (48)	55.0 (104)	0.71 (0.44 to 1.15)	0.75 (0.42 to 1.34)
Witness status, % (N)				
Unwitnessed	9.7 (10)	31.2 (59)	Reference	Reference
Bystander-witnessed	67.0 (69)	49.7 (94)	4.33 (2.07 to 9.07)	4.29 (1.92 to 9.62)
EMS-witnessed	23.3 (24)	19.1 (36)	3.93 (1.69 to 9.17)	3.16 (1.25 to 7.94)
Shockable initial rhythm, % (N)	9.7 (10)	4.8 (9)	2.15 (0.84 to 5.48)	1.80 (0.42 to 7.64)
Prehospital defibrillation, % (N)	13.6 (14)	7.4 (14)	1.97 (0.90 to 4.30)	2.10 (0.61 to 6.56)
Prehospital epinephrine administration, % (N)	12.6 (13)	29.1 (55)	0.35 (0.18 to 0.68)	0.45 (0.21 to 0.97)
Advanced airway management, % (N)	11.7 (12)	37.0 (70)	0.22 (0.11 to 0.44)	0.28 (0.14 to 0.58)
Advanced life support by physician, % (N)	17.5 (18)	28.6 (54)	0.53 (0.29 to 0.96)	0.47 (0.21 to 1.05)
Physician in ambulance, % (N)	10.7 (11)	11.6 (22)	0.91 (0.42 to 1.95)	1.01 (0.36 to 2.84)
Time intervals, min, median (IQR)				
EMS response time	8 (7–11)	10 (8–14)	P <0.01	0.93 (0.87 to 0.99) /1 min
EMS transportation time	24 (17–33)	26 (18–34)	P = 0.09	1.06 (0.89 to 1.24) /10 min

1M, 1-month; CI, confidence interval; EMS, emergency medical service; IQR, interquartile range; OHCA, out-of-hospital cardiac arrest; OR, odds ratio.


1.0
0.8
0.6
0.4
0.2
0
Cumulative probability
0
10
20
30
Time interval between EMS contact to patient and epinephrine administration
N = 68