Original Article

Outcomes after out-of-hospital cardiac arrests by anaphylaxis: A nationwide population-based observational study

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Aim: The objective of this study was to focus on outcomes of anaphylaxis-associated out-of hospital cardiac arrest (OHCA) in non-cardiac cases.

Methods: All residents with OHCA due to non-cardiac cause in Japan from 2013 to 2015 were included for analysis. Propensity score matching and logistic regression analyses were used to assess outcome-related factors in anaphylaxis cases and non-anaphylaxis cases. The comparison group was comprised of non-anaphylaxis cases, which consisted of other cases of non-cardiac etiology.

Results: A total of 375,874 OHCA cases were included, of which 148,598 were due to non-cardiac cause. In these non-cardiac OHCA cases, 147 were due to anaphylaxis, with an annual incidence of 0.04 per 100,000. In the patients' characteristics, witnessed ratio, shockable rhythm, defibrillation by emergency medical services (EMS), and treatment with adrenaline by EMS were significantly greater in the anaphylaxis cases compared with the non-anaphylaxis cases. In anaphylaxis cases, the crude 1-month survival rate (32.7% versus 5.3%) and crude favorable neurological outcomes rate (24.5% versus 2.2%) were higher compared with non-anaphylaxis cases ($P < 0.001$). The differences in outcomes between the two types of cases were also marked after we adjusted these variables by propensity score matching. By logistic regression analyses, administration of a drug by EMS was negatively associated with good neurological outcomes (odds ratio, 0.27; 95% confidence interval, 0.09–0.87), but bystander cardiopulmonary resuscitation was positively associated with good neurological outcomes (odds ratio, 2.33; 95% confidence interval, 0.99–5.52).

Conclusion: Neurological outcome was markedly more favorable in cases with anaphylaxis than non-anaphylaxis cases. Further studies are needed to explain this result.

Key words: Anaphylaxis, logistic regression analysis, non-cardiac etiology, out-of-hospital cardiac arrest, propensity score matching

INTRODUCTION

THE CAUSES OF out-of hospital cardiac arrest (OHCA) have been broadly categorized into cardiac and non-cardiac causes.[1–3] According to the current concept of OHCA, major attention has focused on cardiac causes, for which resuscitation of patients is considered possible and a favorable prognosis can be expected;[4] OHCAs of non-cardiac origin have not been paid as much attention. The lower survival outcome has been hypothesized to be due to the lower percentage of ventricular fibrillation in these patients.[5,6] However, this hypothesis has been confirmed in only some patients with relatively common causes.[7,8] As anaphylaxis is a potentially life-threatening condition, current guidelines for cardiopulmonary resuscitation and emergency care have a section specifically for anaphylaxis. However, evidence for anaphylaxis-associated cardiac arrest has been mainly based on case reports, studies of non-arrest cases, physiological theories, and animal experiments.[9,10] To our knowledge, reports of anaphylaxis-associated OHCA has been very limited. In this article, we focus on OHCAs caused by anaphylaxis. The specific features of these patients might provide some clues that can be used to improve outcomes of OHCA with non-cardiac etiology.

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METHODS

Study design and participants

THE ALL -Japan Utstein Registry of the Fire and Disaster Management Agency is a prospective, nationwide, population-based registry system of OHCAs based on the Utstein style.[1] Patients who had OHCA and for whom resuscitation was attempted by emergency medical services (EMS) personnel, with subsequent transport to medical institutions, from 2013 to 2015 were eligible for our analysis. Patients with non-cardiac origin OHCA, including children, were eligible for our analysis. The population of Japan was 127,094,745 according to the results of the national census taken on 1 October, 2015.[11] The ethics committee at Kindai University Faculty of Medicine (Higashiosaka, Japan) approved the study (30-057).

Data collection

Data were collected prospectively with an Utstein-style format including age, sex, etiology of arrest, initial cardiac rhythm, and time factors for resuscitation of the patient. The data also included whether the arrest was witnessed by a bystander, whether cardiopulmonary resuscitation (CPR) was started by a bystander, whether the patient was defibrillated by EMS, whether the airway device was used for the patient, and whether adrenaline was administered to the patient by EMS personnel. The etiology of arrest was determined clinically by the physicians in charge, in collaboration with the EMS personnel. Outcome measures were neurological status, survival 1 month after the event, and return of spontaneous circulation prior to hospital arrival. The number of deaths by anaphylaxis per year was collected from Japan's national statistics.[12]

Study end-points

The primary end-point was favorable neurological outcome 1 month after cardiac arrest, which was defined a priori as Glasgow–Pittsburgh cerebral performance category 1 (good performance) or 2 (moderate disability). The other categories—3 (severe cerebral disability), 4 (vegetative state), and 5 (death)—were regarded as unfavorable neurological outcome.[1] The secondary outcome measure was 1-month survival.

Analyses

In this study, outcomes and related factors were investigated in anaphylaxis cases. The comparison group was defined as non-anaphylaxis cases, which consisted of other cases of non-cardiac etiology. In this study, outcomes and related factors were compared between different groups using Fisher's exact test for categorical variables and the Wilcoxon rank sum test for numerical variables. In order to adjust the differences of these variables between the two groups, we undertook case matching based on propensity score. For the propensity score matching, we included the following variables: sex, age, whether the arrest was witnessed by a bystander, whether initial rhythm was shockable, whether dispatcher instruction was received, whether CPR was started by a bystander, whether the patient was defibrillated by EMS, whether drug was administered by EMS, whether an airway device was used for the patient, and EMS response time, defined as the time from receipt of the call to first EMS contact with the patient. The matching was carried out with the use of a 1:1 matching protocol without replacement with a caliper width equal to 0.20 of the square root of the mean of unbiased variance of the logit of propensity scores of the two groups.[13] C-statistics (concordance index) was used to confirm the fit of this model.

To assess the factors associated with 1-month survival and favorable neurological outcome, we first used the univariate logistic regression model for potential predictor variables. The potential candidate predictor variables were sex, age, witnessed by bystander, whether initial rhythm was shockable, whether the patient was defibrillated by EMS, whether the patient was administered drug by EMS, whether an airway device was used, and EMS response time, defined as the time from the ambulance call to first EMS contact with the patient. We then undertook a stepwise regression analysis to determine the explanatory variables for multiple logistic regression analysis. In the stepwise analysis, we selected the variables by maximum *P*-value 0.25 and minimum *P*-value 0.1 in the forward direction method. In the logistic regression models, odds ratios (ORs) and their 95% confidence intervals (95% CIs) were calculated.

All statistical analyses were carried out using JMP version 14 (SAS Institute, Tokyo, Japan).

RESULTS

Features of anaphylaxis cases in non-cardiac causes

OF THE 373,870 OHCA cases considered for resuscitation and for which etiology was determined during the study period, 225,272 cases were of cardiac origin and 148,598 (39.7%) cases were of non-cardiac origin (Table S1).

Out-of hospital cardiac arrest cases of non-cardiac origin included 147 anaphylaxis cases. The number of annual cases was 54, 47, and 46 in 2013, 2014, and 2015, respectively. The incidence rates per 100,000 persons were 0.042 (2013), 0.037 (2014), and 0.036 (2015). These data were comparable with death registrations due to anaphylaxis in Japan, which were 61, 58, and 56 in 2013, 2014, and 2015, respectively (Table S2).[12] The classification of non-anaphylaxis cases is shown in Table S3.

In the characteristics of the patients, witnessed ratio, shockable rhythm, defibrillation by EMS, and administration of adrenaline by EMS were significantly greater in the anaphylaxis cases compared with the non-anaphylaxis cases (Table 1). Female gender, receipt of dispatcher instructions, and airway device usage were less frequent in anaphylaxis cases (Table 1). The time factors were not significantly different between the two groups except CPR start time by EMS and time to hospital arrival (Table 2). Other characteristics of anaphylaxis cases are shown in Table S4.

In propensity score matching, 145 patients were matched in each case. We confirmed that there were no significant differences in the characteristics of the patients between the two cases (Table 1, propensity score-matched patients). C-statistics (concordance index), which indicates the fit of the estimation model, was 0.74, showing a good fit of this model (Figure S1).

Outcomes of anaphylaxis cases

In terms of outcomes, crude 1-month survival rates and favorable neurological outcomes were significantly better in cases with anaphylaxis (32.7% and 24.5%, respectively) than in non-anaphylaxis cases (Table 3). The crude outcomes from bystander-witnessed cases were 37.4% (1-month survival) and 27.1% (favorable neurological outcome).

After the matching of cases of the two groups based on propensity score, the significant differences in outcomes

Table 1. Characteristics of Japanese patients with out-of-hospital cardiac arrest of non-cardiac origin: anaphylaxis versus non-anaphylaxis cases

	Anaphylaxis, *n* = 147	Non-anaphylaxis, *n* = 148,451	Significance, anaphylaxis versus non-anaphylaxis
Female sex, *n* (%)	47 (32.0)	63,229 (42.6)†	$P < 0.010$
Age, median (IQR)	73 (20)	76 (24)	$P = 0.054$
Arrest witnessed, *n* (%)	107 (72.8)	62,940 (42.4)	$P < 0.001$
Initial rhythm shockable, *n* (%)‡	9 (7.3)	3871 (2.6)	$P < 0.010$
Receipt of dispatcher instructions, *n* (%)	37 (25.2)	75,792 (51.1)	$P < 0.001$
Bystander CPR, *n* (%)	67 (45.6)	66,980 (45.1)	$P = 0.934$
Defibrillation by EMS, *n* (%)	19 (12.3)	5986 (4.0)	$P < 0.001$
Drug administration by EMS, *n* (%)	33 (22.5)	22,597 (15.2)	$P < 0.05$
Airway device usage by EMS, *n* (%)	42 (28.6)	53,435 (36.0)	$P = 0.071$
EMS response time, min; median (IQR)§	9.0 (5.0)	9.0 (4.0)	$P = 0.071$
Propensity score-matched patients	*n* = 145	*n* = 145	
Female sex, *n* (%)	46 (31.7)	54 (37.2)	$P = 0.387$
Age, median (IQR)	72 (20.0)	71 (27.5)	$P = 0.242$
Arrest witnessed, *n* (%)	106 (73.1)	115 (79.3)	$P = 0.270$
Initial rhythm shockable, *n* (%)	9 (6.2)	15 (1.3)	$P = 0.287$
Receipt of dispatcher instruction, *n* (%)	37 (25.5)	49 (33.8)	$P = 0.157$
Bystander CPR, *n* (%)	67 (46.2)	74 (51.0)	$P = 0.481$
Defibrillation by EMS, *n* (%)	19 (13.1)	29 (20.0)	$P = 0.155$
Drug administration by EMS, *n* (%)	33 (22.8)	41 (28.3)	$P = 0.346$
Airway device usage by EMS, *n* (%)	42 (29.0)	55 (37.9)	$P = 0.135$
EMS response time, min; median (IQR)§	9.0 (5.0)	9.0 (7.5)	$P = 0.667$

†One datum missing.
‡Ambulance crew did not define rhythm in 23 (15.6%) and 8186 (5.5%) anaphylaxis and non-anaphylaxis cases, respectively.
§Time from call to first emergency medical services (EMS) contact with patient.
CPR, cardiopulmonary resuscitation; IQR, interquartile range.

Table 2. Emergency medical services (EMS) time factors for out-of-hospital cardiac arrest (OHCA) of non-cardiac cause: anaphylaxis versus non-anaphylaxis cases

	Anaphylaxis	Non-anaphylaxis	Significance, anaphylaxis versus non-anaphylaxis
Call to arrival at the scene			
n	145	147,945	
Median (IQR)	8 (4)	7 (3)	$P = 0.580$
Call to start of CPR by EMS			
n	135	143,026	
Median (IQR)	10 (8)	12 (9)	$P < 0.01$
Call to defibrillation by EMS			
n	12	6000	
Median (IQR)	9 (5)	9 (4)	$P = 0.967$
Call to drug administration by EMS			
n	33	22,600	
Median (IQR)	28 (8)	24 (12)	$P = 0.050$
Call to insertion of airway devices			
n	25	37,680	
Median (IQR)	24 (19)	18 (9)	$P = 0.155$
Call to hospital arrival			
n	33	147,711	
Median (IQR)	35 (18)	32 (14)	$P < 0.01$

CPR, cardiopulmonary resuscitation; IQR, interquartile range.

between two cases were also marked like crude outcomes ($P < 0.001$) (Table 3, propensity score-matched patients).

Factors associated with outcomes

The results of univariate logistic regression show the existence of a witness and the shockable initial electrocardiogram rhythm might be associated with greater 1-month survival in anaphylaxis cases (Table 4). In addition to the witness status and the initial electrocardiogram rhythm, female sex, younger age, and existence of bystander CPR were favorable for 1-month survival in non-anaphylaxis cases. Among the treatments, EMS defibrillation was significant in non-anaphylaxis cases. In contrast, the use of drug and an airway device were not associated with improved 1-month survival. An increase in EMS response time, which was defined as the time interval between the emergency call and contact with patients, was unfavorable for 1-month survival.

For favorable neurological outcomes, a similar tendency was shown in crude ORs evaluated by univariate logistic regression, although significance was not demonstrated in all variables of anaphylaxis cases nor for the variable of sex in non-anaphylaxis cases.

By stepwise regression for 1-month survival in anaphylaxis cases, sex, age, existence of a witness, bystander CPR before EMS arrival, and use of defibrillation and drugs were selected as variables for analysis. The increase in age and use of drug were unfavorable for 1-month survival, and the other variables were favorable for survival, as indicated by adjusted ORs (Table 5). In non-anaphylaxis cases, all variables were selected and female sex, existence of a witness, bystander CPR, shockable rhythm, and use of defibrillation were favorable. Increase in age, use of drug, use of airway devices, and increase in EMS response time were unfavorable.

For favorable neurological outcomes, only two variables were selected in anaphylaxis cases. Bystander CPR before EMS arrival was advantageous for favorable neurological outcomes. The use of drug was not favorable for neurological outcomes. Although all variables except sex were chosen in non-anaphylaxis cases by stepwise regression for favorable neurological outcomes, only EMS response time was significant. Increase in EMS time was negatively related with favorable neurological outcomes (Table 5).

DISCUSSION

THE IMPORTANT AND unexpected result in this study is the clear favorable outcome of OHCA in anaphylaxis cases. The OHCA registries have reported that the survival rate of OHCA of non-cardiac origin is poor in general.[5,6] This holds true in our registry (Table S1). However, our results indicate that approximately one-third of anaphylaxis cases survived for 1 month and one-quarter of anaphylaxis cases had favorable neurological outcomes when there was a non-cardiac cause. These outcomes were markedly better than OHCA cases of cardiac cause.

Recent guidelines for CPR and emergency cardiovascular care include a chapter titled "Cardiac arrest associated with anaphylaxis" in the "Special circumstances of resuscitation" section.[9,10] However, the evidence on OHCA caused by anaphylaxis is not sufficient and is mostly from critical care, forensic, and physiological sciences rather than population-based studies of OHCA.

Among studies of OHCA, we could find only one study from Korea on this topic.[14] Lee *et al*. reported 233 anaphylaxis cases over 8 years, using their nationwide registry. This means that the annual incidence rate per 100,000 population is 0.058 in Korea. Our annual incidence rate of 0.036 to 0.042 per 100,000 might be comparable. Out-of-hospital cardiac arrest with anaphylaxis is rare and we need nationwide registries to investigate.

Table 3. Outcomes of out-of-hospital cardiac arrest with non-cardiac cause: anaphylaxis versus non-anaphylaxis cases

	Anaphylaxis, *n* (%)	Non-anaphylaxis, *n* (%)	Significance, anaphylaxis versus non-anaphylaxis
Overall cases	*n* = 147	*n* = 148,451	
1-month survival	48 (32.7)†	7933 (5.3)†	$P < 0.001$
Favorable neurological outcome	36 (24.5)	3219 (2.2)‡	$P < 0.001$
Witnessed cases	*n* = 107	*n* = 62,940	
1-month survival	40 (37.4)	5872 (9.3)†	$P < 0.001$
Favorable neurological outcome	29 (27.1)	2452 (3.9)§	$P < 0.001$
Propensity score-matched patients			
Overall cases	*n* = 145	*n* = 145	
1-month survival	48 (33.1)	13 (9.0)	$P < 0.001$
Favorable neurological outcome	36 (24.8)	5 (3.5)	$P < 0.001$
Witnessed cases	*n* = 106	*n* = 115	
1-month survival	40 (37.7)	13 (11.3)	$P < 0.001$
Favorable neurological outcome	29 (27.4)	5 (4.4)	$P < 0.001$

†One datum missing.
‡Three data missing.
§Two data missing.

Table 4. Univariate odds ratios (95% confidence interval) for factors contributing to 1-month survival and favorable neurological outcomes in patients with out-of-hospital cardiac arrest of non-cardiac cause: anaphylaxis versus non-anaphylaxis cases

	1-month survival		Favorable neurological outcomes	
	Anaphylaxis	Non-anaphylaxis	Anaphylaxis	Non-anaphylaxis
Sex female (versus male)	1.90 (0.92–3.93)	1.05 (1.01–1.10)	1.76 (0.81–3.85)	0.95 (0.89–1.02)
Age (1-year increments)	0.99 (0.97–1.00)	0.99 (0.99–0.99)	0.99 (0.97–1.01)	0.98 (0.98–0.99)
Witnessed by bystander	2.39 (1.00–5.69)	4.17 (3.96–4.39)	1.47 (0.69–3.12)	4.48 (4.13–4.86)
Bystander CPR	1.48 (0.74–2.95)	1.38 (1.32–1.44)	1.76 (0.81–3.85)	1.76 (1.64–1.89)
Initial rhythm shockable (versus non-shockable)	5.67 (1.33–24.09)	3.13 (2.81–3.49)	3.58 (0.89–14.48)	6.93 (5.97–8.05)
Defibrillation by EMS	2.29 (0.85–6.20)	1.53 (1.39–1.69)	1.42 (0.49–4.15)	1.85 (1.60–2.12)
Drug administration by EMS	0.46 (0.18–1.13)	0.89 (0.83–0.95)	0.30 (0.09–0.93)	0.27 (0.23–0.31)
Airway device usage by EMS	0.86 (0.40–1.86)	0.49(0.47–0.52)	0.80 (0.35–1.83)	0.29 (0.27–0.31)
EMS response time† (1-min increments)	0.99 (0.99–1.00)	0.99 (0.99–0.99)	1.00 (0.99–1.00)	0.99 (0.99–0.99)

†Time from call to first emergency medical services (EMS) contact with patient.
CPR, cardiopulmonary resuscitation.

To investigate the background of favorable outcome in anaphylaxis cases, we assumed that adrenaline administration might contribute to resuscitation outcome. However, drug administration was associated with unfavorable outcome in both anaphylaxis and non-anaphylaxis cases. In our observational study, we must consider potential bias, in that severely affected patients tend to need adrenaline compared to patients who resuscitated easily.[14] Recent studies have reported that the use of adrenaline was not necessarily associated with good neurological outcomes, even in a randomized trial.[15,16] Some studies emphasized the importance of time of first adrenaline administration.[17,18] It has been reported that adrenaline improved neurological outcomes when it was given within 20 min of an emergency call for witnessed cardiogenic OHCA.[19] Our data indicated that the median time interval of drug administration from an emergency call was 28 min (Table 2). It might be possible that a time delay of drug administration was related to our negative results for neurological outcome in anaphylaxis cases. Airway treatment in the prehospital setting also did

Table 5. Multivariate odds ratio (95% confidence interval) for variables predicting 1-month survival and favorable neurological outcomes following out-of-hospital cardiac arrest of non-cardiac origin (variables chosen by stepwise methods)

	1-month survival		Favorable neurological outcomes	
	Anaphylaxis	Non-anaphylaxis	Anaphylaxis	Non-anaphylaxis
Sex female (versus male)	2.78 (1.05–7.34)	1.10 (1.05–1.17)		
Age (1-year increments)	0.98 (0.96–1.01)	0.99 (0.98–0.99)		0.99 (0.96–1.02)
Witnessed by bystander	1.88 (0.67–5.41)	4.75 (4.50–5.05)		1.45 (0.47–4.43)
Bystander CPR	1.94 (0.83–4.52)	1.58 (1.50–1.67)	2.33 (0.99–5.52)	2.00 (0.80–5.02)
Initial rhythm shockable (versus non-shockable)		1.32 (1.14–1.54)		1.34 (0.10–17.33)
Defibrillation by EMS	3.53 (1.01–12.43)	1.17 (1.02–1.34)		1.13 (0.19–6.71)
Drug administration by EMS	0.34 (0.12–0.99)	0.79 (0.73–0.85)	0.27(0.09–0.87)	0.22 (0.06–0.86)
Airway device usage by EMS		0.48 (0.45–0.51)		0.93 (0.34–2.61)
EMS response time† (1-min increments)		0.99 (0.99–0.99)		0.99 (0.99–0.99)

†Time from call to first emergency medical service (EMS) contact with patient.
CPR, cardiopulmonary resuscitation.

not contribute to a favorable outcome. Prehospital defibrillation was the only factor contributing positively to resuscitation outcomes. However, the percentage of defibrillated cases was limited (12.3%), similar to other non-cardiac OHCA cases.

Our results by both propensity score matching and stepwise regression analyses indicate that prehospital treatment by EMS as well as other characteristics cannot explain the difference of outcomes between anaphylaxis and non-anaphylaxis cases. Another possible factor that might have contributed to the difference in outcomes is bystander intervention. It has been reported that the incidence of anaphylaxis increased over a 10-year period.[20] Nowadays, there is more awareness of the potential risk faced by those with a history of allergies. Anaphylaxis guidelines emphasize bystander intervention, which starts with first-line treatment with intramuscular adrenaline administration followed by second-line interventions of removing the trigger, calling for help, and correctly positioning the patient.[21]

The limitation of this study is the insufficiency of information about the bystander and resuscitation situation before EMS arrival. We did not collect information directly from bystanders but instead obtained information from EMS records. There was only a write-in column regarding defibrillation treatment by bystanders. We did not obtain further information, including regarding adrenaline administration before EMS arrival. The insufficiency of detailed information that supported the diagnosis of anaphylaxis is also a limitation of this study. Dumas *et al.*[22] indicated that an etiology-specific approach was necessary to improve resuscitation care for OHCA with non-cardiac etiology. To clarify the concealed factors, other than defibrillation, we believe that treatment and procedures before EMS arrival should be included in the current targets for investigation of OHCA with anaphylaxis.

CONCLUSION

THE CURRENT THINKING that the outcome of OHCA of non-cardiac etiology is uniformly poor should be reconsidered. Neurological outcome was markedly more favorable in cases with anaphylaxis than non-anaphylaxis cases. Further studies are needed to explain this result, including performance of the bystanders.

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DISCLOSURE

Approval of the research protocol: The protocol was approved by the Ethics Committee of Kindai University as the corresponding institution (30-057). All participating

hospitals, including our hospital, approved the JAAM-OHCA registry protocol.
Informed consent: The requirement for informed consent of patients was waived.
Registry and the registration no. of the study/trial: This study was not registered.
Animal studies: N/A.
Conflict of interest: None declared.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Fig. S1 Receiver operating characteristic (ROC) curve and C-statistics (concordance index). C-statistics (concordance index) is a measure of goodness of fit of the model and is equal to the area under the ROC curve ranging from 0.5 to 1.

Table S1 Outcomes of out-of-hospital cardiac arrest (OHCA) due to non-cardiac causes were poor compared to OHCA due to cardiac causes.

Table S2 Number of deaths by anaphylaxis per year in Japan based on ICD-10 from the national death statistics: cause of death.[12] The incidence rates of anaphylaxis-associated out-of-hospital cardiac arrest from 2013 to 2015 were comparable with the number of deaths from anaphylaxis registered in Japan.

Table S3 Patient classification of non-cardiac cardiac arrests except anaphylaxis-associated cardiac arrests (non-anaphylaxis cases).

Table S4 Background characteristics of cases of out-of-hospital cardiac arrest of non-cardiac origin: anaphylaxis versus non-anaphylaxis cases. Background characteristics such as age distribution, time frame in which arrests occurred, and season in which arrests occurred are listed.