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Epidemiology and outcome of out-of-hospital cardiac arrest with non-cardiac origin in Osaka: a population-based study

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ABSTRACT

Objectives: To evaluate epidemiological characteristics of out-of-hospital cardiac arrests (OHCAs) by detailed non-cardiac cause and factors associated with the outcomes after OHCAs with non-cardiac origin.

Design: A prospective, population-based observational study.

Setting: The Utstein Osaka Project.

Participants: 14,164 adult patients with OHCAs due to non-cardiac origin who were resuscitated by emergency-medical-service personnel or bystanders, and then were transported to medical institutions from January 2005 to December 2011.

Primary outcome measures: One-month survival after OHCA. Multiple logistic regression analysis was used to assess factors that were potentially associated with the outcome.

Results: During the study period, the one-month survival rate was 5.3% (755/14,164). The proportion of one-month survival was 6.2% (510/8239) in external causes, 6.5% (94/1148) in respiratory diseases, 0.8% (11/1309) in malignant tumors, 4.9% (55/1114) in cerebrovascular diseases, and 4.1% (85/2054) in others. As for external causes, the proportion of one-month survival was 14.3% (382/2670) in asphyxia, 4.2% (84/1999) in hanging, 0.7% (9/1300) in fall, 1.1% (12/1062) in drowning, 1.6% (12/765) in

traffic injury, 3.7% (7/187) in drug overuse, and 1.6% (4/256) in unclassified external causes. In a multivariate analysis, arrests witnessed by bystanders, good activities of daily living before arrests, ventricular fibrillation arrests, public places, intravenous fluid, and early emergency-medical-service response time were significant predictors for one-month outcome after OHCAs with cardiac origin. The proportion of one-month survival of the whole OHCAs with non-cardiac origin did not significantly increase (from 4.3% [86/2023] in 2005 to 4.9% [105/2126] in 2011) and the adjusted odds ratio for one-increment of year was 1.01 (95% confidence interval 0.97-1.06).

Conclusions: From a large OHCA registry in Osaka, we demonstrated that one-month survival after OHCAs with non-cardiac origin was poor and stable.

Strengths and limitations of this study

- This study showed that one-month survival after OHCAs with non-cardiac origin was poor and the survival trends did not improve year-by-year in Osaka during the study period from 2005 to 2011. In addition, the survivals exceedingly differed by detailed non-cardiac origin.
- The category of presumed non-cardiac causes is made clinically, as per the Utstein-style international guidelines for cardiac arrest data reporting.

INTRODUCTION

Out-of-hospital cardiac arrest (OHCA) is one of the leading causes of death in the industrialized world.[1-4] Although improvements in the chain of survival including the development of a public-access defibrillation system and revisions to cardiopulmonary resuscitation (CPR) guidelines have led to increased survival after OHCA with cardiac origin in some communities,[5-7] the outcome after OHCAs with non-cardiac origin remains generally poor.[7-13]

Importantly, 20% to 40% of adult OHCAs were reportedly of non-cardiac origin.[7-13] However, epidemiological characteristics of OHCA with non-cardiac origin have not been sufficiently investigated as much as those of OHCA with cardiac origin. Therefore, the evaluation of characteristics, trends, and outcomes by detailed non-cardiac cause and understanding the factors associated with the outcomes are needed to improve the survival after OHCAs with non-cardiac origin.

The Utstein Osaka Project is a large prospective population-based cohort study of OHCA in Osaka, Japan, covering about 8.8 million residents.[5] During the 7 years from 2005 to 2011, we enrolled approximately 14,000 OHCAs with non-cardiac origin before emergency-medical-service (EMS) arrival. The present study aimed to evaluate the epidemiological characteristics of OHCAs by detailed non-cardiac cause. In

addition, we evaluated factors associated with the outcomes after OHCAs with non-cardiac origin in a multivariate analysis.

METHODS

Study design and setting

The Utstein Osaka Project is a prospective, population-based registry of OHCA that is based on the standardized Utstein style.[14,15] This study enrolled adult patients aged =>20 years suffering OHCAs with non-cardiac origin before EMS arrival, who were resuscitated by EMS personnel or bystanders, and were transported to medical institutions in Osaka Prefecture from January 1, 2005 to December 31, 2011.

Cardiac arrest was defined as the cessation of cardiac mechanical activity as confirmed by the absence of signs of circulation.[14,15] In this study, the arrests were classified into those of presumed cardiac origin and non-cardiac origin, the latter resulting from external causes, respiratory diseases, malignant tumors, cerebrovascular diseases, and any other non-cardiac causes. Furthermore, external causes were divided into the seven categories: asphyxia, hanging, fall, drowning, traffic injury, drug overuse, and unclassified external causes. These diagnoses were made clinically by the physician in charge, working in collaboration with the EMS personnel.

EMS organization in Osaka

Details of the EMS system in Osaka were described previously.[5] Osaka is the second

largest prefecture in Japan with a population of approximately 8.8 million inhabitants in an area of 1892 km^2. In Osaka, there are 34 fire stations with emergency dispatch centers. The EMS system is operated by the local fire stations. When called, an ambulance is dispatched from the nearest fire station. Emergency services are provided 24 hours each day by them, which is single-tiered in 32 stations and two-tiered in two stations. The latter uses medics followed by physicians.

Most highly-trained prehospital emergency care providers are called Emergency Life-Saving Technicians (ELSTs). Usually, each ambulance has a crew of three emergency providers including at least one ELST. They were allowed to insert an intravenous line and an adjunct airway, and to use a semi-automated external defibrillator for OHCA patients. Specially trained ELSTs were permitted to tracheal intubation since July 2004 and administer intravenous epinephrine since April 2006.

Do-not-resuscitate (DNR) orders or living wills are not generally accepted in Japan. EMS providers are not permitted to terminate resuscitation in the field. Therefore, almost patients with OHCA who were treated by EMS personnel were transported to a hospital and enrolled in the Utstein Osaka Project, excluding those with decapitation, incineration, decomposition, rigor mortis, or dependent cyanosis.

CPR and AED training for the general public

The use of an automated external defibrillator (AED) by citizens was permitted legally in July 2004. In Osaka, approximately 14,000 citizens per year participated in the CPR training programs, consisting of conventional CPR including chest compressions, mouth-to-mouth ventilation, and AED usage by local fire departments, the Japan Red Cross, Inc., and the Osaka Life Support Association.[5] All EMS providers perform CPR according to the Japanese CPR guidelines.[4]

Data collection and quality control

Data collection were prospectively conducted using a form that included data recommended in the Utstein-style reporting guidelines for cardiac arrests.[14,15] These data included gender, age, first documented cardiac rhythm, witness status, location of arrests, activity of daily living (ADL) before arrests, time-courses of resuscitation, type of bystander-initiated CPR, public-access AED use, intravascular fluid, tracheal intubation, and intravascular epinephrine as well as prehospital return of spontaneous circulation (ROSC), total ROSC, one-month survival, and neurological status one month after the event. First documented rhythm was recorded and diagnosed by the EMS personnel with semi-automated defibrillators on the scene, and confirmed by the

physician who was responsible for the on-line medical direction. Bystander CPR included chest compression-only CPR and conventional CPR with rescue breathing. A series of EMS times of call receipt, vehicle arrival at the scene, contact with patients, initiation of CPR, defibrillation by EMS, and hospital arrival were recorded automatically at the dispatch center.

The data form was completed by the EMS personnel in cooperation with the physicians in charge of the patients, and the data were integrated into the registry system on the Information Center for Emergency Medical Services of Osaka, and then checked by the investigators. If the data sheet was incomplete, the relevant EMS personnel were contacted and questioned for data completion.

All survivors suffering OHCA were followed up for up to one-month after the event by the EMS personnel in charge. One-month neurological outcomes were determined by the physician responsible for treating the patient, using the cerebral performance category (CPC) scale: category 1, good cerebral performance; category 2, moderate cerebral disability; category 3, severe cerebral disability; category 4, coma or vegetative state; and category 5, death.[14,15]

Outcome measures

The main outcome measure was one-month survival. Secondary outcome measures included prehospital and total ROSCs, admission to hospital, and one-month survival with neurologically favorable outcome. Neurologically intact outcome was defined as CPC category 1 or 2.[14,15]

Statistical analysis

In this study, patient and EMS characteristics of OHCAs with non-cardiac origin and their outcomes were compared between the groups using unpaired analysis of variance for numerical variables, and chi-square test or Fisher's exact test for categorical variables by cause of arrest. First, non-cardiac causes were divided into the following five groups; external causes, respiratory diseases, malignant tumors, cerebrovascular diseases, and any other non-cardiac causes. Next, external causes were further divided into asphyxia, hanging, fall, drowning, traffic injury, drug overuse, and unclassified external causes. Age-adjusted annual incidence of OHCAs by non-cardiac origin was calculated by the direct method using 2005 census data and 1985 Japanese model population.[16,17] Poisson regression models for the trends in the incidence were used. Multiple logistic regression analysis assessed the factors associated with one-month survival and neurological favorable outcome, and adjusted odds ratios (AORs) and

their 95% confidence intervals (CIs) were calculated. As potential confounders, factors that were biologically essential and considered to be associated with clinical outcomes were taken in the multivariable analyses.[7] These variables included age (20-64, >=65 years old), gender (men, women), witness status (none, witnessed by bystanders), ADL before arrests (good, other), first documented rhythm (VF, non-VF), bystander CPR status (none, compression-only CPR, conventional CPR), type of non-cardiac causes (the 11 categories described above), location of arrests (homes, public places, work places, health care facilities, others), intravascular fluid (yes, no), intubation (yes, no), epinephrine (yes, no), EMS response time (call to contact with patients), and year of arrest.

All statistical analyses were performed using the SPSS statistical package ver21.0J (IBM Corp. Armonk, NY). All of the tests were 2-tailed and *P* values of <0.05 were considered statistically significant.

RESULTS

Figure 1 shows an overview of the study patients based on the Utstein template. A total of 47,735 adult arrests were documented during these seven years. Resuscitation was attempted in 43,845, and 15,505 of them were of non-cardiac origin. Excluding 1341 victims who were witnessed by EMS (arrests after EMS arrival), 14,164 (5561 in bystander-witnessed cases and 8603 in non-witnessed cases) were eligible for our analyses. Among these arrests, 8239 (58.2%) were due to external causes, 1448 (10.2%) respiratory diseases, 1309 (9.2%) malignant tumors, 1114 cerebrovascular (7.9%) diseases, and 2054 (14.5%) others. Among external causes, 2670 (16.5%) were of asphyxia, 1999 (14.1%) hanging, 1300 (9.2%) fall, 1062 (7.5%) drowning, 765 (5.4%) traffic injury, and 256 (1.8%) unclassified external cause.

The age-adjusted annual incidence rates per 100,000 persons by non-cardiac cause were calculated over time (Table 1). The incidence rate of OHCAs with external causes significantly increased from 12.4 in 2005 to 13.3 in 2011 (P for trend=0.024). The incidence rate significantly decreased among OHCA patients with respiratory diseases (from 2.2 in 2005 to 1.6 in 2011, P for trend=0.018) and cerebrovascular diseases (from 2.0 in 2005 to 1.3 in 2011, P for trend<0.001).

Patient and EMS characteristics of OHCAs with non-cardiac origin according to the

cause are shown in Table 2, and their outcomes in Table 4. The mean age of all OHCA patients with non-cardiac origin was 66.8 years and males were 58.0%. The proportion of bystander-witnessed arrests, ADL before arrests, first documented rhythm, type of bystander CPR, and advanced life supports such as intravascular fluid, intubation, and epinephrine exceedingly varied between the five groups. In the whole patients, the rate of one-month survival and neurologically favorable outcome was 5.3% and 1.3%. The proportion of one-month survival was 6.2% in external causes, 6.5% in respiratory diseases, 0.8% in malignant tumors, 4.9% in cerebrovascular diseases, and 4.1% in others. Furthermore, patient and EMS characteristics of OHCAs in external causes are shown in Table 3, and their outcomes in Table 5. The characteristics and outcomes varied between the seven groups. The proportion of one-month survival was 14.3% in asphyxia, 4.2% in hanging, 0.7% in fall, 1.1% in submersion, 1.6% in traffic injury, 3.7% in drug overuse, and 1.6% in unclassified external cause.

Table 6 shows factors contributing to one-month survival and neurologically favorable outcome after OHCAs with non-cardiac origin. In one-month survival, arrests witnessed by bystanders (AOR 4.13, 95% CI 3.35-5.09), good ADL before arrests (AOR 1.23, 95% CI 1.03-1.47), VF as first documented rhythm (AOR 2.04, 95% CI 1.42-2.92), public places (AOR 1.45, 95% CI 1.10-1.91), intravenous fluid

(AOR 1.45, 95% CI 1.14-1.84), and early EMS response time (AOR for one-increment of minute 1.45, 95% CI 1.10-1.91) were associated with improving outcome. However, type of bystander CPR, intubation, and epinephrine were not associated with better outcome. Compared with asphyxia, the AORs were significantly lower in respiratory diseases (0.51, 95% CI 0.40-0.65), malignant tumors (0.06, 95% CI 0.03-0.11), cerebrovascular disease (0.27, 95% CI 0.20-0.38), hanging (0.56, 95% CI 0.41-0.77), fall (0.03, 95% CI 0.01-0.06), drowning (0.16, 95% CI 0.09-0.29), and traffic injury (0.05, 95% CI 0.03-0.10). The proportion of one-month survival of the whole OHCAs with non-cardiac origin did not significantly increase (from 4.3% [86/2023] in 2005 to 4.9% [105/2126] in 2011) and the AOR for one-increment of year was 1.01 (95% CI 0.97-1.06). The AORs of neurologically favorable outcome after OHCAs with non-cardiac origin were almost similar to those of one-month survival.

DISCUSSION

The extensive OHCA registry in Osaka showed that one-month survival after OHCAs with non-cardiac origin was poor and the survival trends did not improve year-by-year. In addition, the survivals differed by detailed non-cardiac origin. To further improve survival after OHCAs, sufficient attention should be paid to the epidemiological characteristics of OHCAs with non-cardiac origin as much as those of OHCA with cardiac origin, and this study describing the actual situation regarding the incidence and outcome of OHCAs with non-cardiac origin provides valuable information to improve the survival.

Our study observed that the outcomes of OHCAs with non-cardiac origin were poor and stable during the seven years. In a previous study in Japan, neurologically favorable outcome of bystander-witnessed OHCAs with non-cardiac origin increased from 2005 to 2011, but the absolute survival was very low,[7] and this result was similar with ours. Improving the outcome of OHCAs with non-cardiac origin poses an important problem in resuscitation science because 20~40% of adult OHCAs are of non-cardiac origin.[7-13] In addition, the survivals exceedingly differed by detailed non-cardiac origin, which also suggests the need and importance of an origin-specific strategy for improving the outcomes.

We also showed that the OHCA incidence trends differed by detailed non-cardiac origin. For instance, the incidence rate of OHCAs due to cerebrovascular diseases significantly decreased during the study period. Although the reasons for the decrement were unclear, better blood pressure control and decreasing smoking rate in recent years of Japan might be one of the possible explanations for this phenomenon.[18] In fact, the numbers of stroke patients in Japan has also been decreasing.[19] On the other hand, the incidence rates of OHCAs with external causes increased and the outcomes after OHCAs with external causes excluding asphyxia were miserable. Therefore, most importantly, more efforts should focus on prevention of OHCAs with external causes because many of them are preventable.[1-4]

In a multivariable analysis, intravenous fluid administration was associated with better one-month survival after OHCAs with non-cardiac origin. In preceding studies, prehospital intravenous fluid for OHCAs including both cardiac and non-cardiac origins was not associated with the improved outcome,[20] whereas intravenous access were associated with a reduction in hospital mortality among non-injured, non-cardiac arrest patients.[21] Thus, the effects of fluid administration on prehospital emergency patients were under debate, and further investigations by other cohorts or randomized controlled trials are needed to confirm these associations.

In this study, a multivariate analysis also underscored that either bystander-initiated chest compression-only CPR or conventional CPR with rescue breathing was not effective for OHCAs with non-cardiac origin. From a nationwide study focused on 43,000 bystander-witnessed OHCAs with non-cardiac origin, we demonstrated that conventional CPR with rescue breathing had an incremental benefit for OHCAs with non-cardiac origin, but the impact on the overall survival after OHCA was small.[8] Considering these results, the effectiveness of bystander CPR on OHCAs with cardiac non-cardiac origin might be limited. However, as recommended in the CPR guidelines,[1-4] bystander CPR plays a key role in the "chain of survival" and increasing the proportion of bystander CPR for OHCA patients is important.

Furthermore, factors such as arrests witnessed by bystanders and earlier EMS response time were also independent predictors of better outcome after OHCAs with non-cardiac origin in a multivariate analysis. This would indicate the importance of an early EMS activation in the chain of survival[1-4] and suggests that activating the EMS system quickly leads to improving the outcomes after OHCAs with non-cardiac origin. In addition, the verification of the effects on prehospital emergency care as well as in-hospital treatment is essential to improve survival after OHCAs with non-cardiac origin.

The present study has some inherent limitations. First, the category of presumed cardiac or non-cardiac causes is made clinically, as per the Utstein-style international guidelines for cardiac arrest data reporting.[14,15] Second, information on post-arrest care is lacking. In-hospital treatment (e.g., hemodynamic support, cardiovascular intervention, induced hypothermia) might affect survival after OHCA.[22] Third, unmeasured confounding factors may have influenced the association between OHCAs with non-cardiac origin and the outcome.

CONCLUSION

The large OHCA registry in Osaka demonstrated that one-month survival after OHCAs with non-cardiac origin was poor, the survival trends did not improve year-by-year, and the survivals differed by detailed non-cardiac origin. Further monitoring and discussion for epidemiology and outcome of OHCAs with non-cardiac origin are warranted to improve survival after OHCA in this group.

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Contributors

All authors (TK, KK, TS, TI, CN, KK, TN, YH, YK, KY, and TS) participated in the study conception and design, acquisition of data, analysis and interpretation of data, drafting the article and revising it critically for important intellectual content, and final approval of the manuscript.

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Competing interests

None.

Ethics approval

The study was approved by the institutional review board of Osaka University with the assent of the EMS authorities of the local governments in Osaka Prefecture.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data sharing statement

TK had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Figure Legends

Figure 1 Overview of EMS-treated cardiac arrests with an abridged Utstein template from January 1, 2005 to December 31, 2011. EMS, emergency medical service.

Figure 1

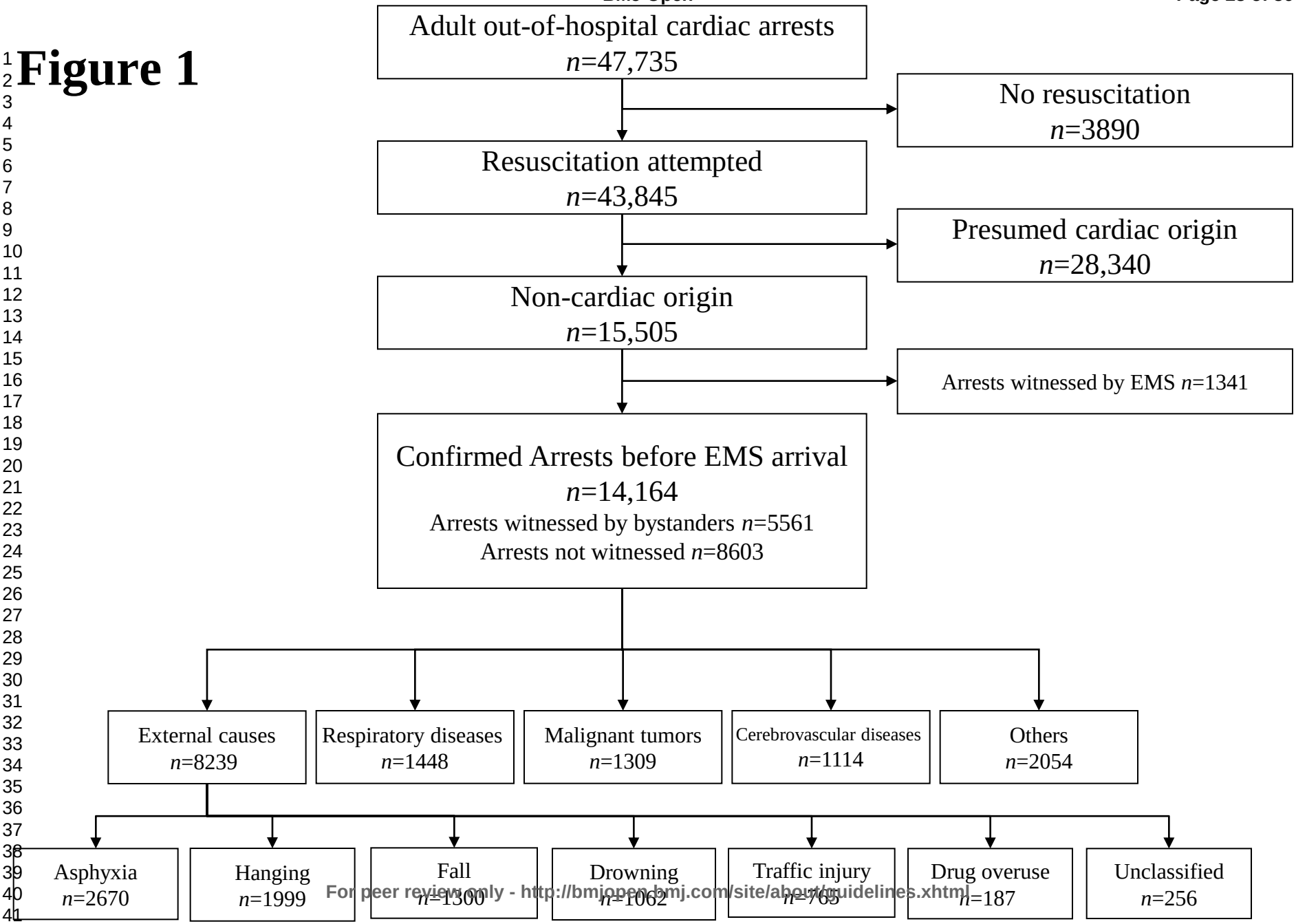

Table 1 Age-adjusted incidences of out-of-hospital cardiac arrests with non-cardiac origin according to the cause over time

	Incidence per 100,000 persons							
	2005	2006	2007	2008	2009	2010	2011	P for trend
External causes	12.4	12.3	13.2	12.8	13.2	13.3	13.3	0.024
Asphyxia	2.7	3.0	2.8	3.4	3.1	2.9	2.9	0.726
Hanging	3.4	3.4	4.1	3.4	3.7	3.9	3.9	0.158
Fall	2.4	2.5	3.1	2.4	2.9	3.0	2.7	0.396
Drowning	1.2	1.1	1.2	1.4	1.2	1.3	1.6	0.065
Traffic injury	1.6	1.5	1.4	1.4	1.4	1.5	1.4	0.229
Drug overdose	0.5	0.4	0.2	0.4	0.4	0.4	0.3	0.304
Unclassified	0.5	0.5	0.4	0.3	0.5	0.4	0.5	0.447
Respiratory diseases	2.2	1.8	1.8	1.7	1.3	1.3	1.6	0.018
Malignant tumors	1.6	1.8	1.8	1.7	1.5	1.3	1.6	0.109
Cerebrovascular diseases	2.0	1.8	1.8	1.6	1.4	1.2	1.3	< 0.001
Others	2.7	3.3	3.1	2.9	2.7	2.5	2.4	0.087

Table 2 Patient and EMS characteristics of out-of-hospital cardiac arrests with non-cardiac origin according to the cause

	Total (n =14,164)	External causes (n = 8239)	Respiratory diseases (n =1448)	Malignat tumors (n =1309)	Cerebrovascular diseases (n =1114)	Others (n =2054)	*P* value*
Age, yr, mean (SD)	66.8 (19.0)	63.5 (20.5)	76.1 (14.2)	71.9 (12.0)	67.7 (14.7)	69.8 (17.6)	< 0.001
Age group, n (%)							< 0.001
Adults aged 20-64 years	5513 (38.9)	3826 (46.4)	229 (15.8)	345 (26.4)	447 (40.1)	666 (32.4)	
Elderly aged >=65 years	8651 (61.1)	4413 (53.6)	1219 (84.2)	964 (73.6)	667 (59.9)	1388 (67.6)	
Men, n (%)	8215 (58.0)	4789 (58.1)	844 (58.3)	881 (67.3)	559 (50.2)	1142 (55.6)	< 0.001
Arrests witnessed by bystanders, n (%)	5561 (39.3)	2952 (35.8)	682 (47.1)	639 (48.8)	493 (44.3)	795 (38.7)	< 0.001
Good activities of daily living, n (%)	8522 (60.2)	5213 (63.3)	653 (45.1)	443 (33.8)	896 (80.4)	1317 (64.1)	< 0.001
First documented rhythm, n (%)							< 0.001
VF	324 (2.3)	119 (1.4)	35 (2.4)	26 (2.0)	69 (6.2)	75 (3.7)	
PEA	3356 (23.7)	1853 (22.5)	394 (27.2)	262 (20.0)	329 (29.5)	518 (25.2)	
Asystole	10196 (72.0)	6124 (74.3)	983 (67.9)	1008 (77.0)	647 (58.1)	1434 (69.8)	
Others	288 (2.0)	143 (1.7)	36 (2.5)	13 (1.0)	69 (6.2)	27 (1.3)	
Location of arrest, n (%)							< 0.001
Homes	9010 (63.6)	4435 (53.8)	1098 (75.8)	1217 (93.0)	801 (71.9)	1459 (71.0)	
Public places	2035 (14.4)	1608 (19.5)	59 (4.1)	24 (1.8)	156 (14.0)	188 (9.2)	
Work places	346 (2.4)	223 (2.7)	7 (0.5)	4 (0.3)	48 (4.3)	64 (3.1)	
Health care facilities	1505 (10.6)	904 (11.0)	248 (17.1)	55 (4.2)	63 (5.7)	235 (11.4)	
Others	1268 (9.0)	1069 (13.0)	36 (2.5)	9 (0.7)	46 (4.1)	108 (5.3)	
Public-access AED use, n (%)	13 (0.1)	4 (0.05)	2 (0.1)	0 (0.0)	5 (0.4)	2 (0.1)	0.001
Type of Bystander CPR, n (%)							< 0.001
No CPR	9023 (63.7)	5383 (65.3)	836 (57.7)	889 (67.9)	633 (56.8)	1282 (62.4)	
Chest compression-only CPR	3288 (23.2)	1811 (22.0)	408 (28.2)	297 (22.7)	283 (25.4)	489 (23.8)	
Conventional CPR with rescue breathing	1853 (13.1)	1045 (12.7)	204 (14.1)	123 (9.4)	198 (17.8)	283 (13.8)	
Intravascular fluid, n (%)	2320 (16.4)	1458 (17.7)	202 (14.0)	113 (8.6)	230 (20.6)	317 (15.4)	< 0.001
Intubation, n (%)	2639 (18.6)	1364 (16.6)	338 (23.3)	242 (18.5)	257 (23.1)	438 (21.3)	< 0.001
Epinephrine, n (%)	987 (7.0)	572 (6.9)	88 (6.1)	49 (3.7)	125 (11.2)	153 (7.4)	< 0.001
Call to contact with a patient by EMS (EMS response time), min, mean (SD)	7.9 (4.1)	8.0 (4.6)	7.7 (3.0)	7.7 (2.7)	7.7 (2.8)	7.9 (3.8)	0.003
Call to CPR by EMS, min, mean (SD)	8.5 (4.5)	8.8 (5.1)	8.1 (3.1)	8.1 (2.8)	8.2 (2.9)	8.4 (4.2)	< 0.001
Call to hospital arrival, min, mean (SD)	28.2 (8.6)	28.4 (8.6)	27.3 (8.2)	28.0 (8.9)	28.2 (8.4)	28.1 (8.7)	0.001

*P values are calculated to test the homogeneity among the 5 cause groups.

EMS indicates emergency medical services; CPR, cardiopulmonary resuscitation; VF, ventricular fibrillation; PEA, pulseless electrical activity; AED, automated external defibrillator; SD, standard deviation.

Table 3 Patient and EMS characteristics of out-of-hospital cardiac arrests with external causes according to the cause

	Asphyxia (n = 2670)	Hanging (n = 1999)	Fall (n = 1300)	Drowning (n = 1062)	Traffic injury (n = 765)	Drug overdose (n = 187)	Unclassified (n = 256)	*P* value*
Age, yr, mean (SD)	77.9 (14.4)	55.6 (17.4)	47.4 (17.4)	73.1 (14.8)	52.6 (19.0)	49.9 (19.5)	58.1 (19.3)	< 0.001
Age group, n (%)								< 0.001
Adults aged 20-64 years	403 (15.1)	1136 (66.8)	1055 (81.2)	210 (19.8)	523 (68.4)	141 (75.4)	158 (61.7)	
Elderly aged >=65 years	2267 (84.9)	663 (33.2)	245 (18.8)	852 (80.2)	242 (31.6)	46 (24.6)	98 (38.3)	
Men, n (%)	1345 (50.4)	1290 (64.5)	781 (60.1)	530 (49.9)	558 (72.9)	117 (62.6)	168 (65.6)	< 0.001
Arrests witnessed by bystanders, n (%)	1801 (67.5)	27 (1.4)	510 (39.2)	56 (5.3)	476 (62.2)	10 (5.3)	72 (28.1)	< 0.001
Good activities of daily living, n (%)	1099 (41.2)	1769 (88.5)	685 (52.7)	854 (80.4)	517 (67.6)	133 (71.1)	156 (60.9)	< 0.001
First documented rhythm, n (%)								< 0.001
VF	56 (2.1)	13 (0.7)	19 (1.5)	12 (1.1)	14 (1.8)	1 (0.5)	4 (1.6)	
PEA	960 (36.0)	198 (9.9)	274 (21.1)	72 (6.8)	259 (33.9)	20 (10.7)	70 (27.3)	
Asystole	1589 (59.5)	1775 (88.8)	985 (75.8)	970 (91.3)	469 (61.3)	160 (85.6)	176 (68.8)	
Others	65 (2.4)	13 (0.7)	22 (1.7)	8 (0.8)	23 (3.0)	6 (3.2)	6 (2.3)	
Location of arrest, n (%)								< 0.001
Homes	1596 (59.8)	1667 (83.4)	139 (10.7)	770 (72.5)	2 (0.3)	150 (80.2)	111 (43.4)	
Public places	139 (5.2)	86 (4.3)	553 (42.5)	83 (7.8)	677 (88.5)	14 (7.5)	56 (21.9)	
Workplaces	35 (1.3)	94 (4.7)	44 (3.4)	3 (0.3)	7 (0.9)	7 (3.7)	33 (12.9)	
Health care facilities	835 (31.3)	27 (1.4)	12 (0.9)	14 (1.3)	1 (0.1)	0 (0.0)	15 (5.9)	
Others	65 (2.4)	125 (6.3)	552 (42.5)	192 (18.1)	78 (10.2)	16 (8.6)	41 (16.0)	
Public-access AED use, n (%)	4 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.214
Type of Bystander CPR, n (%)								< 0.001
No CPR	1386 (51.9)	1174 (58.7)	1191 (91.6)	608 (57.3)	673 (88.0)	154 (82.4)	197 (77.0)	
Chest compression-only CPR	748 (28.0)	549 (27.5)	93 (7.2)	281 (26.5)	74 (9.7)	23 (12.3)	43 (16.8)	
Conventional CPR with rescue breathing	536 (20.1)	276 (13.8)	16 (1.2)	173 (16.3)	18 (2.4)	10 (5.3)	16 (6.2)	
Intravascular fluid, n (%)	540 (20.2)	393 (19.7)	107 (8.2)	281 (26.5)	76 (9.9)	27 (14.4)	34 (13.3)	< 0.001
Intubation, n (%)	800 (30.0)	167 (8.4)	41 (3.2)	251 (23.6)	31 (4.1)	33 (17.6)	41 (16.0)	< 0.001
Epinephrine, n (%)	326 (12.2)	83 (4.2)	41 (3.2)	68 (6.4)	37 (4.8)	6 (3.2)	11 (4.3)	< 0.001
Call to contact with a patient by EMS (EMS response time), min, mean (SD)	7.6 (2.9)	7.8 (3.3)	7.4 (3.3)	9.4 (7.6)	7.6 (4.2)	14.2 (10.7)	9.4 (7.3)	< 0.001
Call to CPR by EMS personnel, min, mean (SD)	7.9 (3.1)	8.6 (3.9)	8.2 (3.8)	10.0 (7.5)	9.3 (5.9)	14.4 (10.0)	11.0 (8.7)	< 0.001
Call to hospital arrival, min, mean (SD)	28.6 (8.6)	28.2 (7.9)	27.5 (8.3)	29.1 (9.3)	27.1 (8.8)	32.1 (11.1)	29.5 (9.4)	< 0.001

*P values are calculated to test the homogeneity among the 7 cause groups.

EMS indicates emergency medical services; CPR, cardiopulmonary resuscitation; VF, ventricular fibrillation; PEA, pulseless electrical activity; AED, automated external defibrillator; SD, standard deviation.

Table 4 Outcomes after out-of-hospital cardiac arrests with non-cardiac origin according to the cause

	Total (n = 1,4164)	External causes (n = 8239)	Respiratory diseases (n = 1148)	Malignat tumors (n = 1309)	Cerebrovascular diseases (n = 1114)	Others (n =2054)	*P* value*
Prehospital ROSC, n (%)	1229 (8.7)	703 (8.5)	114 (7.9)	57 (4.4)	216 (19.4)	139 (6.8)	< 0.001
Total ROSC, n (%)	4744 (33.5)	2638 (32.0)	620 (42.8)	234 (17.9)	650 (58.3)	602 (29.3)	< 0.001
Hospital admission, n (%)	4142 (29.2)	2356 (28.6)	530 (36.6)	173 (13.2)	585 (52.5)	498 (24.2)	< 0.001
One-month survival, n (%)	755 (5.3)	510 (6.2)	94 (6.5)	11 (0.8)	55 (4.9)	85 (4.1)	< 0.001
Neurologically favorable outcome, n (%)	188 (1.3)	37 (1.3)	27 (1.9)	2 (0.2)	17 (1.5)	37 (1.8)	< 0.001

*P values are calculated to test the homogeneity among the 5 cause groups.
ROSC indicates return of spontaneous circulation.

Table 5 Outcomes after out-of-hospital cardiac arrests with external causes according to the cause

	Asphyxia (n = 2670)	Hanging (n = 1999)	Fall (n = 1300)	Drowning (n = 1062)	Traffic injury (n = 765)	Drug overdose (n = 187)	Unclassified (n = 256)	*P* value*
Prehospital ROSC, n (%)	463 (17.3)	144 (7.2)	22 (1.7)	36 (3.4)	28 (3.7)	4 (2.1)	6 (2.3)	< 0.001
Total ROSC, n (%)	1003 (37.6)	1500 (75.0)	1213 (93.3)	894 (84.2)	637 (83.3)	143 (76.5)	211 (82.4)	< 0.001
Hospital admission, n (%)	1529 (57.3)	453 (22.7)	62 (4.8)	147 (13.8)	92 (12.0)	40 (21.4)	33 (12.9)	< 0.001
One-month survival, n (%)	382 (14.3)	84 (4.2)	9 (0.7)	12 (1.1)	12 (1.6)	7 (3.7)	4 (1.6)	< 0.001
Neurologically favorable outcome, n (%)	71 (2.7)	17 (0.9)	1 (0.1)	4 (0.4)	6 (0.8)	4 (2.1)	2 (0.8)	< 0.001

*P values are calculated to test the homogeneity among the 7 cause groups.
ROSC indicates return of spontaneous circulation.

Table 6 Factors associated with outcomes after out-of-Hospital cardiac arrests with non-cardiac origin

	One-month survival		Neurologically favorable outcome	
	Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)
Adults (versus elderly)	0.75 (0.64-0.88)	0.99 (0.84-1.16)	1.09 (0.81-1.46)	0.91 (0.67-1.24)
Men	0.95 (0.82-1.10)	1.36 (1.12-1.65)	1.02 (0.76-1.37)	1.52 (1.07-2.15)
Witnessed by bystanders	4.41 (3.74-5.19)	4.13 (3.35-5.09)	4.48 (3.23-6.21)	4.83 (3.21-7.29)
Good activities of daily living	0.93 (0.80-1.08)	1.23 (1.03-1.47)	1.39 (1.02-1.88)	1.43 (1.02-2.02)
VF	2.74 (1.96-3.82)	2.04 (1.42-2.92)	7.72 (5.05-11.79)	5.40 (3.40-8.59)
Type of bystander CPR				
No CPR	Reference	Reference	Reference	Reference
Chest compression-only CPR	0.97 (0.81-1.16)	0.80 (0.66-0.98)	0.95 (0.67-1.35)	0.92 (0.64-1.33)
Conventional CPR with rescue brething	1.47 (1.20-1.79)	1.07 (0.86-1.34)	1.01 (0.65-1.55)	0.89 (0.56-1.42)
Type of non-cardiac origin				
Respiratory diseases	0.42 (0.33-0.53)	0.51 (0.40-0.65)	0.70 (0.44-1.09)	0.76 (0.48-1.21)
Malignant tumors	0.05 (0.03-0.09)	0.06 (0.03-0.11)	0.06 (0.01-0.23)	0.06 (0.01-0.23)
Cerebrovascular diseases	0.31 (0.23-0.42)	0.27 (0.20-0.38)	0.57 (0.33-0.97)	0.34 (0.19-0.61)
Asphyxia	Reference	Reference	Reference	Reference
Hanging	0.26 (0.21-0.34)	0.56 (0.41-0.77)	0.31 (0.18-0.53)	0.55 (0.28-1.07)
Fall	0.04 (0.02-0.08)	0.03 (0.01-0.06)	0.03 (0.004-0.20)	0.01 (0.002-0.11)
Drowning	0.07 (0.04-0.12)	0.16 (0.09-0.29)	0.14 (0.05-0.38)	0.31 (0.11-0.90)
Traffic injury	0.10 (0.05-0.17)	0.05 (0.03-0.10)	0.29 (0.13-0.67)	0.10 (0.04-0.26)
Drug overdose	0.23 (0.11-0.50)	0.58 (0.26-1.29)	0.80 (0.29-2.21)	1.74 (0.58-5.19)
Others	0.26 (0.20-0.33)	0.29 (0.22-0.38)	0.67 (0.45-1.00)	0.60 (0.39-0.92)
Unclassified	0.10 (0.04-0.26)	0.10 (0.04-0.28)	0.29 (0.07-1.18)	0.27 (0.06-1.16)
Location of arrest				
Homes	Reference	Reference	Reference	Reference
Public places	0.78 (0.61-0.99)	1.45 (1.10-1.91)	1.11 (0.75-1.65)	1.54 (0.97-2.44)
Workplaces	1.29 (0.83-1.98)	1.40 (0.87-2.23)	1.26 (0.55-2.89)	0.95 (0.39-2.30)
Health care facilities	1.69 (1.38-2.07)	0.88 (0.69-1.12)	0.72 (0.42-1.24)	0.47 (0.26-0.85)
Others	0.70 (0.51-0.94)	1.67 (1.19-2.35)	0.68 (0.38-1.24)	1.35 (0.72-2.54)
Intravascular fluid	1.78 (1.50-2.11)	1.45 (1.14-1.84)	1.34 (0.94-1.91)	1.52 (0.97-2.38)
Intubation	1.62 (1.37-1.92)	1.02 (0.84-1.23)	0.73 (0.48-1.10)	0.50 (0.32-0.77)
Epinephrine	2.32 (1.87-2.88)	0.97 (0.71-1.32)	1.25 (0.74-2.09)	0.60 (0.31-1.17)
EMS response time (for one-increment of minute)	0.93 (0.91-0.96)	0.92 (0.90-0.95)	0.91 (0.86-0.96)	0.90 (0.84-0.95)
Year (for one-increment of year)	1.02 (0.98-1.06)	1.01 (0.97-1.06)	1.02 (0.95-1.09)	1.05 (0.97-1.13)

VF denotes ventricular fibrillation; CPR, cardiopulmonary resuscitation; EMS, emergency medical services; OR, odds ratio; CI, confidence interval.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Epidemiology and outcome of out-of-hospital cardiac arrest with non-cardiac origin in Osaka: a population-based study

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Epidemiology and outcome of out-of-hospital cardiac arrest with non-cardiac origin in Osaka: a population-based study

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ABSTRACT

Objectives: To evaluate epidemiological characteristics of out-of-hospital cardiac arrests (OHCAs) by detailed non-cardiac cause and factors associated with the outcomes after OHCAs with non-cardiac origin.

Design: A prospective, population-based observational study.

Setting: The Utstein Osaka Project.

Participants: 14,164 adult patients with OHCAs due to non-cardiac origin who were resuscitated by emergency-medical-service personnel or bystanders, and then were transported to medical institutions from January 2005 to December 2011.

Primary outcome measures: One-month survival after OHCA. Multiple logistic regression analysis was used to assess factors that were potentially associated with the outcome.

Results: During the study period, the one-month survival rate was 5.3% (755/14,164). The proportion of one-month survival was 6.2% (510/8239) in external causes, 6.5% (94/1148) in respiratory diseases, 0.8% (11/1309) in malignant tumors, 4.9% (55/1114) in strokes, and 4.1% (85/2054) in others. As for external causes, the proportion of one-month survival was 14.3% (382/2670) in asphyxia, 4.2% (84/1999) in hanging, 0.7% (9/1300) in fall, 1.1% (12/1062) in drowning, 1.6% (12/765) in traffic injury,

3.7% (7/187) in drug overuse, and 1.6% (4/256) in unclassified external causes. In a multivariate analysis, arrests witnessed by bystanders, good activities of daily living before arrests, ventricular fibrillation arrests, public places, intravenous fluid, and early emergency-medical-service response time were significant predictors for one-month outcome after OHCAs with cardiac origin. The proportion of one-month survival of the whole OHCAs with non-cardiac origin did not significantly increase (from 4.3% [86/2023] in 2005 to 4.9% [105/2126] in 2011) and the adjusted odds ratio for one-increment of year was 1.01 (95% confidence interval 0.97-1.06).

Conclusions: From a large OHCA registry in Osaka, we demonstrated that one-month survival after OHCAs with non-cardiac origin was poor and stable.

Strengths and limitations of this study

- This study showed that one-month survival after OHCAs with non-cardiac origin was poor and the survival trends did not improve year-by-year in Osaka during the study period from 2005 to 2011. In addition, the survivals exceedingly differed by detailed non-cardiac origin.
- The category of presumed non-cardiac causes is made clinically, as per the Utstein-style international guidelines for cardiac arrest data reporting.

INTRODUCTION

Out-of-hospital cardiac arrest (OHCA) is one of the leading causes of death in the industrialized world.[1-4] Although improvements in the chain of survival including the development of a public-access defibrillation system and revisions to cardiopulmonary resuscitation (CPR) guidelines have led to increased survival after OHCA with cardiac origin in some communities,[5-7] the outcome after OHCAs with non-cardiac origin remains generally poor.[7-13]

Importantly, 20% to 40% of adult OHCAs were reportedly of non-cardiac origin.[7-13] However, epidemiological characteristics of OHCA with non-cardiac origin have not been sufficiently investigated as much as those of OHCA with cardiac origin. Therefore, the evaluation of characteristics, trends, and outcomes by detailed non-cardiac cause and understanding the factors associated with the outcomes are needed to improve the survival after OHCAs with non-cardiac origin.

The Utstein Osaka Project is a large prospective population-based cohort study of OHCA in Osaka, Japan, covering about 8.8 million residents.[5] During the 7 years from 2005 to 2011, we enrolled approximately 14,000 OHCAs with non-cardiac origin before emergency-medical-service (EMS) arrival. The present study aimed to evaluate the epidemiological characteristics of OHCAs by detailed non-cardiac cause. In

addition, we evaluated factors associated with the outcomes after OHCAs with non-cardiac origin in a multivariate analysis.

METHODS

Study design and setting

The Utstein Osaka Project is a prospective, population-based registry of OHCA that is based on the standardized Utstein style.[14,15] This study enrolled adult patients aged =>20 years suffering OHCAs with non-cardiac origin before EMS arrival, who were resuscitated by EMS personnel or bystanders, and were transported to medical institutions in Osaka Prefecture from January 1, 2005 to December 31, 2011. In this study, we excluded pediatric OHCA patients because characteristics and outcomes from OHCAs differed between children and adults.[16,17]

Cardiac arrest was defined as the cessation of cardiac mechanical activity as confirmed by the absence of signs of circulation.[14,15] In this study, the arrests were classified into those of presumed cardiac origin and non-cardiac origin, the latter resulting from external causes, respiratory diseases, malignant tumors, strokes, and any other non-cardiac causes based on hospital medical records. Furthermore, external causes were divided into the seven categories: asphyxia, hanging, fall, drowning, traffic injury, drug overuse, and unclassified external causes. These diagnoses were made clinically by the physician in charge, working in collaboration with the EMS personnel.

EMS organization in Osaka

Details of the EMS system in Osaka were described previously.[5] Osaka is the second largest prefecture in Japan with a population of approximately 8.8 million inhabitants in an area of 1892 km^2. In Osaka, there are 34 fire stations with emergency dispatch centers. The EMS system is operated by the local fire stations. When called, an ambulance is dispatched from the nearest fire station. Emergency services are provided 24 hours each day by them, which is single-tiered in 32 stations and two-tiered in two stations. The latter uses medics followed by physicians.

Most highly-trained prehospital emergency care providers are called Emergency Life-Saving Technicians (ELSTs). Usually, each ambulance has a crew of three emergency providers including at least one ELST. They were allowed to insert an intravenous line and an adjunct airway, and to use a semi-automated external defibrillator for OHCA patients. Specially trained ELSTs were permitted to tracheal intubation since July 2004 and administer intravenous epinephrine since April 2006.

Do-not-resuscitate (DNR) orders or living wills are not generally accepted in Japan. EMS providers are not permitted to terminate resuscitation in the field. Therefore, almost patients with OHCA who were treated by EMS personnel were transported to a

hospital and enrolled in the Utstein Osaka Project, excluding those with decapitation, incineration, decomposition, rigor mortis, or dependent cyanosis.

CPR and AED training for the general public

The use of an automated external defibrillator (AED) by citizens was permitted legally in July 2004. In Osaka, approximately 14,000 citizens per year participated in the CPR training programs, consisting of conventional CPR including chest compressions, mouth-to-mouth ventilation, and AED usage by local fire departments, the Japan Red Cross, Inc., and the Osaka Life Support Association.[5] All EMS providers perform CPR according to the Japanese CPR guidelines.[4]

Data collection and quality control

Data collection were prospectively conducted using a form that included data recommended in the Utstein-style reporting guidelines for cardiac arrests.[14,15] These data included gender, age, first documented cardiac rhythm, witness status, location of arrests, activity of daily living (ADL) before arrests, time-courses of resuscitation, type of bystander-initiated CPR, public-access AED use, intravascular fluid, tracheal intubation, and intravascular epinephrine as well as prehospital return of spontaneous

circulation (ROSC), total ROSC, one-month survival, and neurological status one month after the event. First documented rhythm was recorded and diagnosed by the EMS personnel with semi-automated defibrillators on the scene, and confirmed by the physician who was responsible for the on-line medical direction. Bystander CPR included chest compression-only CPR and conventional CPR with rescue breathing. A series of EMS times of call receipt, vehicle arrival at the scene, contact with patients, initiation of CPR, defibrillation by EMS, and hospital arrival were recorded automatically at the dispatch center.

The data form was completed by the EMS personnel in cooperation with the physicians in charge of the patients, and the data were integrated into the registry system on the Information Center for Emergency Medical Services of Osaka, and then checked by the investigators. If the data sheet was incomplete, the relevant EMS personnel were contacted and questioned for data completion.

All survivors suffering OHCA were followed up for up to one-month after the event by the EMS personnel in charge. One-month neurological outcomes were determined by the physician responsible for treating the patient, using the cerebral performance category (CPC) scale: category 1, good cerebral performance; category 2, moderate cerebral disability; category 3, severe cerebral disability; category 4, coma or

vegetative state; and category 5, death.[14,15]

Outcome measures

The main outcome measure was one-month survival. Secondary outcome measures included prehospital and total ROSCs, admission to hospital, and one-month survival with neurologically favorable outcome. Neurologically favorable outcome was defined as CPC category 1 or 2.[14,15]

Statistical analysis

In this study, patient and EMS characteristics of OHCAs with non-cardiac origin and their outcomes were compared between the groups using unpaired analysis of variance for numerical variables, and chi-square test or Fisher's exact test for categorical variables by cause of arrest. First, non-cardiac causes were divided into the following five groups; external causes, respiratory diseases, malignant tumors, strokes, and any other non-cardiac causes. Next, external causes were further divided into asphyxia, hanging, fall, drowning, traffic injury, drug overuse, and unclassified external causes. Age-adjusted annual incidence of OHCAs by non-cardiac origin was calculated by the direct method using 2005 census data and 1985 Japanese model population.[18,19]

Poisson regression models for the trends in the incidence and one-month survival rate were used. Multiple logistic regression analysis assessed the factors associated with one-month survival and neurological favorable outcome, and adjusted odds ratios (AORs) and their 95% confidence intervals (CIs) were calculated. As potential confounders, factors that were biologically essential and considered to be associated with clinical outcomes were taken in the multivariable analyses.[7] These variables included age (20-64, >=65 years old), gender (men, women), witness status (none, witnessed by bystanders), ADL before arrests (good, other), first documented rhythm (VF, non-VF), bystander CPR status (none, compression-only CPR, conventional CPR), type of non-cardiac causes (the 11 categories described above), location of arrests (homes, public places, work places, health care facilities, others), intravascular fluid (yes, no), intubation (yes, no), epinephrine (yes, no), EMS response time (call to contact with patients), and year of arrest. In addition, we conducted a multivariate analysis of one-month survival from OHCAs with non-cardiac origin after dividing the two groups: internal (respiratory diseases, malignant tumors, and strokes) and external (asphyxia, hanging, fall, drowning, traffic injury, and drug overuse) causes.

All statistical analyses were performed using the SPSS statistical package ver21.0J (IBM Corp. Armonk, NY). All of the tests were 2-tailed and *P* values of <0.05 were

considered statistically significant.

RESULTS

Figure 1 shows an overview of the study patients based on the Utstein template. A total of 47,735 adult arrests were documented during these seven years. Resuscitation was attempted in 43,845, and 15,505 of them were of non-cardiac origin. Excluding 1341 victims who were witnessed by EMS (arrests after EMS arrival), 14,164 (5561 in bystander-witnessed cases and 8603 in non-witnessed cases) were eligible for our analyses. Among these arrests, 8239 (58.2%) were due to external causes, 1448 (10.2%) respiratory diseases, 1309 (9.2%) malignant tumors, 1114 (7.9%) strokes, and 2054 (14.5%) others. Among external causes, 2670 (16.5%) were of asphyxia, 1999 (14.1%) hanging, 1300 (9.2%) fall, 1062 (7.5%) drowning, 765 (5.4%) traffic injury, and 256 (1.8%) unclassified external cause.

The age-adjusted annual incidence rates per 100,000 persons by non-cardiac cause were calculated over time (Table 1). The incidence rate of OHCAs with external causes significantly increased from 12.4 in 2005 to 13.3 in 2011 (P for trend=0.024). The incidence rate significantly decreased among OHCA patients with respiratory diseases (from 2.2 in 2005 to 1.6 in 2011, P for trend=0.018) and strokes (from 2.0 in 2005 to 1.3 in 2011, P for trend<0.001). The unadjusted one-month survival rates by non-cardiac cause were almost stable during the study period.

Patient and EMS characteristics of OHCAs with non-cardiac origin according to the cause are shown in Table 2, and their outcomes in Table 4. The mean age of all OHCA patients with non-cardiac origin was 66.8 years and males were 58.0%. The proportion of bystander-witnessed arrests, ADL before arrests, first documented rhythm, type of bystander CPR, and advanced life supports such as intravascular fluid, intubation, and epinephrine exceedingly varied between the five groups. In the whole patients, the rate of one-month survival and neurologically favorable outcome was 5.3% and 1.3%. The proportion of one-month survival was 6.2% in external causes, 6.5% in respiratory diseases, 0.8% in malignant tumors, 4.9% in strokes, and 4.1% in others. Furthermore, patient and EMS characteristics of OHCAs in external causes are shown in Table 3, and their outcomes in Table 5. The characteristics and outcomes varied between the seven groups. The proportion of one-month survival was 14.3% in asphyxia, 4.2% in hanging, 0.7% in fall, 1.1% in submersion, 1.6% in traffic injury, 3.7% in drug overuse, and 1.6% in unclassified external cause. The proportion of bystander chest compression-only CPR and conventional CPR with rescue breathing was 23.2% and 13.1% in whole OHCAs with non-cardiac origin, and 22.1% and 14.3% in bystander-witnessed OHCAs.

Table 6 shows factors contributing to one-month survival and neurologically

favorable outcome after OHCAs with non-cardiac origin. In one-month survival, arrests witnessed by bystanders (AOR 4.13, 95% CI 3.35-5.09), good ADL before arrests (AOR 1.23, 95% CI 1.03-1.47), VF as first documented rhythm (AOR 2.04, 95% CI 1.42-2.92), public places (AOR 1.45, 95% CI 1.10-1.91), intravenous fluid (AOR 1.45, 95% CI 1.14-1.84), and early EMS response time (AOR for one-increment of minute 0.92, 95% CI 0.90-.095) were associated with improving outcome. However, type of bystander CPR, intubation, and epinephrine were not associated with better outcome. Compared with asphyxia, the AORs were significantly lower in respiratory diseases (0.51, 95% CI 0.40-0.65), malignant tumors (0.06, 95% CI 0.03-0.11), stroke (0.27, 95% CI 0.20-0.38), hanging (0.56, 95% CI 0.41-0.77), fall (0.03, 95% CI 0.01-0.06), drowning (0.16, 95% CI 0.09-0.29), and traffic injury (0.05, 95% CI 0.03-0.10). The proportion of one-month survival of the whole OHCAs with non-cardiac origin did not significantly increase (from 4.3% [86/2023] in 2005 to 4.9% [105/2126] in 2011) and the AOR for one-increment of year was 1.01 (95% CI 0.97-1.06). The AORs of neurologically favorable outcome after OHCAs with non-cardiac origin were almost similar to those of one-month survival.

Subgroup analyses after dividing the two groups (internal and external causes) are shown in Supplemental Table. As for internal causes, arrests witnessed by bystanders

(AOR 2.86, 95% CI 1.99-4.11), VF as first documented rhythm (AOR 2.35, 95% CI 1.30-4.24), and public places (AOR 2.01, 95% CI 1.21-3.36) were associated with improving outcome. As for external causes, adults (AOR 1.51, 95% CI 1.17-1.96), arrests witnessed by bystanders (AOR 5.03, 95% CI 3.71-6.81), good ADL before arrests (AOR 1.34, 95% CI 1.08-1.67), intravenous fluid (AOR 1.69, 95% CI 1.27-2.25), and early EMS response time (AOR for one-increment of minute 0.93, 95% CI 0.90-0.96) were associated with improving outcome.

DISCUSSION

The extensive OHCA registry in Osaka showed that one-month survival after OHCAs with non-cardiac origin was poor and the survival trends did not improve year-by-year. In addition, the survivals differed by detailed non-cardiac origin. To further improve survival after OHCAs, sufficient attention should be paid to the epidemiological characteristics of OHCAs with non-cardiac origin as much as those of OHCA with cardiac origin, and this study describing the actual situation regarding the incidence and outcome of OHCAs with non-cardiac origin provides valuable information to improve the survival.

Our study observed that the outcomes of OHCAs with non-cardiac origin were poor and stable during the seven years. In a previous study in Japan, neurologically favorable outcome of bystander-witnessed OHCAs with non-cardiac origin increased from 2005 to 2011, but the absolute survival was very low,[7] and this result was similar with ours. Improving the outcome of OHCAs with non-cardiac origin poses an important problem in resuscitation science because 20~40% of adult OHCAs are of non-cardiac origin.[7-13] In addition, the survivals exceedingly differed by detailed non-cardiac origin, which also suggests the need and importance of an origin-specific strategy for improving the outcomes.

We also showed that the OHCA incidence trends differed by detailed non-cardiac origin. For instance, the incidence rate of OHCAs due to strokes significantly decreased during the study period. Although the reasons for the decrement were unclear, better blood pressure control and decreasing smoking rate in recent years of Japan might be one of the possible explanations for this phenomenon.[20] In fact, the numbers of stroke patients in Japan has also been decreasing.[21] On the other hand, the incidence rates of OHCAs with external causes increased and the outcomes after OHCAs with external causes excluding asphyxia were miserable. For example, external OHCAs due to trauma, drug overdose, or hanging in metropolitan area of Australia were more common and the survivals from traumatic and hanging-associated OHCAs were not always futile. Therefore, there were regional variations on the incidence and outcome from OHCAs with external causes,[22,23] and the countermeasures would differ by regions. However, most importantly, more efforts should focus on prevention of OHCAs with external causes because many of them are preventable.[1-4]

In a multivariable analysis, intravenous fluid administration was associated with better one-month survival after OHCAs with non-cardiac origin. In preceding studies, prehospital intravenous fluid for OHCAs including both cardiac and non-cardiac

origins was not associated with the improved outcome,[24] whereas intravenous access were associated with a reduction in hospital mortality among non-injured, non-cardiac arrest patients.[25] Thus, the effects of fluid administration on prehospital emergency patients were under debate, and further investigations by other cohorts or randomized controlled trials are needed to confirm these associations.

In this study, a multivariate analysis also underscored that either bystander-initiated chest compression-only CPR or conventional CPR with rescue breathing was not effective for OHCAs with non-cardiac origin. From a nationwide study focused on 43,000 bystander-witnessed OHCAs with non-cardiac origin, we demonstrated that conventional CPR with rescue breathing had an incremental benefit for OHCAs with non-cardiac origin, but the impact on the overall survival after OHCA was small.[8] Considering these results, the effectiveness of bystander CPR on OHCAs with non-cardiac origin might be limited. In addition, attempted resuscitation rates in our area was exceedingly higher at 92% compared with those in western countirs,[22,26] which might be also one of the possible explanations for the lack of impact of bystander CPR in our multivariate model. However, as recommended in the CPR guidelines,[1-4] bystander CPR plays a key role in the “chain of survival” and increasing the proportion of bystander CPR for OHCA patients is important.

Furthermore, factors such as arrests witnessed by bystanders and earlier EMS response time were also independent predictors of better outcome after OHCAs with non-cardiac origin in a multivariate analysis. This would indicate the importance of an early EMS activation in the chain of survival[1-4] and suggests that activating the EMS system quickly leads to improving the outcomes after OHCAs with non-cardiac origin. In addition, the verification of the effects on prehospital emergency care as well as in-hospital treatment is essential to improve survival after OHCAs with non-cardiac origin.

The present study has some inherent limitations. First, the category of presumed cardiac or non-cardiac causes is made clinically, as per the Utstein-style international guidelines for cardiac arrest data reporting.[14,15] Second, information on post-arrest care is lacking. In-hospital treatment (e.g., hemodynamic support, cardiovascular intervention, induced hypothermia) might affect survival after OHCA.[27] Third, unmeasured confounding factors may have influenced the association between OHCAs with non-cardiac origin and the outcome.

CONCLUSION

The large OHCA registry in Osaka demonstrated that one-month survival after OHCAs

with non-cardiac origin was poor, the survival trends did not improve year-by-year, and the survivals differed by detailed non-cardiac origin. Further monitoring and discussion for epidemiology and outcome of OHCAs with non-cardiac origin are warranted to improve survival after OHCA in this group.

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Contributors

All authors (TK, KK, TS, TI, CN, KK, TN, YH, YK, KY, and TS) participated in the study conception and design, acquisition of data, analysis and interpretation of data, drafting the article and revising it critically for important intellectual content, and final approval of the manuscript.

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Competing interests

None.

Ethics approval

The study was approved by the institutional review board of Osaka University with the assent of the EMS authorities of the local governments in Osaka Prefecture.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data sharing statement

TK had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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4

Figure Legends

Figure 1 Overview of EMS-treated cardiac arrests with an abridged Utstein template from January 1, 2005 to December 31, 2011. EMS, emergency medical service.

Table 1 Age-adjusted incidences and unadjusted one-month survival rate of out-of-hospital cardiac arrests with non-cardiac origin according to the cause over time

	2005	2006	2007	2008	2009	2010	2011	P for trend
Age-adjusted Incidence per 100,000 persons								
External causes	12.4	12.3	13.2	12.8	13.2	13.3	13.3	0.024
Asphyxia	2.7	3.0	2.8	3.4	3.1	2.9	2.9	0.726
Hanging	3.4	3.4	4.1	3.4	3.7	3.9	3.9	0.158
Fall	2.4	2.5	3.1	2.4	2.9	3.0	2.7	0.396
Drowning	1.2	1.1	1.2	1.4	1.2	1.3	1.6	0.065
Traffic injury	1.6	1.5	1.4	1.4	1.4	1.5	1.4	0.229
Drug overdose	0.5	0.4	0.2	0.4	0.4	0.4	0.3	0.304
Unclassified	0.5	0.5	0.4	0.3	0.5	0.4	0.5	0.447
Respiratory diseases	2.2	1.8	1.8	1.7	1.3	1.3	1.6	0.018
Malignant tumors	1.6	1.8	1.8	1.7	1.5	1.3	1.6	0.109
Strokes	2.0	1.8	1.8	1.6	1.4	1.2	1.3	< 0.001
Others	2.7	3.3	3.1	2.9	2.7	2.5	2.4	0.087
Unadjusted one-month survival, % (n/N)								
External causes	4.8 (53/1100)	6.8 (72/1059)	5.7 (66/1164)	7.2 (85/1184)	7.1 (86/1207)	6.1 (75/1225)	5.6 (73/1300)	0.736
Asphyxia	10.4 (35/337)	15.4 (53/344)	13.0 (44/338)	15.6 (67/430)	16.3 (66/406)	14.8 (58/393)	14.0 (59/422)	0.374
Hanging	4.6 (12/261)	4.7 (12/255)	5 (16/318)	4.8 (13/273)	4.9 (14/287)	3.3 (10/301)	2.3 (7/304)	0.101
Fall	0.6 (1/159)	0.6 (1/169)	0.9 (2/219)	1.2 (2/165)	0.0 (0/197)	0.5 (1/208)	1.1 (2/183)	NA
Drowning	1.3 (2/151)	3.3 (4/120)	0.0 (0/128)	1.3 (2/159)	2.1 (3/144)	0.7 (1/148)	0.0 (0/212)	NA
Traffic injury	0.9 (1/116)	1.0 (1/101)	1.8 (2/109)	0.9 (1/106)	1.9 (2/103)	1.7 (2/115)	2.6 (3/115)	0.027

Drug overdose	3.0 (1/33)	0.0 (0/29)	5.6 (1/18)	0.0 (0/25)	3.3 (1/30)	11.1 (3/27)	4.0 (1/25)	NA
Unclassified	2.3 (1/43)	2.4 (1/41)	2.9 (1/34)	0.0 (0/26)	0.0 (0/40)	0.0 (0/33)	2.6 (1/39)	NA
Respiratory diseases	6.4 (17/267)	3.9 (8/206)	8.0 (17/212)	9.8 (21/214)	6.7 (11/165)	4.7 (8/169)	5.6 (12/215)	0.875
Malignant tumors	0.5 (1/186)	0.5 (1/194)	1.0 (2/202)	1.0 (2/196)	0.0 (0/178)	2.5 (4/159)	0.5 (1/194)	NA
Strokes	3.6 (7/196)	6.1 (11/179)	4.5 (8/176)	3.2 (5/154)	4.9 (7/143)	6.0 (8/134)	6.8 (9/132)	0.241
Others	2.9 (8/277)	7.0 (22/314)	1.3 (4/308)	4.5 (14/311)	4.3 (12/278)	5.3 (15/281)	3.5 (10/285)	0.808

NA indicates not analyzed.

Table 2 Patient and EMS characteristics of out-of-hospital cardiac arrests with non-cardiac origin according to the cause

	Total (n =14,164)		External causes (n = 8239)		Respiratory diseases (n =1448)		Malignant tumors (n =1309)		Strokes (n =1114)		Others (n =2054)		*P* value*
Age, yr, mean (SD)	66.8	(19.0)	63.5	(20.5)	76.1	(14.2)	71.9	(12.0)	67.7	(14.7)	69.8	(17.6)	< 0.001
Age group, n (%)													< 0.001
Adults aged 20-64 years	5513	(38.9)	3826	(46.4)	229	(15.8)	345	(26.4)	447	(40.1)	666	(32.4)	
Elderly aged >=65 years	8651	(61.1)	4413	(53.6)	1219	(84.2)	964	(73.6)	667	(59.9)	1388	(67.6)	
Men, n (%)	8215	(58.0)	4789	(58.1)	844	(58.3)	881	(67.3)	559	(50.2)	1142	(55.6)	< 0.001
Arrests witnessed by bystanders, n (%)	5561	(39.3)	2952	(35.8)	682	(47.1)	639	(48.8)	493	(44.3)	795	(38.7)	< 0.001
Good activities of daily living, n (%)	8522	(60.2)	5213	(63.3)	653	(45.1)	443	(33.8)	896	(80.4)	1317	(64.1)	< 0.001
First documented rhythm, n (%)													< 0.001
VF	324	(2.3)	119	(1.4)	35	(2.4)	26	(2.0)	69	(6.2)	75	(3.7)	
PEA	3356	(23.7)	1853	(22.5)	394	(27.2)	262	(20.0)	329	(29.5)	518	(25.2)	
Asystole	10196	(72.0)	6124	(74.3)	983	(67.9)	1008	(77.0)	647	(58.1)	1434	(69.8)	
Others	288	(2.0)	143	(1.7)	36	(2.5)	13	(1.0)	69	(6.2)	27	(1.3)	
Location of arrest, n (%)													< 0.001
Homes	9010	(63.6)	4435	(53.8)	1098	(75.8)	1217	(93.0)	801	(71.9)	1459	(71.0)	
Public places	2035	(14.4)	1608	(19.5)	59	(4.1)	24	(1.8)	156	(14.0)	188	(9.2)	
Work places	346	(2.4)	223	(2.7)	7	(0.5)	4	(0.3)	48	(4.3)	64	(3.1)	
Health care facilities	1505	(10.6)	904	(11.0)	248	(17.1)	55	(4.2)	63	(5.7)	235	(11.4)	
Others	1268	(9.0)	1069	(13.0)	36	(2.5)	9	(0.7)	46	(4.1)	108	(5.3)	
Public-access AED use, n (%)	13	(0.1)	4	(0.05)	2	(0.1)	0	(0.0)	5	(0.4)	2	(0.1)	0.001
Type of Bystander CPR, n (%)													< 0.001
No CPR	9023	(63.7)	5383	(65.3)	836	(57.7)	889	(67.9)	633	(56.8)	1282	(62.4)	
Chest compression-only CPR	3288	(23.2)	1811	(22.0)	408	(28.2)	297	(22.7)	283	(25.4)	489	(23.8)	

Conventional CPR with rescue breathing	1853	(13.1)	1045	(12.7)	204	(14.1)	123	(9.4)	198	(17.8)	283	(13.8)		
Intravascular fluid, n (%)	2320	(16.4)	1458	(17.7)	202	(14.0)	113	(8.6)	230	(20.6)	317	(15.4)	<	0.001
Intubation, n (%)	2639	(18.6)	1364	(16.6)	338	(23.3)	242	(18.5)	257	(23.1)	438	(21.3)	<	0.001
Epinephrine, n (%)	987	(7.0)	572	(6.9)	88	(6.1)	49	(3.7)	125	(11.2)	153	(7.4)	<	0.001
Call to contact with a patient by EMS (EMS response time), min, mean (SD)	7.9	(4.1)	8.0	(4.6)	7.7	(3.0)	7.7	(2.7)	7.7	(2.8)	7.9	(3.8)		0.003
Call to CPR by EMS, min, mean (SD)	8.5	(4.5)	8.8	(5.1)	8.1	(3.1)	8.1	(2.8)	8.2	(2.9)	8.4	(4.2)	<	0.001
Call to hospital arrival, min, mean (SD)	28.2	(8.6)	28.4	(8.6)	27.3	(8.2)	28.0	(8.9)	28.2	(8.4)	28.1	(8.7)		0.001

*P values are calculated to test the homogeneity among the 5 cause groups.

EMS indicates emergency medical services; CPR, cardiopulmonary resuscitation; VF, ventricular fibrillation; PEA, pulseless electrical activity; AED, automated external defibrillator; SD, standard deviation.

Table 3 Patient and EMS characteristics of out-of-hospital cardiac arrests with external causes according to the cause

	Asphyxia (n = 2670)		Hanging (n = 1999)		Fall (n = 1300)		Drowning (n = 1062)		Traffic injury (n = 765)		Drug overdose (n = 187)		Unclassified (n = 256)		*P* value*
Age, yr, mean (SD)	77.9	(14.4)	55.6	(17.4)	47.4	(17.4)	73.1	(14.8)	52.6	(19.0)	49.9	(19.5)	58.1	(19.3)	< 0.001
Age group, n (%)															< 0.001
Adults aged 20-64 years	403	(15.1)	1136	(66.8)	1055	(81.2)	210	(19.8)	523	(68.4)	141	(75.4)	158	(61.7)	
Elderly aged >=65 years	2267	(84.9)	663	(33.2)	245	(18.8)	852	(80.2)	242	(31.6)	46	(24.6)	98	(38.3)	
Men, n (%)	1345	(50.4)	1290	(64.5)	781	(60.1)	530	(49.9)	558	(72.9)	117	(62.6)	168	(65.6)	< 0.001
Arrests witnessed by bystanders, n (%)	1801	(67.5)	27	(1.4)	510	(39.2)	56	(5.3)	476	(62.2)	10	(5.3)	72	(28.1)	< 0.001
Good activities of daily living, n (%)	1099	(41.2)	1769	(88.5)	685	(52.7)	854	(80.4)	517	(67.6)	133	(71.1)	156	(60.9)	< 0.001
First documented rhythm, n (%)															< 0.001
VF	56	(2.1)	13	(0.7)	19	(1.5)	12	(1.1)	14	(1.8)	1	(0.5)	4	(1.6)	
PEA	960	(36.0)	198	(9.9)	274	(21.1)	72	(6.8)	259	(33.9)	20	(10.7)	70	(27.3)	
Asystole	1589	(59.5)	1775	(88.8)	985	(75.8)	970	(91.3)	469	(61.3)	160	(85.6)	176	(68.8)	
Others	65	(2.4)	13	(0.7)	22	(1.7)	8	(0.8)	23	(3.0)	6	(3.2)	6	(2.3)	
Location of arrest, n (%)															< 0.001
Homes	1596	(59.8)	1667	(83.4)	139	(10.7)	770	(72.5)	2	(0.3)	150	(80.2)	111	(43.4)	
Public places	139	(5.2)	86	(4.3)	553	(42.5)	83	(7.8)	677	(88.5)	14	(7.5)	56	(21.9)	
Workplaces	35	(1.3)	94	(4.7)	44	(3.4)	3	(0.3)	7	(0.9)	7	(3.7)	33	(12.9)	
Health care facilities	835	(31.3)	27	(1.4)	12	(0.9)	14	(1.3)	1	(0.1)	0	(0.0)	15	(5.9)	
Others	65	(2.4)	125	(6.3)	552	(42.5)	192	(18.1)	78	(10.2)	16	(8.6)	41	(16.0)	

Public-access AED use, n (%)	4	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0.214
Type of Bystander CPR, n (%)															< 0.001
No CPR	1386	(51.9)	1174	(58.7)	1191	(91.6)	608	(57.3)	673	(88.0)	154	(82.4)	197	(77.0)	
Chest compression-only CPR	748	(28.0)	549	(27.5)	93	(7.2)	281	(26.5)	74	(9.7)	23	(12.3)	43	(16.8)	
Conventional CPR with rescue breathing	536	(20.1)	276	(13.8)	16	(1.2)	173	(16.3)	18	(2.4)	10	(5.3)	16	(6.2)	
Intravascular fluid, n (%)	540	(20.2)	393	(19.7)	107	(8.2)	281	(26.5)	76	(9.9)	27	(14.4)	34	(13.3)	< 0.001
Intubation, n (%)	800	(30.0)	167	(8.4)	41	(3.2)	251	(23.6)	31	(4.1)	33	(17.6)	41	(16.0)	< 0.001
Epinephrine, n (%)	326	(12.2)	83	(4.2)	41	(3.2)	68	(6.4)	37	(4.8)	6	(3.2)	11	(4.3)	< 0.001
Call to contact with a patient by EMS (EMS response time), min, mean (SD)	7.6	(2.9)	7.8	(3.3)	7.4	(3.3)	9.4	(7.6)	7.6	(4.2)	14.2	(10.7)	9.4	(7.3)	< 0.001
Call to CPR by EMS personnel, min, mean (SD)	7.9	(3.1)	8.6	(3.9)	8.2	(3.8)	10.0	(7.5)	9.3	(5.9)	14.4	(10.0)	11.0	(8.7)	< 0.001
Call to hospital arrival, min, mean (SD)	28.6	(8.6)	28.2	(7.9)	27.5	(8.3)	29.1	(9.3)	27.1	(8.8)	32.1	(11.1)	29.5	(9.4)	< 0.001

*P values are calculated to test the homogeneity among the 7 cause groups.

EMS indicates emergency medical services; CPR, cardiopulmonary resuscitation; VF, ventricular fibrillation; PEA, pulseless electrical activity; AED, automated external defibrillator; SD, standard deviation.

Table 4 Outcomes after out-of-hospital cardiac arrests with non-cardiac origin according to the cause

	Total (n = 1,4164)	External causes (n = 8239)	Respiratory diseases (n = 1448)	Malignant tumors (n = 1309)	Strokes (n = 1114)	Others (n =2054)	*P* value*
Prehospital ROSC, n (%)	1229 (8.7)	703 (8.5)	114 (7.9)	57 (4.4)	216 (19.4)	139 (6.8)	< 0.001
Total ROSC, n (%)	4744 (33.5)	2638 (32.0)	620 (42.8)	234 (17.9)	650 (58.3)	602 (29.3)	< 0.001
Hospital admission, n (%)	4142 (29.2)	2356 (28.6)	530 (36.6)	173 (13.2)	585 (52.5)	498 (24.2)	< 0.001
One-month survival, n (%)	755 (5.3)	510 (6.2)	94 (6.5)	11 (0.8)	55 (4.9)	85 (4.1)	< 0.001
Neurologically favorable outcome, n (%)	188 (1.3)	105 (1.3)	27 (1.9)	2 (0.2)	17 (1.5)	37 (1.8)	< 0.001

*P values are calculated to test the homogeneity among the 5 cause groups.

ROSC indicates return of spontaneous circulation.

Table 5 Outcomes after out-of-hospital cardiac arrests with external causes according to the cause

	Asphyxia (n = 2670)	Hanging (n = 1999)	Fall (n = 1300)	Drowning (n = 1062)	Traffic injury (n = 765)	Drug overdose (n = 187)	Unclassified (n = 256)	*P* value*
Prehospital ROSC, n (%)	463 (17.3)	144 (7.2)	22 (1.7)	36 (3.4)	28 (3.7)	4 (2.1)	6 (2.3)	< 0.001
Total ROSC, n (%)	1003 (37.6)	1500 (75.0)	1213 (93.3)	894 (84.2)	637 (83.3)	143 (76.5)	211 (82.4)	< 0.001
Hospital admission, n (%)	1529 (57.3)	453 (22.7)	62 (4.8)	147 (13.8)	92 (12.0)	40 (21.4)	33 (12.9)	< 0.001
One-month survival, n (%)	382 (14.3)	84 (4.2)	9 (0.7)	12 (1.1)	12 (1.6)	7 (3.7)	4 (1.6)	< 0.001
Neurologically favorable outcome, n (%)	71 (2.7)	17 (0.9)	1 (0.1)	4 (0.4)	6 (0.8)	4 (2.1)	2 (0.8)	< 0.001

*P values are calculated to test the homogeneity among the 7 cause groups.

ROSC indicates return of spontaneous circulation.

Table 6 Factors associated with outcomes after out-of-Hospital cardiac arrests with non-cardiac origin

	One-month survival				Neurologically favorable outcome			
	Crude OR	(95% CI)	Adjusted OR	(95% CI)	Crude OR	(95% CI)	Adjusted OR	(95% CI)
Adults (versus elderly)	0.95	(0.82-1.10)	1.36	(1.12-1.65)	1.02	(0.76-1.37)	1.52	(1.07-2.15)
Men	0.75	(0.64-0.88)	0.99	(0.84-1.16)	1.09	(0.81-1.46)	0.91	(0.67-1.24)
Witnessed by bystanders	4.41	(3.74-5.19)	4.13	(3.35-5.09)	4.48	(3.23-6.21)	4.83	(3.21-7.29)
Good activities of daily living	0.93	(0.80-1.08)	1.23	(1.03-1.47)	1.39	(1.02-1.88)	1.43	(1.02-2.02)
VF	2.74	(1.96-3.82)	2.04	(1.42-2.92)	7.72	(5.05-11.79)	5.40	(3.40-8.59)
Type of bystander CPR								
No CPR	Reference		Reference		Reference		Reference	
Chest compression-only CPR	0.97	(0.81-1.16)	0.80	(0.66-0.98)	0.95	(0.67-1.35)	0.92	(0.64-1.33)
Conventional CPR with rescue breathing	1.47	(1.20-1.79)	1.07	(0.86-1.34)	1.01	(0.65-1.55)	0.89	(0.56-1.42)
Type of non-cardiac origin								
Respiratory diseases	0.42	(0.33-0.53)	0.51	(0.40-0.65)	0.70	(0.44-1.09)	0.76	(0.48-1.21)
Malignant tumors	0.05	(0.03-0.09)	0.06	(0.03-0.11)	0.06	(0.01-0.23)	0.06	(0.01-0.23)
Strokes	0.31	(0.23-0.42)	0.27	(0.20-0.38)	0.57	(0.33-0.97)	0.34	(0.19-0.61)
Asphyxia	Reference		Reference		Reference		Reference	
Hanging	0.26	(0.21-0.34)	0.56	(0.41-0.77)	0.31	(0.18-0.53)	0.55	(0.28-1.07)
Fall	0.04	(0.02-0.08)	0.03	(0.01-0.06)	0.03	(0.004-0.20)	0.01	(0.002-0.11)
Drowning	0.07	(0.04-0.12)	0.16	(0.09-0.29)	0.14	(0.05-0.38)	0.31	(0.11-0.90)

Traffic injury	0.10	(0.05-0.17)	0.05	(0.03-0.10)	0.29	(0.13-0.67)	0.10	(0.04-0.26)
Drug overdose	0.23	(0.11-0.50)	0.58	(0.26-1.29)	0.80	(0.29-2.21)	1.74	(0.58-5.19)
Others	0.26	(0.20-0.33)	0.29	(0.22-0.38)	0.67	(0.45-1.00)	0.60	(0.39-0.92)
Unclassified	0.10	(0.04-0.26)	0.10	(0.04-0.28)	0.29	(0.07-1.18)	0.27	(0.06-1.16)
Location of arrest								
Homes	Reference		Reference		Reference		Reference	
Public places	0.78	(0.61-0.99)	1.45	(1.10-1.91)	1.11	(0.75-1.65)	1.54	(0.97-2.44)
Workplaces	1.29	(0.83-1.98)	1.40	(0.87-2.23)	1.26	(0.55-2.89)	0.95	(0.39-2.30)
Health care facilities	1.69	(1.38-2.07)	0.88	(0.69-1.12)	0.72	(0.42-1.24)	0.47	(0.26-0.85)
Others	0.70	(0.51-0.94)	1.67	(1.19-2.35)	0.68	(0.38-1.24)	1.35	(0.72-2.54)
Intravascular fluid	1.78	(1.50-2.11)	1.45	(1.14-1.84)	1.34	(0.94-1.91)	1.52	(0.97-2.38)
Intubation	1.62	(1.37-1.92)	1.02	(0.84-1.23)	0.73	(0.48-1.10)	0.50	(0.32-0.77)
Epinephrine	2.32	(1.87-2.88)	0.97	(0.71-1.32)	1.25	(0.74-2.09)	0.60	(0.31-1.17)
EMS response time (for one-increment of minute)	0.93	(0.91-0.96)	0.92	(0.90-0.95)	0.91	(0.86-0.96)	0.90	(0.84-0.95)
Year (for one-increment of year)	1.02	(0.98-1.06)	1.01	(0.97-1.06)	1.02	(0.95-1.09)	1.05	(0.97-1.13)

VF denotes ventricular fibrillation; CPR, cardiopulmonary resuscitation; EMS, emergency medical services; OR, odds ratio; CI, confidence interval.

Epidemiology and outcome of out-of-hospital cardiac arrest with non-cardiac origin in Osaka: a population-based study

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ABSTRACT

Objectives: To evaluate epidemiological characteristics of out-of-hospital cardiac arrests (OHCAs) by detailed non-cardiac cause and factors associated with the outcomes after OHCAs with non-cardiac origin.

Design: A prospective, population-based observational study.

Setting: The Utstein Osaka Project.

Participants: 14,164 adult patients with OHCAs due to non-cardiac origin who were resuscitated by emergency-medical-service personnel or bystanders, and then were transported to medical institutions from January 2005 to December 2011.

Primary outcome measures: One-month survival after OHCA. Multiple logistic regression analysis was used to assess factors that were potentially associated with the outcome.

Results: During the study period, the one-month survival rate was 5.3% (755/14,164). The proportion of one-month survival was 6.2% (510/8239) in external causes, 6.5% (94/1148) in respiratory diseases, 0.8% (11/1309) in malignant tumors, 4.9% (55/1114) in strokes, and 4.1% (85/2054) in others. As for external causes, the proportion of one-month survival was 14.3% (382/2670) in asphyxia, 4.2% (84/1999) in hanging, 0.7% (9/1300) in fall, 1.1% (12/1062) in drowning, 1.6% (12/765) in traffic injury,

3.7% (7/187) in drug overuse, and 1.6% (4/256) in unclassified external causes. In a multivariate analysis, arrests witnessed by bystanders, good activities of daily living before arrests, ventricular fibrillation arrests, public places, intravenous fluid, and early emergency-medical-service response time were significant predictors for one-month outcome after OHCAs with cardiac origin. The proportion of one-month survival of the whole OHCAs with non-cardiac origin did not significantly increase (from 4.3% [86/2023] in 2005 to 4.9% [105/2126] in 2011) and the adjusted odds ratio for one-increment of year was 1.01 (95% confidence interval 0.97-1.06).

Conclusions: From a large OHCA registry in Osaka, we demonstrated that one-month survival after OHCAs with non-cardiac origin was poor and stable.

Strengths and limitations of this study

- This study showed that one-month survival after OHCAs with non-cardiac origin was poor and the survival trends did not improve year-by-year in Osaka during the study period from 2005 to 2011. In addition, the survivals exceedingly differed by detailed non-cardiac origin.
- The category of presumed non-cardiac causes is made clinically, as per the Utstein-style international guidelines for cardiac arrest data reporting.

INTRODUCTION

Out-of-hospital cardiac arrest (OHCA) is one of the leading causes of death in the industrialized world.[1-4] Although improvements in the chain of survival including the development of a public-access defibrillation system and revisions to cardiopulmonary resuscitation (CPR) guidelines have led to increased survival after OHCA with cardiac origin in some communities,[5-7] the outcome after OHCAs with non-cardiac origin remains generally poor.[7-13]

Importantly, 20% to 40% of adult OHCAs were reportedly of non-cardiac origin.[7-13] However, epidemiological characteristics of OHCA with non-cardiac origin have not been sufficiently investigated as much as those of OHCA with cardiac origin. Therefore, the evaluation of characteristics, trends, and outcomes by detailed non-cardiac cause and understanding the factors associated with the outcomes are needed to improve the survival after OHCAs with non-cardiac origin.

The Utstein Osaka Project is a large prospective population-based cohort study of OHCA in Osaka, Japan, covering about 8.8 million residents.[5] During the 7 years from 2005 to 2011, we enrolled approximately 14,000 OHCAs with non-cardiac origin before emergency-medical-service (EMS) arrival. The present study aimed to evaluate the epidemiological characteristics of OHCAs by detailed non-cardiac cause. In

addition, we evaluated factors associated with the outcomes after OHCAs with non-cardiac origin in a multivariate analysis.

METHODS

Study design and setting

The Utstein Osaka Project is a prospective, population-based registry of OHCA that is based on the standardized Utstein style.[14,15] This study enrolled adult patients aged =>20 years suffering OHCAs with non-cardiac origin before EMS arrival, who were resuscitated by EMS personnel or bystanders, and were transported to medical institutions in Osaka Prefecture from January 1, 2005 to December 31, 2011. In this study, we excluded pediatric OHCA patients because characteristics and outcomes from OHCAs differed between children and adults.[16,17]

Cardiac arrest was defined as the cessation of cardiac mechanical activity as confirmed by the absence of signs of circulation.[14,15] In this study, the arrests were classified into those of presumed cardiac origin and non-cardiac origin, the latter resulting from external causes, respiratory diseases, malignant tumors, strokes, and any other non-cardiac causes based on hospital medical records. Furthermore, external causes were divided into the seven categories: asphyxia, hanging, fall, drowning, traffic injury, drug overuse, and unclassified external causes. These diagnoses were made clinically by the physician in charge, working in collaboration with the EMS personnel.

EMS organization in Osaka

Details of the EMS system in Osaka were described previously.[5] Osaka is the second largest prefecture in Japan with a population of approximately 8.8 million inhabitants in an area of 1892 km^2. In Osaka, there are 34 fire stations with emergency dispatch centers. The EMS system is operated by the local fire stations. When called, an ambulance is dispatched from the nearest fire station. Emergency services are provided 24 hours each day by them, which is single-tiered in 32 stations and two-tiered in two stations. The latter uses medics followed by physicians.

Most highly-trained prehospital emergency care providers are called Emergency Life-Saving Technicians (ELSTs). Usually, each ambulance has a crew of three emergency providers including at least one ELST. They were allowed to insert an intravenous line and an adjunct airway, and to use a semi-automated external defibrillator for OHCA patients. Specially trained ELSTs were permitted to tracheal intubation since July 2004 and administer intravenous epinephrine since April 2006.

Do-not-resuscitate (DNR) orders or living wills are not generally accepted in Japan. EMS providers are not permitted to terminate resuscitation in the field. Therefore, almost patients with OHCA who were treated by EMS personnel were transported to a

hospital and enrolled in the Utstein Osaka Project, excluding those with decapitation, incineration, decomposition, rigor mortis, or dependent cyanosis.

CPR and AED training for the general public

The use of an automated external defibrillator (AED) by citizens was permitted legally in July 2004. In Osaka, approximately 14,000 citizens per year participated in the CPR training programs, consisting of conventional CPR including chest compressions, mouth-to-mouth ventilation, and AED usage by local fire departments, the Japan Red Cross, Inc., and the Osaka Life Support Association.[5] All EMS providers perform CPR according to the Japanese CPR guidelines.[4]

Data collection and quality control

Data collection were prospectively conducted using a form that included data recommended in the Utstein-style reporting guidelines for cardiac arrests.[14,15] These data included gender, age, first documented cardiac rhythm, witness status, location of arrests, activity of daily living (ADL) before arrests, time-courses of resuscitation, type of bystander-initiated CPR, public-access AED use, intravascular fluid, tracheal intubation, and intravascular epinephrine as well as prehospital return of spontaneous

circulation (ROSC), total ROSC, one-month survival, and neurological status one month after the event. First documented rhythm was recorded and diagnosed by the EMS personnel with semi-automated defibrillators on the scene, and confirmed by the physician who was responsible for the on-line medical direction. Bystander CPR included chest compression-only CPR and conventional CPR with rescue breathing. A series of EMS times of call receipt, vehicle arrival at the scene, contact with patients, initiation of CPR, defibrillation by EMS, and hospital arrival were recorded automatically at the dispatch center.

The data form was completed by the EMS personnel in cooperation with the physicians in charge of the patients, and the data were integrated into the registry system on the Information Center for Emergency Medical Services of Osaka, and then checked by the investigators. If the data sheet was incomplete, the relevant EMS personnel were contacted and questioned for data completion.

All survivors suffering OHCA were followed up for up to one-month after the event by the EMS personnel in charge. One-month neurological outcomes were determined by the physician responsible for treating the patient, using the cerebral performance category (CPC) scale: category 1, good cerebral performance; category 2, moderate cerebral disability; category 3, severe cerebral disability; category 4, coma or

vegetative state; and category 5, death.[14,15]

Outcome measures

The main outcome measure was one-month survival. Secondary outcome measures included prehospital and total ROSCs, admission to hospital, and one-month survival with neurologically favorable outcome. Neurologically favorable outcome was defined as CPC category 1 or 2.[14,15]

Statistical analysis

In this study, patient and EMS characteristics of OHCAs with non-cardiac origin and their outcomes were compared between the groups using unpaired analysis of variance for numerical variables, and chi-square test or Fisher's exact test for categorical variables by cause of arrest. First, non-cardiac causes were divided into the following five groups; external causes, respiratory diseases, malignant tumors, strokes, and any other non-cardiac causes. Next, external causes were further divided into asphyxia, hanging, fall, drowning, traffic injury, drug overuse, and unclassified external causes. Age-adjusted annual incidence of OHCAs by non-cardiac origin was calculated by the direct method using 2005 census data and 1985 Japanese model population.[18,19]

Poisson regression models for the trends in the incidence and one-month survival rate were used. Multiple logistic regression analysis assessed the factors associated with one-month survival and neurological favorable outcome, and adjusted odds ratios (AORs) and their 95% confidence intervals (CIs) were calculated. As potential confounders, factors that were biologically essential and considered to be associated with clinical outcomes were taken in the multivariable analyses.[7] These variables included age (20-64, >=65 years old), gender (men, women), witness status (none, witnessed by bystanders), ADL before arrests (good, other), first documented rhythm (VF, non-VF), bystander CPR status (none, compression-only CPR, conventional CPR), type of non-cardiac causes (the 11 categories described above), location of arrests (homes, public places, work places, health care facilities, others), intravascular fluid (yes, no), intubation (yes, no), epinephrine (yes, no), EMS response time (call to contact with patients), and year of arrest. In addition, we conducted a multivariate analysis of one-month survival from OHCAs with non-cardiac origin after dividing the two groups: internal (respiratory diseases, malignant tumors, and strokes) and external (asphyxia, hanging, fall, drowning, traffic injury, and drug overuse) causes.

All statistical analyses were performed using the SPSS statistical package ver21.0J (IBM Corp. Armonk, NY). All of the tests were 2-tailed and *P* values of <0.05 were

considered statistically significant.

RESULTS

Figure 1 shows an overview of the study patients based on the Utstein template. A total of 47,735 adult arrests were documented during these seven years. Resuscitation was attempted in 43,845, and 15,505 of them were of non-cardiac origin. Excluding 1341 victims who were witnessed by EMS (arrests after EMS arrival), 14,164 (5561 in bystander-witnessed cases and 8603 in non-witnessed cases) were eligible for our analyses. Among these arrests, 8239 (58.2%) were due to external causes, 1448 (10.2%) respiratory diseases, 1309 (9.2%) malignant tumors, 1114 (7.9%) strokes, and 2054 (14.5%) others. Among external causes, 2670 (16.5%) were of asphyxia, 1999 (14.1%) hanging, 1300 (9.2%) fall, 1062 (7.5%) drowning, 765 (5.4%) traffic injury, and 256 (1.8%) unclassified external cause.

The age-adjusted annual incidence rates per 100,000 persons by non-cardiac cause were calculated over time (Table 1). The incidence rate of OHCAs with external causes significantly increased from 12.4 in 2005 to 13.3 in 2011 (P for trend=0.024). The incidence rate significantly decreased among OHCA patients with respiratory diseases (from 2.2 in 2005 to 1.6 in 2011, P for trend=0.018) and strokes (from 2.0 in 2005 to 1.3 in 2011, P for trend<0.001). The unadjusted one-month survival rates by non-cardiac cause were almost stable during the study period.

Patient and EMS characteristics of OHCAs with non-cardiac origin according to the cause are shown in Table 2, and their outcomes in Table 4. The mean age of all OHCA patients with non-cardiac origin was 66.8 years and males were 58.0%. The proportion of bystander-witnessed arrests, ADL before arrests, first documented rhythm, type of bystander CPR, and advanced life supports such as intravascular fluid, intubation, and epinephrine exceedingly varied between the five groups. In the whole patients, the rate of one-month survival and neurologically favorable outcome was 5.3% and 1.3%. The proportion of one-month survival was 6.2% in external causes, 6.5% in respiratory diseases, 0.8% in malignant tumors, 4.9% in strokes, and 4.1% in others. Furthermore, patient and EMS characteristics of OHCAs in external causes are shown in Table 3, and their outcomes in Table 5. The characteristics and outcomes varied between the seven groups. The proportion of one-month survival was 14.3% in asphyxia, 4.2% in hanging, 0.7% in fall, 1.1% in submersion, 1.6% in traffic injury, 3.7% in drug overuse, and 1.6% in unclassified external cause. The proportion of bystander chest compression-only CPR and conventional CPR with rescue breathing was 23.2% and 13.1% in whole OHCAs with non-cardiac origin, and 22.1% and 14.3% in bystander-witnessed OHCAs.

Table 6 shows factors contributing to one-month survival and neurologically

favorable outcome after OHCAs with non-cardiac origin. In one-month survival, arrests witnessed by bystanders (AOR 4.13, 95% CI 3.35-5.09), good ADL before arrests (AOR 1.23, 95% CI 1.03-1.47), VF as first documented rhythm (AOR 2.04, 95% CI 1.42-2.92), public places (AOR 1.45, 95% CI 1.10-1.91), intravenous fluid (AOR 1.45, 95% CI 1.14-1.84), and early EMS response time (AOR for one-increment of minute 0.92, 95% CI 0.90-.095) were associated with improving outcome. However, type of bystander CPR, intubation, and epinephrine were not associated with better outcome. Compared with asphyxia, the AORs were significantly lower in respiratory diseases (0.51, 95% CI 0.40-0.65), malignant tumors (0.06, 95% CI 0.03-0.11), stroke (0.27, 95% CI 0.20-0.38), hanging (0.56, 95% CI 0.41-0.77), fall (0.03, 95% CI 0.01-0.06), drowning (0.16, 95% CI 0.09-0.29), and traffic injury (0.05, 95% CI 0.03-0.10). The proportion of one-month survival of the whole OHCAs with non-cardiac origin did not significantly increase (from 4.3% [86/2023] in 2005 to 4.9% [105/2126] in 2011) and the AOR for one-increment of year was 1.01 (95% CI 0.97-1.06). The AORs of neurologically favorable outcome after OHCAs with non-cardiac origin were almost similar to those of one-month survival.

Subgroup analyses after dividing the two groups (internal and external causes) are shown in Supplemental Table. As for internal causes, arrests witnessed by bystanders

(AOR 2.86, 95% CI 1.99-4.11), VF as first documented rhythm (AOR 2.35, 95% CI 1.30-4.24), and public places (AOR 2.01, 95% CI 1.21-3.36) were associated with improving outcome. As for external causes, adults (AOR 1.51, 95% CI 1.17-1.96), arrests witnessed by bystanders (AOR 5.03, 95% CI 3.71-6.81), good ADL before arrests (AOR 1.34, 95% CI 1.08-1.67), intravenous fluid (AOR 1.69, 95% CI 1.27-2.25), and early EMS response time (AOR for one-increment of minute 0.93, 95% CI 0.90-0.96) were associated with improving outcome.

DISCUSSION

The extensive OHCA registry in Osaka showed that one-month survival after OHCAs with non-cardiac origin was poor and the survival trends did not improve year-by-year. In addition, the survivals differed by detailed non-cardiac origin. To further improve survival after OHCAs, sufficient attention should be paid to the epidemiological characteristics of OHCAs with non-cardiac origin as much as those of OHCA with cardiac origin, and this study describing the actual situation regarding the incidence and outcome of OHCAs with non-cardiac origin provides valuable information to improve the survival.

Our study observed that the outcomes of OHCAs with non-cardiac origin were poor and stable during the seven years. In a previous study in Japan, neurologically favorable outcome of bystander-witnessed OHCAs with non-cardiac origin increased from 2005 to 2011, but the absolute survival was very low,[7] and this result was similar with ours. Improving the outcome of OHCAs with non-cardiac origin poses an important problem in resuscitation science because 20~40% of adult OHCAs are of non-cardiac origin.[7-13] In addition, the survivals exceedingly differed by detailed non-cardiac origin, which also suggests the need and importance of an origin-specific strategy for improving the outcomes.

We also showed that the OHCA incidence trends differed by detailed non-cardiac origin. For instance, the incidence rate of OHCAs due to strokes significantly decreased during the study period. Although the reasons for the decrement were unclear, better blood pressure control and decreasing smoking rate in recent years of Japan might be one of the possible explanations for this phenomenon.[20] In fact, the numbers of stroke patients in Japan has also been decreasing.[21] On the other hand, the incidence rates of OHCAs with external causes increased and the outcomes after OHCAs with external causes excluding asphyxia were miserable. For example, external OHCAs due to trauma, drug overdose, or hanging in metropolitan area of Australia were more common and the survivals from traumatic and hanging-associated OHCAs were not always futile. Therefore, there were regional variations on the incidence and outcome from OHCAs with external causes,[22,23] and the countermeasures would differ by regions. However, most importantly, more efforts should focus on prevention of OHCAs with external causes because many of them are preventable.[1-4]

In a multivariable analysis, intravenous fluid administration was associated with better one-month survival after OHCAs with non-cardiac origin. In preceding studies, prehospital intravenous fluid for OHCAs including both cardiac and non-cardiac

origins was not associated with the improved outcome,[24] whereas intravenous access were associated with a reduction in hospital mortality among non-injured, non-cardiac arrest patients.[25] Thus, the effects of fluid administration on prehospital emergency patients were under debate, and further investigations by other cohorts or randomized controlled trials are needed to confirm these associations.

In this study, a multivariate analysis also underscored that either bystander-initiated chest compression-only CPR or conventional CPR with rescue breathing was not effective for OHCAs with non-cardiac origin. From a nationwide study focused on 43,000 bystander-witnessed OHCAs with non-cardiac origin, we demonstrated that conventional CPR with rescue breathing had an incremental benefit for OHCAs with non-cardiac origin, but the impact on the overall survival after OHCA was small.[8] Considering these results, the effectiveness of bystander CPR on OHCAs with non-cardiac origin might be limited. In addition, attempted resuscitation rates in our area was exceedingly higher at 92% compared with those in western countirs,[22,26] which might be also one of the possible explanations for the lack of impact of bystander CPR in our multivariate model. However, as recommended in the CPR guidelines,[1-4] bystander CPR plays a key role in the “chain of survival” and increasing the proportion of bystander CPR for OHCA patients is important.

Furthermore, factors such as arrests witnessed by bystanders and earlier EMS response time were also independent predictors of better outcome after OHCAs with non-cardiac origin in a multivariate analysis. This would indicate the importance of an early EMS activation in the chain of survival[1-4] and suggests that activating the EMS system quickly leads to improving the outcomes after OHCAs with non-cardiac origin. In addition, the verification of the effects on prehospital emergency care as well as in-hospital treatment is essential to improve survival after OHCAs with non-cardiac origin.

The present study has some inherent limitations. First, the category of presumed cardiac or non-cardiac causes is made clinically, as per the Utstein-style international guidelines for cardiac arrest data reporting.[14,15] Second, information on post-arrest care is lacking. In-hospital treatment (e.g., hemodynamic support, cardiovascular intervention, induced hypothermia) might affect survival after OHCA.[27] Third, unmeasured confounding factors may have influenced the association between OHCAs with non-cardiac origin and the outcome.

CONCLUSION

The large OHCA registry in Osaka demonstrated that one-month survival after OHCAs

with non-cardiac origin was poor, the survival trends did not improve year-by-year, and the survivals differed by detailed non-cardiac origin. Further monitoring and discussion for epidemiology and outcome of OHCAs with non-cardiac origin are warranted to improve survival after OHCA in this group.

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Contributors

All authors (TK, KK, TS, TI, CN, KK, TN, YH, YK, KY, and TS) participated in the study conception and design, acquisition of data, analysis and interpretation of data, drafting the article and revising it critically for important intellectual content, and final approval of the manuscript.

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Competing interests

None.

Ethics approval

The study was approved by the institutional review board of Osaka University with the assent of the EMS authorities of the local governments in Osaka Prefecture.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data sharing statement

TK had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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4

Figure Legends

Figure 1 Overview of EMS-treated cardiac arrests with an abridged Utstein template from January 1, 2005 to December 31, 2011. EMS, emergency medical service.

Table 1 Age-adjusted incidences and unadjusted one-month survival rate of out-of-hospital cardiac arrests with non-cardiac origin according to the cause over time

	2005	2006	2007	2008	2009	2010	2011	P for trend
Age-adjusted Incidence per 100,000 persons								
External causes	12.4	12.3	13.2	12.8	13.2	13.3	13.3	0.024
Asphyxia	2.7	3.0	2.8	3.4	3.1	2.9	2.9	0.726
Hanging	3.4	3.4	4.1	3.4	3.7	3.9	3.9	0.158
Fall	2.4	2.5	3.1	2.4	2.9	3.0	2.7	0.396
Drowning	1.2	1.1	1.2	1.4	1.2	1.3	1.6	0.065
Traffic injury	1.6	1.5	1.4	1.4	1.4	1.5	1.4	0.229
Drug overdose	0.5	0.4	0.2	0.4	0.4	0.4	0.3	0.304
Unclassified	0.5	0.5	0.4	0.3	0.5	0.4	0.5	0.447
Respiratory diseases	2.2	1.8	1.8	1.7	1.3	1.3	1.6	0.018
Malignant tumors	1.6	1.8	1.8	1.7	1.5	1.3	1.6	0.109
Strokes	2.0	1.8	1.8	1.6	1.4	1.2	1.3	< 0.001
Others	2.7	3.3	3.1	2.9	2.7	2.5	2.4	0.087
Unadjusted one-month survival, % (n/N)								
External causes	4.8 (53/1100)	6.8 (72/1059)	5.7 (66/1164)	7.2 (85/1184)	7.1 (86/1207)	6.1 (75/1225)	5.6 (73/1300)	0.736
Asphyxia	10.4 (35/337)	15.4 (53/344)	13.0 (44/338)	15.6 (67/430)	16.3 (66/406)	14.8 (58/393)	14.0 (59/422)	0.374
Hanging	4.6 (12/261)	4.7 (12/255)	5 (16/318)	4.8 (13/273)	4.9 (14/287)	3.3 (10/301)	2.3 (7/304)	0.101
Fall	0.6 (1/159)	0.6 (1/169)	0.9 (2/219)	1.2 (2/165)	0.0 (0/197)	0.5 (1/208)	1.1 (2/183)	NA
Drowning	1.3 (2/151)	3.3 (4/120)	0.0 (0/128)	1.3 (2/159)	2.1 (3/144)	0.7 (1/148)	0.0 (0/212)	NA
Traffic injury	0.9 (1/116)	1.0 (1/101)	1.8 (2/109)	0.9 (1/106)	1.9 (2/103)	1.7 (2/115)	2.6 (3/115)	0.027

Drug overdose	3.0 (1/33)	0.0 (0/29)	5.6 (1/18)	0.0 (0/25)	3.3 (1/30)	11.1 (3/27)	4.0 (1/25)	NA
Unclassified	2.3 (1/43)	2.4 (1/41)	2.9 (1/34)	0.0 (0/26)	0.0 (0/40)	0.0 (0/33)	2.6 (1/39)	NA
Respiratory diseases	6.4 (17/267)	3.9 (8/206)	8.0 (17/212)	9.8 (21/214)	6.7 (11/165)	4.7 (8/169)	5.6 (12/215)	0.875
Malignant tumors	0.5 (1/186)	0.5 (1/194)	1.0 (2/202)	1.0 (2/196)	0.0 (0/178)	2.5 (4/159)	0.5 (1/194)	NA
Strokes	3.6 (7/196)	6.1 (11/179)	4.5 (8/176)	3.2 (5/154)	4.9 (7/143)	6.0 (8/134)	6.8 (9/132)	0.241
Others	2.9 (8/277)	7.0 (22/314)	1.3 (4/308)	4.5 (14/311)	4.3 (12/278)	5.3 (15/281)	3.5 (10/285)	0.808

NA indicates not analyzed.

Table 2 Patient and EMS characteristics of out-of-hospital cardiac arrests with non-cardiac origin according to the cause

	Total (n =14,164)		External causes (n = 8239)		Respiratory diseases (n =1448)		Malignant tumors (n =1309)		Strokes (n =1114)		Others (n =2054)		*P* value*
Age, yr, mean (SD)	66.8	(19.0)	63.5	(20.5)	76.1	(14.2)	71.9	(12.0)	67.7	(14.7)	69.8	(17.6)	< 0.001
Age group, n (%)													< 0.001
Adults aged 20-64 years	5513	(38.9)	3826	(46.4)	229	(15.8)	345	(26.4)	447	(40.1)	666	(32.4)	
Elderly aged >=65 years	8651	(61.1)	4413	(53.6)	1219	(84.2)	964	(73.6)	667	(59.9)	1388	(67.6)	
Men, n (%)	8215	(58.0)	4789	(58.1)	844	(58.3)	881	(67.3)	559	(50.2)	1142	(55.6)	< 0.001
Arrests witnessed by bystanders, n (%)	5561	(39.3)	2952	(35.8)	682	(47.1)	639	(48.8)	493	(44.3)	795	(38.7)	< 0.001
Good activities of daily living, n (%)	8522	(60.2)	5213	(63.3)	653	(45.1)	443	(33.8)	896	(80.4)	1317	(64.1)	< 0.001
First documented rhythm, n (%)													< 0.001
VF	324	(2.3)	119	(1.4)	35	(2.4)	26	(2.0)	69	(6.2)	75	(3.7)	
PEA	3356	(23.7)	1853	(22.5)	394	(27.2)	262	(20.0)	329	(29.5)	518	(25.2)	
Asystole	10196	(72.0)	6124	(74.3)	983	(67.9)	1008	(77.0)	647	(58.1)	1434	(69.8)	
Others	288	(2.0)	143	(1.7)	36	(2.5)	13	(1.0)	69	(6.2)	27	(1.3)	
Location of arrest, n (%)													< 0.001
Homes	9010	(63.6)	4435	(53.8)	1098	(75.8)	1217	(93.0)	801	(71.9)	1459	(71.0)	
Public places	2035	(14.4)	1608	(19.5)	59	(4.1)	24	(1.8)	156	(14.0)	188	(9.2)	
Work places	346	(2.4)	223	(2.7)	7	(0.5)	4	(0.3)	48	(4.3)	64	(3.1)	
Health care facilities	1505	(10.6)	904	(11.0)	248	(17.1)	55	(4.2)	63	(5.7)	235	(11.4)	
Others	1268	(9.0)	1069	(13.0)	36	(2.5)	9	(0.7)	46	(4.1)	108	(5.3)	
Public-access AED use, n (%)	13	(0.1)	4	(0.05)	2	(0.1)	0	(0.0)	5	(0.4)	2	(0.1)	0.001
Type of Bystander CPR, n (%)													< 0.001
No CPR	9023	(63.7)	5383	(65.3)	836	(57.7)	889	(67.9)	633	(56.8)	1282	(62.4)	
Chest compression-only CPR	3288	(23.2)	1811	(22.0)	408	(28.2)	297	(22.7)	283	(25.4)	489	(23.8)	

Conventional CPR with rescue breathing	1853	(13.1)	1045	(12.7)	204	(14.1)	123	(9.4)	198	(17.8)	283	(13.8)		
Intravascular fluid, n (%)	2320	(16.4)	1458	(17.7)	202	(14.0)	113	(8.6)	230	(20.6)	317	(15.4)	<	0.001
Intubation, n (%)	2639	(18.6)	1364	(16.6)	338	(23.3)	242	(18.5)	257	(23.1)	438	(21.3)	<	0.001
Epinephrine, n (%)	987	(7.0)	572	(6.9)	88	(6.1)	49	(3.7)	125	(11.2)	153	(7.4)	<	0.001
Call to contact with a patient by EMS (EMS response time), min, mean (SD)	7.9	(4.1)	8.0	(4.6)	7.7	(3.0)	7.7	(2.7)	7.7	(2.8)	7.9	(3.8)		0.003
Call to CPR by EMS, min, mean (SD)	8.5	(4.5)	8.8	(5.1)	8.1	(3.1)	8.1	(2.8)	8.2	(2.9)	8.4	(4.2)	<	0.001
Call to hospital arrival, min, mean (SD)	28.2	(8.6)	28.4	(8.6)	27.3	(8.2)	28.0	(8.9)	28.2	(8.4)	28.1	(8.7)		0.001

*P values are calculated to test the homogeneity among the 5 cause groups.

EMS indicates emergency medical services; CPR, cardiopulmonary resuscitation; VF, ventricular fibrillation; PEA, pulseless electrical activity; AED, automated external defibrillator; SD, standard deviation.

Table 3 Patient and EMS characteristics of out-of-hospital cardiac arrests with external causes according to the cause

	Asphyxia (n = 2670)	Hanging (n = 1999)	Fall (n = 1300)	Drowning (n = 1062)	Traffic injury (n = 765)	Drug overdose (n = 187)	Unclassified (n = 256)	*P* value*
Age, yr, mean (SD)	77.9 (14.4)	55.6 (17.4)	47.4 (17.4)	73.1 (14.8)	52.6 (19.0)	49.9 (19.5)	58.1 (19.3)	< 0.001
Age group, n (%)								< 0.001
Adults aged 20-64 years	403 (15.1)	1136 (66.8)	1055 (81.2)	210 (19.8)	523 (68.4)	141 (75.4)	158 (61.7)	
Elderly aged >=65 years	2267 (84.9)	663 (33.2)	245 (18.8)	852 (80.2)	242 (31.6)	46 (24.6)	98 (38.3)	
Men, n (%)	1345 (50.4)	1290 (64.5)	781 (60.1)	530 (49.9)	558 (72.9)	117 (62.6)	168 (65.6)	< 0.001
Arrests witnessed by bystanders, n (%)	1801 (67.5)	27 (1.4)	510 (39.2)	56 (5.3)	476 (62.2)	10 (5.3)	72 (28.1)	< 0.001
Good activities of daily living, n (%)	1099 (41.2)	1769 (88.5)	685 (52.7)	854 (80.4)	517 (67.6)	133 (71.1)	156 (60.9)	< 0.001
First documented rhythm, n (%)								< 0.001
VF	56 (2.1)	13 (0.7)	19 (1.5)	12 (1.1)	14 (1.8)	1 (0.5)	4 (1.6)	
PEA	960 (36.0)	198 (9.9)	274 (21.1)	72 (6.8)	259 (33.9)	20 (10.7)	70 (27.3)	
Asystole	1589 (59.5)	1775 (88.8)	985 (75.8)	970 (91.3)	469 (61.3)	160 (85.6)	176 (68.8)	
Others	65 (2.4)	13 (0.7)	22 (1.7)	8 (0.8)	23 (3.0)	6 (3.2)	6 (2.3)	
Location of arrest, n (%)								< 0.001
Homes	1596 (59.8)	1667 (83.4)	139 (10.7)	770 (72.5)	2 (0.3)	150 (80.2)	111 (43.4)	
Public places	139 (5.2)	86 (4.3)	553 (42.5)	83 (7.8)	677 (88.5)	14 (7.5)	56 (21.9)	
Workplaces	35 (1.3)	94 (4.7)	44 (3.4)	3 (0.3)	7 (0.9)	7 (3.7)	33 (12.9)	
Health care facilities	835 (31.3)	27 (1.4)	12 (0.9)	14 (1.3)	1 (0.1)	0 (0.0)	15 (5.9)	
Others	65 (2.4)	125 (6.3)	552 (42.5)	192 (18.1)	78 (10.2)	16 (8.6)	41 (16.0)	

Public-access AED use, n (%)	4	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0.214
Type of Bystander CPR, n (%)															< 0.001
No CPR	1386	(51.9)	1174	(58.7)	1191	(91.6)	608	(57.3)	673	(88.0)	154	(82.4)	197	(77.0)	
Chest compression-only CPR	748	(28.0)	549	(27.5)	93	(7.2)	281	(26.5)	74	(9.7)	23	(12.3)	43	(16.8)	
Conventional CPR with rescue breathing	536	(20.1)	276	(13.8)	16	(1.2)	173	(16.3)	18	(2.4)	10	(5.3)	16	(6.2)	
Intravascular fluid, n (%)	540	(20.2)	393	(19.7)	107	(8.2)	281	(26.5)	76	(9.9)	27	(14.4)	34	(13.3)	< 0.001
Intubation, n (%)	800	(30.0)	167	(8.4)	41	(3.2)	251	(23.6)	31	(4.1)	33	(17.6)	41	(16.0)	< 0.001
Epinephrine, n (%)	326	(12.2)	83	(4.2)	41	(3.2)	68	(6.4)	37	(4.8)	6	(3.2)	11	(4.3)	< 0.001
Call to contact with a patient by EMS (EMS response time), min, mean (SD)	7.6	(2.9)	7.8	(3.3)	7.4	(3.3)	9.4	(7.6)	7.6	(4.2)	14.2	(10.7)	9.4	(7.3)	< 0.001
Call to CPR by EMS personnel, min, mean (SD)	7.9	(3.1)	8.6	(3.9)	8.2	(3.8)	10.0	(7.5)	9.3	(5.9)	14.4	(10.0)	11.0	(8.7)	< 0.001
Call to hospital arrival, min, mean (SD)	28.6	(8.6)	28.2	(7.9)	27.5	(8.3)	29.1	(9.3)	27.1	(8.8)	32.1	(11.1)	29.5	(9.4)	< 0.001

*P values are calculated to test the homogeneity among the 7 cause groups.

EMS indicates emergency medical services; CPR, cardiopulmonary resuscitation; VF, ventricular fibrillation; PEA, pulseless electrical activity; AED, automated external defibrillator; SD, standard deviation.

Table 4 Outcomes after out-of-hospital cardiac arrests with non-cardiac origin according to the cause

	Total (n = 1,4164)	External causes (n = 8239)	Respiratory diseases (n = 1448)	Malignant tumors (n = 1309)	Strokes (n = 1114)	Others (n =2054)	*P* value*
Prehospital ROSC, n (%)	1229 (8.7)	703 (8.5)	114 (7.9)	57 (4.4)	216 (19.4)	139 (6.8)	< 0.001
Total ROSC, n (%)	4744 (33.5)	2638 (32.0)	620 (42.8)	234 (17.9)	650 (58.3)	602 (29.3)	< 0.001
Hospital admission, n (%)	4142 (29.2)	2356 (28.6)	530 (36.6)	173 (13.2)	585 (52.5)	498 (24.2)	< 0.001
One-month survival, n (%)	755 (5.3)	510 (6.2)	94 (6.5)	11 (0.8)	55 (4.9)	85 (4.1)	< 0.001
Neurologically favorable outcome, n (%)	188 (1.3)	105 (1.3)	27 (1.9)	2 (0.2)	17 (1.5)	37 (1.8)	< 0.001

*P values are calculated to test the homogeneity among the 5 cause groups.

ROSC indicates return of spontaneous circulation.

Table 5 Outcomes after out-of-hospital cardiac arrests with external causes according to the cause

	Asphyxia (n = 2670)	Hanging (n = 1999)	Fall (n = 1300)	Drowning (n = 1062)	Traffic injury (n = 765)	Drug overdose (n = 187)	Unclassified (n = 256)	*P* value*
Prehospital ROSC, n (%)	463 (17.3)	144 (7.2)	22 (1.7)	36 (3.4)	28 (3.7)	4 (2.1)	6 (2.3)	< 0.001
Total ROSC, n (%)	1003 (37.6)	1500 (75.0)	1213 (93.3)	894 (84.2)	637 (83.3)	143 (76.5)	211 (82.4)	< 0.001
Hospital admission, n (%)	1529 (57.3)	453 (22.7)	62 (4.8)	147 (13.8)	92 (12.0)	40 (21.4)	33 (12.9)	< 0.001
One-month survival, n (%)	382 (14.3)	84 (4.2)	9 (0.7)	12 (1.1)	12 (1.6)	7 (3.7)	4 (1.6)	< 0.001
Neurologically favorable outcome, n (%)	71 (2.7)	17 (0.9)	1 (0.1)	4 (0.4)	6 (0.8)	4 (2.1)	2 (0.8)	< 0.001

*P values are calculated to test the homogeneity among the 7 cause groups.

ROSC indicates return of spontaneous circulation.

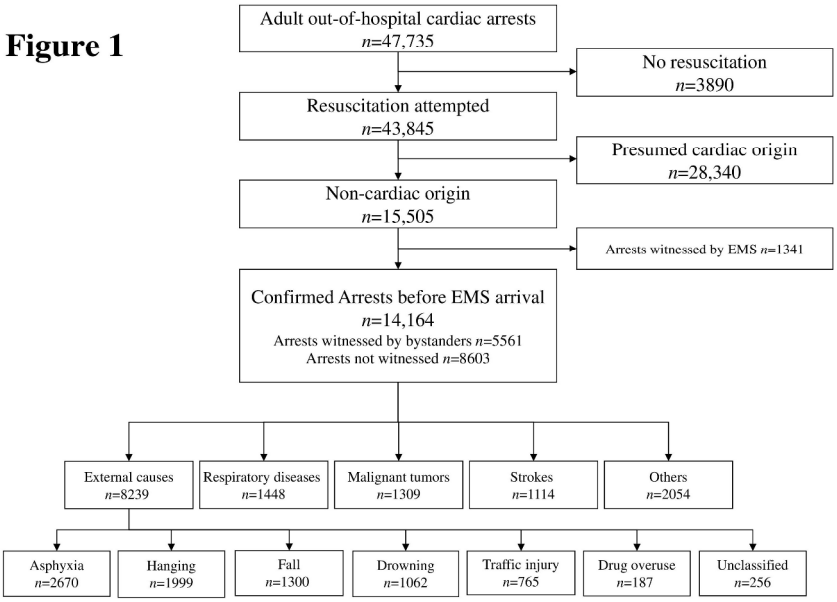
Table 6 Factors associated with outcomes after out-of-Hospital cardiac arrests with non-cardiac origin

	One-month survival				Neurologically favorable outcome			
	Crude OR	(95% CI)	Adjusted OR	(95% CI)	Crude OR	(95% CI)	Adjusted OR	(95% CI)
Adults (versus elderly)	0.95	(0.82-1.10)	1.36	(1.12-1.65)	1.02	(0.76-1.37)	1.52	(1.07-2.15)
Men	0.75	(0.64-0.88)	0.99	(0.84-1.16)	1.09	(0.81-1.46)	0.91	(0.67-1.24)
Witnessed by bystanders	4.41	(3.74-5.19)	4.13	(3.35-5.09)	4.48	(3.23-6.21)	4.83	(3.21-7.29)
Good activities of daily living	0.93	(0.80-1.08)	1.23	(1.03-1.47)	1.39	(1.02-1.88)	1.43	(1.02-2.02)
VF	2.74	(1.96-3.82)	2.04	(1.42-2.92)	7.72	(5.05-11.79)	5.40	(3.40-8.59)
Type of bystander CPR								
No CPR	Reference		Reference		Reference		Reference	
Chest compression-only CPR	0.97	(0.81-1.16)	0.80	(0.66-0.98)	0.95	(0.67-1.35)	0.92	(0.64-1.33)
Conventional CPR with rescue breathing	1.47	(1.20-1.79)	1.07	(0.86-1.34)	1.01	(0.65-1.55)	0.89	(0.56-1.42)
Type of non-cardiac origin								
Respiratory diseases	0.42	(0.33-0.53)	0.51	(0.40-0.65)	0.70	(0.44-1.09)	0.76	(0.48-1.21)
Malignant tumors	0.05	(0.03-0.09)	0.06	(0.03-0.11)	0.06	(0.01-0.23)	0.06	(0.01-0.23)
Strokes	0.31	(0.23-0.42)	0.27	(0.20-0.38)	0.57	(0.33-0.97)	0.34	(0.19-0.61)
Asphyxia	Reference		Reference		Reference		Reference	
Hanging	0.26	(0.21-0.34)	0.56	(0.41-0.77)	0.31	(0.18-0.53)	0.55	(0.28-1.07)
Fall	0.04	(0.02-0.08)	0.03	(0.01-0.06)	0.03	(0.004-0.20)	0.01	(0.002-0.11)
Drowning	0.07	(0.04-0.12)	0.16	(0.09-0.29)	0.14	(0.05-0.38)	0.31	(0.11-0.90)

Traffic injury	0.10 (0.05-0.17)	0.05 (0.03-0.10)	0.29 (0.13-0.67)	0.10 (0.04-0.26)
Drug overdose	0.23 (0.11-0.50)	0.58 (0.26-1.29)	0.80 (0.29-2.21)	1.74 (0.58-5.19)
Others	0.26 (0.20-0.33)	0.29 (0.22-0.38)	0.67 (0.45-1.00)	0.60 (0.39-0.92)
Unclassified	0.10 (0.04-0.26)	0.10 (0.04-0.28)	0.29 (0.07-1.18)	0.27 (0.06-1.16)
Location of arrest				
Homes	Reference	Reference	Reference	Reference
Public places	0.78 (0.61-0.99)	1.45 (1.10-1.91)	1.11 (0.75-1.65)	1.54 (0.97-2.44)
Workplaces	1.29 (0.83-1.98)	1.40 (0.87-2.23)	1.26 (0.55-2.89)	0.95 (0.39-2.30)
Health care facilities	1.69 (1.38-2.07)	0.88 (0.69-1.12)	0.72 (0.42-1.24)	0.47 (0.26-0.85)
Others	0.70 (0.51-0.94)	1.67 (1.19-2.35)	0.68 (0.38-1.24)	1.35 (0.72-2.54)
Intravascular fluid	1.78 (1.50-2.11)	1.45 (1.14-1.84)	1.34 (0.94-1.91)	1.52 (0.97-2.38)
Intubation	1.62 (1.37-1.92)	1.02 (0.84-1.23)	0.73 (0.48-1.10)	0.50 (0.32-0.77)
Epinephrine	2.32 (1.87-2.88)	0.97 (0.71-1.32)	1.25 (0.74-2.09)	0.60 (0.31-1.17)
EMS response time (for one-increment of minute)	0.93 (0.91-0.96)	0.92 (0.90-0.95)	0.91 (0.86-0.96)	0.90 (0.84-0.95)
Year (for one-increment of year)	1.02 (0.98-1.06)	1.01 (0.97-1.06)	1.02 (0.95-1.09)	1.05 (0.97-1.13)

VF denotes ventricular fibrillation; CPR, cardiopulmonary resuscitation; EMS, emergency medical services; OR, odds ratio; CI, confidence interval.

Figure 1



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Sapplemental Table Factors associated with one-month survival after out-of-hospital cardiac arrests with non-cardiac origin by internal and external causes

	One-month survival	
	Internal causes	External causes
	Adjusted OR (95% CI)	Adjusted OR (95% CI)
Adults (versus elderly)	1.01 (0.68 - 1.50)	1.51 (1.17 - 1.96)
Men	0.99 (0.71 - 1.40)	0.91 (0.75 - 1.11)
Witnessed by bystanders	2.86 (1.99 - 4.11)	5.03 (3.71 - 6.81)
Good activities of daily living	1.27 (0.87 - 1.85)	1.34 (1.08 - 1.67)
VF	2.35 (1.30 - 4.24)	0.44 (0.17 - 1.11)
Type of bystander CPR		
No CPR	Reference	Reference
Chest compression-only CPR	0.66 (0.43 - 1.01)	0.79 (0.61 - 1.01)
Conventional CPR with rescue brething	0.83 (0.51 - 1.36)	1.18 (0.89 - 1.54)
Type of non-cardiac origin		
Respiratory diseases	Reference	– –
Malignant tumors	0.12 (0.06 - 0.23)	– –
Strokes	0.55 (0.37 - 0.82)	– –
Asphyxia	– –	Reference
Hanging	– –	0.60 (0.41 - 0.87)
Fall	– –	0.03 (0.01 - 0.06)
Drowning	– –	0.05 (0.03 - 0.11)
Traffic injury	– –	0.17 (0.09 - 0.31)
Drug overdose	– –	0.60 (0.26 - 1.36)
Location of arrest		
Homes	Reference	Reference
Public places	2.01 (1.21 - 3.36)	1.39 (0.94 - 2.04)
Workplaces	1.88 (0.69 - 5.15)	1.47 (0.77 - 2.80)
Health care facilities	1.00 (0.55 - 1.81)	0.82 (0.62 - 1.09)
Others	2.10 (0.99 - 4.47)	1.72 (1.12 - 2.63)
Intravascular fluid	0.65 (0.33 - 1.29)	1.69 (1.27 - 2.25)
Intubation	0.62 (0.39 - 0.97)	1.21 (0.96 - 1.52)
Epinephrine	1.89 (0.82 - 4.34)	0.93 (0.64 - 1.35)
EMS response time (for one-increment of minute)	0.97 (0.91 - 1.03)	0.93 (0.90 - 0.96)
Year (for one-increment of year)	1.02 (0.94 - 1.11)	1.01 (0.96 - 1.06)

VF denotes ventricular fibrillation; CPR, cardiopulmonary resuscitation; EMS, emergency medical services; OR, odds ratio; CI, confidence interval.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Epidemiology and outcome of adult out-of-hospital cardiac arrest with non-cardiac origin in Osaka: a population-based study

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Epidemiology and outcome of adult out-of-hospital cardiac arrest with non-cardiac origin in Osaka: a population-based study

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ABSTRACT

Objectives: To evaluate epidemiological characteristics of out-of-hospital cardiac arrests (OHCAs) by detailed non-cardiac cause and factors associated with the outcomes after OHCAs with non-cardiac origin.

Design: A prospective, population-based observational study.

Setting: The Utstein Osaka Project.

Participants: 14,164 adult patients aged >=20 years old with OHCAs due to non-cardiac origin who were resuscitated by emergency-medical-service personnel or bystanders, and then were transported to medical institutions from January 2005 to December 2011.

Primary outcome measures: One-month survival after OHCA. Multiple logistic regression analysis was used to assess factors that were potentially associated with the outcome.

Results: During the study period, the one-month survival rate was 5.3% (755/14,164). The proportion of one-month survival was 6.2% (510/8239) in external causes, 6.5% (94/1148) in respiratory diseases, 0.8% (11/1309) in malignant tumors, 4.9% (55/1114) in strokes, and 4.1% (85/2054) in others. As for external causes, the proportion of one-month survival was 14.3% (382/2670) in asphyxia, 4.2% (84/1999) in hanging,

0.7% (9/1300) in fall, 1.1% (12/1062) in drowning, 1.6% (12/765) in traffic injury, 3.7% (7/187) in drug overuse, and 1.6% (4/256) in unclassified external causes. In a multivariate analysis, adults aged <65 years old, arrests witnessed by bystanders, good activities of daily living before arrests, ventricular fibrillation arrests, public places, intravenous fluid, and early emergency-medical-service response time were significant predictors for one-month outcome after OHCAs with non-cardiac origin. The proportion of one-month survival of the whole OHCAs with non-cardiac origin did not significantly increase (from 4.3% [86/2023] in 2005 to 4.9% [105/2126] in 2011) and the adjusted odds ratio for one-increment of year was 1.01 (95% confidence interval 0.97-1.06).

Conclusions: From a large OHCA registry in Osaka, we demonstrated that one-month survival after OHCAs with non-cardiac origin was poor and stable.

Strengths and limitations of this study

- This study showed that one-month survival after OHCAs with non-cardiac origin was poor and the survival trends did not improve year-by-year in Osaka during the study period from 2005 to 2011. In addition, the survivals exceedingly differed by detailed non-cardiac origin.
- The category of presumed non-cardiac causes is made clinically, as per the Utstein-style international guidelines for cardiac arrest data reporting.

INTRODUCTION

Out-of-hospital cardiac arrest (OHCA) is one of the leading causes of death in the industrialized world.[1-4] Although improvements in the chain of survival including the development of a public-access defibrillation system and revisions to cardiopulmonary resuscitation (CPR) guidelines have led to increased survival after OHCA with cardiac origin in some communities,[5-7] the outcome after OHCAs with non-cardiac origin remains generally poor.[7-13]

Importantly, 20% to 40% of adult OHCAs were reportedly of non-cardiac origin.[7-13] However, epidemiological characteristics of OHCA with non-cardiac origin have not been sufficiently investigated as much as those of OHCA with cardiac origin. Therefore, the evaluation of characteristics, trends, and outcomes by detailed non-cardiac cause and understanding the factors associated with the outcomes are needed to improve the survival after OHCAs with non-cardiac origin.

The Utstein Osaka Project is a large prospective population-based cohort study of OHCA in Osaka, Japan, covering about 8.8 million residents.[5] During the 7 years from 2005 to 2011, we enrolled approximately 14,000 OHCAs with non-cardiac origin before emergency-medical-service (EMS) arrival. The present study aimed to evaluate the epidemiological characteristics of OHCAs by detailed non-cardiac cause. In

addition, we evaluated factors associated with the outcomes after OHCAs with non-cardiac origin in a multivariate analysis.

METHODS

Study design and setting

The Utstein Osaka Project is a prospective, population-based registry of OHCA that is based on the standardized Utstein style.[14,15] This study enrolled adult patients aged =>20 years suffering OHCAs with non-cardiac origin before EMS arrival, who were resuscitated by EMS personnel or bystanders, and were transported to medical institutions in Osaka Prefecture from January 1, 2005 to December 31, 2011. In this study, we excluded pediatric OHCA patients because characteristics and outcomes from OHCAs differed between children and adults.[16,17]

Cardiac arrest was defined as the cessation of cardiac mechanical activity as confirmed by the absence of signs of circulation.[14,15] In this study, the arrests were classified into those of presumed cardiac origin and non-cardiac origin, the latter resulting from external causes, respiratory diseases, malignant tumors, strokes, and any other non-cardiac causes based on hospital medical records. Furthermore, external causes were divided into the seven categories: asphyxia, hanging, fall, drowning, traffic injury, drug overuse, and unclassified external causes. These diagnoses were made clinically by the physician in charge, working in collaboration with the EMS personnel.

EMS organization in Osaka

Details of the EMS system in Osaka were described previously.[5] Osaka is the second largest prefecture in Japan with a population of approximately 8.8 million inhabitants in an area of 1892 km^2. In Osaka, there are 34 fire stations with emergency dispatch centers. The EMS system is operated by the local fire stations. When called, an ambulance is dispatched from the nearest fire station. Emergency services are provided 24 hours each day by them, which is single-tiered in 32 stations and two-tiered in two stations. The latter uses medics followed by physicians.

Most highly-trained prehospital emergency care providers are called Emergency Life-Saving Technicians (ELSTs). Usually, each ambulance has a crew of three emergency providers including at least one ELST. They were allowed to insert an intravenous line and an adjunct airway, and to use a semi-automated external defibrillator for OHCA patients. Specially trained ELSTs were permitted to tracheal intubation since July 2004 and administer intravenous epinephrine since April 2006.

Do-not-resuscitate (DNR) orders or living wills are not generally accepted in Japan. EMS providers are not permitted to terminate resuscitation in the field. Therefore, almost patients with OHCA who were treated by EMS personnel were transported to a

hospital and enrolled in the Utstein Osaka Project, excluding those with decapitation, incineration, decomposition, rigor mortis, or dependent cyanosis.

CPR and AED training for the general public

The use of an automated external defibrillator (AED) by citizens was permitted legally in July 2004. In Osaka, approximately 14,000 citizens per year participated in the CPR training programs, consisting of conventional CPR including chest compressions, mouth-to-mouth ventilation, and AED usage by local fire departments, the Japan Red Cross, Inc., and the Osaka Life Support Association.[5] All EMS providers perform CPR according to the Japanese CPR guidelines.[4]

Data collection and quality control

Data collection were prospectively conducted using a form that included data recommended in the Utstein-style reporting guidelines for cardiac arrests.[14,15] These data included gender, age, first documented cardiac rhythm, witness status, location of arrests, activity of daily living (ADL) before arrests, time-courses of resuscitation, type of bystander-initiated CPR, public-access AED use, intravascular fluid, tracheal intubation, and intravascular epinephrine as well as prehospital return of spontaneous

circulation (ROSC), total ROSC, one-month survival, and neurological status one month after the event. First documented rhythm was recorded and diagnosed by the EMS personnel with semi-automated defibrillators on the scene, and confirmed by the physician who was responsible for the on-line medical direction. Bystander CPR included chest compression-only CPR and conventional CPR with rescue breathing. A series of EMS times of call receipt, vehicle arrival at the scene, contact with patients, initiation of CPR, defibrillation by EMS, and hospital arrival were recorded automatically at the dispatch center.

The data form was completed by the EMS personnel in cooperation with the physicians in charge of the patients, and the data were integrated into the registry system on the Information Center for Emergency Medical Services of Osaka, and then checked by the investigators. If the data sheet was incomplete, the relevant EMS personnel were contacted and questioned for data completion.

All survivors suffering OHCA were followed up for up to one-month after the event by the EMS personnel in charge. One-month neurological outcomes were determined by the physician responsible for treating the patient, using the cerebral performance category (CPC) scale: category 1, good cerebral performance; category 2, moderate cerebral disability; category 3, severe cerebral disability; category 4, coma or

vegetative state; and category 5, death.[14,15]

Outcome measures

The main outcome measure was one-month survival. Secondary outcome measures included prehospital and total ROSCs, admission to hospital, and one-month survival with neurologically favorable outcome. Neurologically favorable outcome was defined as CPC category 1 or 2.[14,15]

Statistical analysis

In this study, patient and EMS characteristics of OHCAs with non-cardiac origin and their outcomes were compared between the groups using unpaired analysis of variance for numerical variables, and chi-square test or Fisher's exact test for categorical variables by cause of arrest. First, non-cardiac causes were divided into the following five groups; external causes, respiratory diseases, malignant tumors, strokes, and any other non-cardiac causes. Next, external causes were further divided into asphyxia, hanging, fall, drowning, traffic injury, drug overuse, and unclassified external causes. Age-adjusted annual incidence of OHCAs by non-cardiac origin was calculated by the direct method using 2005 census data and 1985 Japanese model population.[18,19]

Poisson regression models for the trends in the incidence and one-month survival rate were used. Multiple logistic regression analysis assessed the factors associated with one-month survival and neurological favorable outcome, and adjusted odds ratios (AORs) and their 95% confidence intervals (CIs) were calculated. As potential confounders, factors that were biologically essential and considered to be associated with clinical outcomes were taken in the multivariable analyses.[7] These variables included age (20-64, >=65 years old), gender (men, women), witness status (none, witnessed by bystanders), ADL before arrests (good, other), first documented rhythm (VF, non-VF), bystander CPR status (none, compression-only CPR, conventional CPR), type of non-cardiac causes (the 11 categories described above), location of arrests (homes, public places, work places, health care facilities, others), intravascular fluid (yes, no), intubation (yes, no), epinephrine (yes, no), EMS response time (call to contact with patients), and year of arrest. In addition, we conducted a multivariate analysis of one-month survival from OHCAs with non-cardiac origin after dividing the two groups: internal (respiratory diseases, malignant tumors, and strokes) and external (asphyxia, hanging, fall, drowning, traffic injury, and drug overuse) causes.

All statistical analyses were performed using the SPSS statistical package ver21.0J (IBM Corp. Armonk, NY). All of the tests were 2-tailed and *P* values of <0.05 were

considered statistically significant.

RESULTS

Figure 1 shows an overview of the study patients based on the Utstein template. A total of 47,735 adult arrests were documented during these seven years. Resuscitation was attempted in 43,845, and 15,505 of them were of non-cardiac origin. Excluding 1341 victims who were witnessed by EMS (arrests after EMS arrival), 14,164 (5561 in bystander-witnessed cases and 8603 in non-witnessed cases) were eligible for our analyses. Among these arrests, 8239 (58.2%) were due to external causes, 1448 (10.2%) respiratory diseases, 1309 (9.2%) malignant tumors, 1114 (7.9%) strokes, and 2054 (14.5%) others. Among external causes, 2670 (16.5%) were of asphyxia, 1999 (14.1%) hanging, 1300 (9.2%) fall, 1062 (7.5%) drowning, 765 (5.4%) traffic injury, and 256 (1.8%) unclassified external cause. We could not obtain information on one-month survival and neurological status for 7 (0.05%) among 14,164 eligible victims.

The age-adjusted annual incidence rates per 100,000 persons by non-cardiac cause were calculated over time (Table 1). The incidence rate of OHCAs with external causes significantly increased from 12.4 in 2005 to 13.3 in 2011 (P for trend=0.024). The incidence rate significantly decreased among OHCA patients with respiratory diseases (from 2.2 in 2005 to 1.6 in 2011, P for trend=0.018) and strokes (from 2.0 in

2005 to 1.3 in 2011, P for trend<0.001). The unadjusted one-month survival rates by non-cardiac cause were almost stable during the study period.

Patient and EMS characteristics of OHCAs with non-cardiac origin according to the cause are shown in Table 2, and their outcomes in Table 4. The mean age of all OHCA patients with non-cardiac origin was 66.8 years and males were 58.0%. The proportion of bystander-witnessed arrests, ADL before arrests, first documented rhythm, type of bystander CPR, and advanced life supports such as intravascular fluid, intubation, and epinephrine exceedingly varied between the five groups. In the whole patients, the rate of one-month survival and neurologically favorable outcome was 5.3% and 1.3%. The proportion of one-month survival was 6.2% in external causes, 6.5% in respiratory diseases, 0.8% in malignant tumors, 4.9% in strokes, and 4.1% in others. Furthermore, patient and EMS characteristics of OHCAs in external causes are shown in Table 3, and their outcomes in Table 5. The characteristics and outcomes varied between the seven groups. The proportion of one-month survival was 14.3% in asphyxia, 4.2% in hanging, 0.7% in fall, 1.1% in submersion, 1.6% in traffic injury, 3.7% in drug overuse, and 1.6% in unclassified external cause. The proportion of bystander chest compression-only CPR and conventional CPR with rescue breathing was 23.2% and 13.1% in whole OHCAs with non-cardiac origin, and 22.1% and 14.3% in

bystander-witnessed OHCAs.

Table 6 shows factors contributing to one-month survival and neurologically favorable outcome after OHCAs with non-cardiac origin. In one-month survival, adults aged <65 years old (AOR 1.36, 95% CI 1.12-1.65), arrests witnessed by bystanders (AOR 4.13, 95% CI 3.35-5.09), good ADL before arrests (AOR 1.23, 95% CI 1.03-1.47), VF as first documented rhythm (AOR 2.04, 95% CI 1.42-2.92), public places (AOR 1.45, 95% CI 1.10-1.91), intravenous fluid (AOR 1.45, 95% CI 1.14-1.84), and early EMS response time (AOR for one-increment of minute 0.92, 95% CI 0.90-.095) were associated with improving outcome. However, type of bystander CPR, intubation, and epinephrine were not associated with better outcome. Compared with asphyxia, the AORs were significantly lower in respiratory diseases (0.51, 95% CI 0.40-0.65), malignant tumors (0.06, 95% CI 0.03-0.11), stroke (0.27, 95% CI 0.20-0.38), hanging (0.56, 95% CI 0.41-0.77), fall (0.03, 95% CI 0.01-0.06), drowning (0.16, 95% CI 0.09-0.29), and traffic injury (0.05, 95% CI 0.03-0.10). The proportion of one-month survival of the whole OHCAs with non-cardiac origin did not significantly increase (from 4.3% [86/2023] in 2005 to 4.9% [105/2126] in 2011) and the AOR for one-increment of year was 1.01 (95% CI 0.97-1.06). The AORs of neurologically favorable outcome after OHCAs with non-cardiac origin were almost

similar to those of one-month survival.

Subgroup analyses after dividing the two groups (internal and external causes) are shown in Supplemental Table. As for internal causes, arrests witnessed by bystanders (AOR 2.86, 95% CI 1.99-4.11), VF as first documented rhythm (AOR 2.35, 95% CI 1.30-4.24), and public places (AOR 2.01, 95% CI 1.21-3.36) were associated with improving outcome. As for external causes, adults (AOR 1.51, 95% CI 1.17-1.96), arrests witnessed by bystanders (AOR 5.03, 95% CI 3.71-6.81), good ADL before arrests (AOR 1.34, 95% CI 1.08-1.67), intravenous fluid (AOR 1.69, 95% CI 1.27-2.25), and early EMS response time (AOR for one-increment of minute 0.93, 95% CI 0.90-0.96) were associated with improving outcome.

DISCUSSION

The extensive OHCA registry in Osaka showed that one-month survival after OHCAs with non-cardiac origin was poor and the survival trends did not improve year-by-year. In addition, the survivals differed by detailed non-cardiac origin. To further improve survival after OHCAs, sufficient attention should be paid to the epidemiological characteristics of OHCAs with non-cardiac origin as much as those of OHCA with cardiac origin, and this study describing the actual situation regarding the incidence and outcome of OHCAs with non-cardiac origin provides valuable information to improve the survival.

Our study observed that the outcomes of OHCAs with non-cardiac origin were poor and stable during the seven years. In a previous study in Japan, neurologically favorable outcome of bystander-witnessed OHCAs with non-cardiac origin increased from 2005 to 2011, but the absolute survival was very low,[7] and this result was similar with ours. Improving the outcome of OHCAs with non-cardiac origin poses an important problem in resuscitation science because 20~40% of adult OHCAs are of non-cardiac origin.[7-13] In addition, the survivals exceedingly differed by detailed non-cardiac origin, which also suggests the need and importance of an origin-specific strategy for improving the outcomes.

We also showed that the OHCA incidence trends differed by detailed non-cardiac origin. For instance, the incidence rate of OHCAs due to strokes significantly decreased during the study period. Although the reasons for the decrement were unclear, better blood pressure control and decreasing smoking rate in recent years of Japan might be one of the possible explanations for this phenomenon.[20] In fact, the numbers of stroke patients in Japan has also been decreasing.[21] On the other hand, the incidence rates of OHCAs with external causes in our region increased and the outcomes after OHCAs with external causes excluding asphyxia were miserable. However, there were regional variations on the incidence and outcome from OHCAs with external causes.[22,23] For example, external OHCAs due to trauma, drug overdose, or hanging in metropolitan area of Australia were more common and the survivals from traumatic and hanging-associated OHCAs were not always futile, and the countermeasures would, therefore, differ by regions. Most importantly, more efforts should focus on prevention of OHCAs with external causes because many of them are preventable.[1-4]

In a multivariable analysis, intravenous fluid administration was associated with better one-month survival after OHCAs with non-cardiac origin. In preceding studies, prehospital intravenous fluid for OHCAs including both cardiac and non-cardiac

origins was not associated with the improved outcome,[24] whereas intravenous access were associated with a reduction in hospital mortality among non-injured, non-cardiac arrest patients.[25] Thus, the effects of fluid administration on prehospital emergency patients were under debate, and further investigations by other cohorts or randomized controlled trials are needed to confirm these associations.

In this study, a multivariate analysis also underscored that either bystander-initiated chest compression-only CPR or conventional CPR with rescue breathing was not effective for OHCAs with non-cardiac origin. From a nationwide study focused on 43,000 bystander-witnessed OHCAs with non-cardiac origin, we demonstrated that conventional CPR with rescue breathing had an incremental benefit for OHCAs with non-cardiac origin, but the impact on the overall survival after OHCA was small.[8] Considering these results, the effectiveness of bystander CPR on OHCAs with non-cardiac origin in our region might be related to the significantly high rates of attempted EMS resuscitation in Japan compared with western countirs.[22,26] However, as recommended in the CPR guidelines,[1-4] bystander CPR plays a key role in the "chain of survival" and increasing the proportion of bystander CPR for OHCA patients is important.

Furthermore, factors such as arrests witnessed by bystanders and earlier EMS

response time were also independent predictors of better outcome after OHCAs with non-cardiac origin in a multivariate analysis. This would indicate the importance of an early EMS activation in the chain of survival[1-4] and suggests that activating the EMS system quickly leads to improving the outcomes after OHCAs with non-cardiac origin. In addition, the verification of the effects on prehospital emergency care as well as in-hospital treatment is essential to improve survival after OHCAs with non-cardiac origin.

The present study has some inherent limitations. First, the category of presumed cardiac or non-cardiac causes is made clinically, as per the Utstein-style international guidelines for cardiac arrest data reporting.[14,15] Second, information on post-arrest care is lacking. In-hospital treatment (e.g., hemodynamic support, cardiovascular intervention, induced hypothermia) might affect survival after OHCA.[27] Third, unmeasured confounding factors may have influenced the association between OHCAs with non-cardiac origin and the outcome.

CONCLUSION

The large OHCA registry in Osaka demonstrated that one-month survival after OHCAs with non-cardiac origin was poor, the survival trends did not improve year-by-year, and

the survivals differed by detailed non-cardiac origin. Further monitoring and discussion for epidemiology and outcome of OHCAs with non-cardiac origin are warranted to improve survival after OHCA in this group.

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Contributors

All authors (TK, KK, TS, TI, CN, KK, TN, YH, YK, KY, and TS) participated in the study conception and design, acquisition of data, analysis and interpretation of data, drafting the article and revising it critically for important intellectual content, and final approval of the manuscript.

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Competing interests

None.

Ethics approval

The study was approved by the institutional review board of Osaka University with the assent of the EMS authorities of the local governments in Osaka Prefecture.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data sharing statement

TK had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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2

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Figure Legends

Figure 1 Overview of EMS-treated cardiac arrests with an abridged Utstein template from January 1, 2005 to December 31, 2011. EMS, emergency medical service.

Table 1 Age-adjusted incidences and unadjusted one-month survival rate of out-of-hospital cardiac arrests with non-cardiac origin according to the cause over time

	2005	2006	2007	2008	2009	2010	2011	P for trend
Age-adjusted Incidence per 100,000 persons								
External causes	12.4	12.3	13.2	12.8	13.2	13.3	13.3	0.024
Asphyxia	2.7	3.0	2.8	3.4	3.1	2.9	2.9	0.726
Hanging	3.4	3.4	4.1	3.4	3.7	3.9	3.9	0.158
Fall	2.4	2.5	3.1	2.4	2.9	3.0	2.7	0.396
Drowning	1.2	1.1	1.2	1.4	1.2	1.3	1.6	0.065
Traffic injury	1.6	1.5	1.4	1.4	1.4	1.5	1.4	0.229
Drug overdose	0.5	0.4	0.2	0.4	0.4	0.4	0.3	0.304
Unclassified	0.5	0.5	0.4	0.3	0.5	0.4	0.5	0.447
Respiratory diseases	2.2	1.8	1.8	1.7	1.3	1.3	1.6	0.018
Malignant tumors	1.6	1.8	1.8	1.7	1.5	1.3	1.6	0.109
Strokes	2.0	1.8	1.8	1.6	1.4	1.2	1.3	< 0.001
Others	2.7	3.3	3.1	2.9	2.7	2.5	2.4	0.087
Unadjusted one-month survival, % (n/N)								
External causes	4.8 (53/1100)	6.8 (72/1059)	5.7 (66/1164)	7.2 (85/1184)	7.1 (86/1207)	6.1 (75/1225)	5.6 (73/1300)	0.736
Asphyxia	10.4 (35/337)	15.4 (53/344)	13.0 (44/338)	15.6 (67/430)	16.3 (66/406)	14.8 (58/393)	14.0 (59/422)	0.374
Hanging	4.6 (12/261)	4.7 (12/255)	5 (16/318)	4.8 (13/273)	4.9 (14/287)	3.3 (10/301)	2.3 (7/304)	0.101
Fall	0.6 (1/159)	0.6 (1/169)	0.9 (2/219)	1.2 (2/165)	0.0 (0/197)	0.5 (1/208)	1.1 (2/183)	NA
Drowning	1.3 (2/151)	3.3 (4/120)	0.0 (0/128)	1.3 (2/159)	2.1 (3/144)	0.7 (1/148)	0.0 (0/212)	NA
Traffic injury	0.9 (1/116)	1.0 (1/101)	1.8 (2/109)	0.9 (1/106)	1.9 (2/103)	1.7 (2/115)	2.6 (3/115)	0.027

Drug overdose	3.0 (1/33)	0.0 (0/29)	5.6 (1/18)	0.0 (0/25)	3.3 (1/30)	11.1 (3/27)	4.0 (1/25)	NA
Unclassified	2.3 (1/43)	2.4 (1/41)	2.9 (1/34)	0.0 (0/26)	0.0 (0/40)	0.0 (0/33)	2.6 (1/39)	NA
Respiratory diseases	6.4 (17/267)	3.9 (8/206)	8.0 (17/212)	9.8 (21/214)	6.7 (11/165)	4.7 (8/169)	5.6 (12/215)	0.875
Malignant tumors	0.5 (1/186)	0.5 (1/194)	1.0 (2/202)	1.0 (2/196)	0.0 (0/178)	2.5 (4/159)	0.5 (1/194)	NA
Strokes	3.6 (7/196)	6.1 (11/179)	4.5 (8/176)	3.2 (5/154)	4.9 (7/143)	6.0 (8/134)	6.8 (9/132)	0.241
Others	2.9 (8/277)	7.0 (22/314)	1.3 (4/308)	4.5 (14/311)	4.3 (12/278)	5.3 (15/281)	3.5 (10/285)	0.808

NA indicates not analyzed.

Table 2 Patient and EMS characteristics of out-of-hospital cardiac arrests with non-cardiac origin according to the cause

	Total (n =14,164)		External causes (n = 8239)		Respiratory diseases (n =1448)		Malignant tumors (n =1309)		Strokes (n =1114)		Others (n =2054)		*P* value*
Age, yr, mean (SD)	66.8	(19.0)	63.5	(20.5)	76.1	(14.2)	71.9	(12.0)	67.7	(14.7)	69.8	(17.6)	< 0.001
Age group, n (%)													< 0.001
Adults aged 20-64 years	5513	(38.9)	3826	(46.4)	229	(15.8)	345	(26.4)	447	(40.1)	666	(32.4)	
Elderly aged >=65 years	8651	(61.1)	4413	(53.6)	1219	(84.2)	964	(73.6)	667	(59.9)	1388	(67.6)	
Men, n (%)	8215	(58.0)	4789	(58.1)	844	(58.3)	881	(67.3)	559	(50.2)	1142	(55.6)	< 0.001
Arrests witnessed by bystanders, n (%)	5561	(39.3)	2952	(35.8)	682	(47.1)	639	(48.8)	493	(44.3)	795	(38.7)	< 0.001
Good activities of daily living, n (%)	8522	(60.2)	5213	(63.3)	653	(45.1)	443	(33.8)	896	(80.4)	1317	(64.1)	< 0.001
First documented rhythm, n (%)													< 0.001
VF	324	(2.3)	119	(1.4)	35	(2.4)	26	(2.0)	69	(6.2)	75	(3.7)	
PEA	3356	(23.7)	1853	(22.5)	394	(27.2)	262	(20.0)	329	(29.5)	518	(25.2)	
Asystole	10196	(72.0)	6124	(74.3)	983	(67.9)	1008	(77.0)	647	(58.1)	1434	(69.8)	
Others	288	(2.0)	143	(1.7)	36	(2.5)	13	(1.0)	69	(6.2)	27	(1.3)	
Location of arrest, n (%)													< 0.001
Homes	9010	(63.6)	4435	(53.8)	1098	(75.8)	1217	(93.0)	801	(71.9)	1459	(71.0)	
Public places	2035	(14.4)	1608	(19.5)	59	(4.1)	24	(1.8)	156	(14.0)	188	(9.2)	
Work places	346	(2.4)	223	(2.7)	7	(0.5)	4	(0.3)	48	(4.3)	64	(3.1)	
Health care facilities	1505	(10.6)	904	(11.0)	248	(17.1)	55	(4.2)	63	(5.7)	235	(11.4)	
Others	1268	(9.0)	1069	(13.0)	36	(2.5)	9	(0.7)	46	(4.1)	108	(5.3)	
Public-access AED use, n (%)	13	(0.1)	4	(0.05)	2	(0.1)	0	(0.0)	5	(0.4)	2	(0.1)	0.001
Type of Bystander CPR, n (%)													< 0.001
No CPR	9023	(63.7)	5383	(65.3)	836	(57.7)	889	(67.9)	633	(56.8)	1282	(62.4)	
Chest compression-only CPR	3288	(23.2)	1811	(22.0)	408	(28.2)	297	(22.7)	283	(25.4)	489	(23.8)	

Conventional CPR with rescue breathing	1853	(13.1)	1045	(12.7)	204	(14.1)	123	(9.4)	198	(17.8)	283	(13.8)		
Intravascular fluid, n (%)	2320	(16.4)	1458	(17.7)	202	(14.0)	113	(8.6)	230	(20.6)	317	(15.4)	<	0.001
Intubation, n (%)	2639	(18.6)	1364	(16.6)	338	(23.3)	242	(18.5)	257	(23.1)	438	(21.3)	<	0.001
Epinephrine, n (%)	987	(7.0)	572	(6.9)	88	(6.1)	49	(3.7)	125	(11.2)	153	(7.4)	<	0.001
Call to contact with a patient by EMS (EMS response time), min, mean (SD)	7.9	(4.1)	8.0	(4.6)	7.7	(3.0)	7.7	(2.7)	7.7	(2.8)	7.9	(3.8)		0.003
Call to CPR by EMS, min, mean (SD)	8.5	(4.5)	8.8	(5.1)	8.1	(3.1)	8.1	(2.8)	8.2	(2.9)	8.4	(4.2)	<	0.001
Call to hospital arrival, min, mean (SD)	28.2	(8.6)	28.4	(8.6)	27.3	(8.2)	28.0	(8.9)	28.2	(8.4)	28.1	(8.7)		0.001

*P values are calculated to test the homogeneity among the 5 cause groups.

EMS indicates emergency medical services; CPR, cardiopulmonary resuscitation; VF, ventricular fibrillation; PEA, pulseless electrical activity; AED, automated external defibrillator; SD, standard deviation.

Data on the times from call to contact with a patient, CPR by EMS, and hospital arrival were missing for 33, 40, and 166 victims, respectively.

Table 3 Patient and EMS characteristics of out-of-hospital cardiac arrests with external causes according to the cause

	Asphyxia (n = 2670)	Hanging (n = 1999)	Fall (n = 1300)	Drowning (n = 1062)	Traffic injury (n = 765)	Drug overdose (n = 187)	Unclassified (n = 256)	*P* value*
Age, yr, mean (SD)	77.9 (14.4)	55.6 (17.4)	47.4 (17.4)	73.1 (14.8)	52.6 (19.0)	49.9 (19.5)	58.1 (19.3)	< 0.001
Age group, n (%)								< 0.001
Adults aged 20-64 years	403 (15.1)	1136 (66.8)	1055 (81.2)	210 (19.8)	523 (68.4)	141 (75.4)	158 (61.7)	
Elderly aged >=65 years	2267 (84.9)	663 (33.2)	245 (18.8)	852 (80.2)	242 (31.6)	46 (24.6)	98 (38.3)	
Men, n (%)	1345 (50.4)	1290 (64.5)	781 (60.1)	530 (49.9)	558 (72.9)	117 (62.6)	168 (65.6)	< 0.001
Arrests witnessed by bystanders, n (%)	1801 (67.5)	27 (1.4)	510 (39.2)	56 (5.3)	476 (62.2)	10 (5.3)	72 (28.1)	< 0.001
Good activities of daily living, n (%)	1099 (41.2)	1769 (88.5)	685 (52.7)	854 (80.4)	517 (67.6)	133 (71.1)	156 (60.9)	< 0.001
First documented rhythm, n (%)								< 0.001
VF	56 (2.1)	13 (0.7)	19 (1.5)	12 (1.1)	14 (1.8)	1 (0.5)	4 (1.6)	
PEA	960 (36.0)	198 (9.9)	274 (21.1)	72 (6.8)	259 (33.9)	20 (10.7)	70 (27.3)	
Asystole	1589 (59.5)	1775 (88.8)	985 (75.8)	970 (91.3)	469 (61.3)	160 (85.6)	176 (68.8)	
Others	65 (2.4)	13 (0.7)	22 (1.7)	8 (0.8)	23 (3.0)	6 (3.2)	6 (2.3)	
Location of arrest, n (%)								< 0.001
Homes	1596 (59.8)	1667 (83.4)	139 (10.7)	770 (72.5)	2 (0.3)	150 (80.2)	111 (43.4)	
Public places	139 (5.2)	86 (4.3)	553 (42.5)	83 (7.8)	677 (88.5)	14 (7.5)	56 (21.9)	
Workplaces	35 (1.3)	94 (4.7)	44 (3.4)	3 (0.3)	7 (0.9)	7 (3.7)	33 (12.9)	
Health care facilities	835 (31.3)	27 (1.4)	12 (0.9)	14 (1.3)	1 (0.1)	0 (0.0)	15 (5.9)	
Others	65 (2.4)	125 (6.3)	552 (42.5)	192 (18.1)	78 (10.2)	16 (8.6)	41 (16.0)	

Public-access AED use, n (%)	4	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0.214
Type of Bystander CPR, n (%)															< 0.001
No CPR	1386	(51.9)	1174	(58.7)	1191	(91.6)	608	(57.3)	673	(88.0)	154	(82.4)	197	(77.0)	
Chest compression-only CPR	748	(28.0)	549	(27.5)	93	(7.2)	281	(26.5)	74	(9.7)	23	(12.3)	43	(16.8)	
Conventional CPR with rescue breathing	536	(20.1)	276	(13.8)	16	(1.2)	173	(16.3)	18	(2.4)	10	(5.3)	16	(6.2)	
Intravascular fluid, n (%)	540	(20.2)	393	(19.7)	107	(8.2)	281	(26.5)	76	(9.9)	27	(14.4)	34	(13.3)	< 0.001
Intubation, n (%)	800	(30.0)	167	(8.4)	41	(3.2)	251	(23.6)	31	(4.1)	33	(17.6)	41	(16.0)	< 0.001
Epinephrine, n (%)	326	(12.2)	83	(4.2)	41	(3.2)	68	(6.4)	37	(4.8)	6	(3.2)	11	(4.3)	< 0.001
Call to contact with a patient by EMS (EMS response time), min, mean (SD)	7.6	(2.9)	7.8	(3.3)	7.4	(3.3)	9.4	(7.6)	7.6	(4.2)	14.2	(10.7)	9.4	(7.3)	< 0.001
Call to CPR by EMS personnel, min, mean (SD)	7.9	(3.1)	8.6	(3.9)	8.2	(3.8)	10.0	(7.5)	9.3	(5.9)	14.4	(10.0)	11.0	(8.7)	< 0.001
Call to hospital arrival, min, mean (SD)	28.6	(8.6)	28.2	(7.9)	27.5	(8.3)	29.1	(9.3)	27.1	(8.8)	32.1	(11.1)	29.5	(9.4)	< 0.001

*P values are calculated to test the homogeneity among the 7 cause groups.

EMS indicates emergency medical services; CPR, cardiopulmonary resuscitation; VF, ventricular fibrillation; PEA, pulseless electrical activity; AED, automated external defibrillator; SD, standard deviation.

Table 4 Outcomes after out-of-hospital cardiac arrests with non-cardiac origin according to the cause

	Total (n = 1,4164)	External causes (n = 8239)	Respiratory diseases (n = 1448)	Malignant tumors (n = 1309)	Strokes (n = 1114)	Others (n =2054)	*P* value*
Prehospital ROSC, n (%)	1229 (8.7)	703 (8.5)	114 (7.9)	57 (4.4)	216 (19.4)	139 (6.8)	< 0.001
Total ROSC, n (%)	4744 (33.5)	2638 (32.0)	620 (42.8)	234 (17.9)	650 (58.3)	602 (29.3)	< 0.001
Hospital admission, n (%)	4142 (29.2)	2356 (28.6)	530 (36.6)	173 (13.2)	585 (52.5)	498 (24.2)	< 0.001
One-month survival, n (%)	755 (5.3)	510 (6.2)	94 (6.5)	11 (0.8)	55 (4.9)	85 (4.1)	< 0.001
Neurologically favorable outcome, n (%)	188 (1.3)	105 (1.3)	27 (1.9)	2 (0.2)	17 (1.5)	37 (1.8)	< 0.001

*P values are calculated to test the homogeneity among the 5 cause groups.

ROSC indicates return of spontaneous circulation.

Data on one-month survival and neurological status were missing for 7 victims.

Table 5 Outcomes after out-of-hospital cardiac arrests with external causes according to the cause

	Asphyxia (n = 2670)	Hanging (n = 1999)	Fall (n = 1300)	Drowning (n = 1062)	Traffic injury (n = 765)	Drug overdose (n = 187)	Unclassified (n = 256)	*P* value*
Prehospital ROSC, n (%)	463 (17.3)	144 (7.2)	22 (1.7)	36 (3.4)	28 (3.7)	4 (2.1)	6 (2.3)	< 0.001
Total ROSC, n (%)	1003 (37.6)	1500 (75.0)	1213 (93.3)	894 (84.2)	637 (83.3)	143 (76.5)	211 (82.4)	< 0.001
Hospital admission, n (%)	1529 (57.3)	453 (22.7)	62 (4.8)	147 (13.8)	92 (12.0)	40 (21.4)	33 (12.9)	< 0.001
One-month survival, n (%)	382 (14.3)	84 (4.2)	9 (0.7)	12 (1.1)	12 (1.6)	7 (3.7)	4 (1.6)	< 0.001
Neurologically favorable outcome, n (%)	71 (2.7)	17 (0.9)	1 (0.1)	4 (0.4)	6 (0.8)	4 (2.1)	2 (0.8)	< 0.001

*P values are calculated to test the homogeneity among the 7 cause groups.

ROSC indicates return of spontaneous circulation.

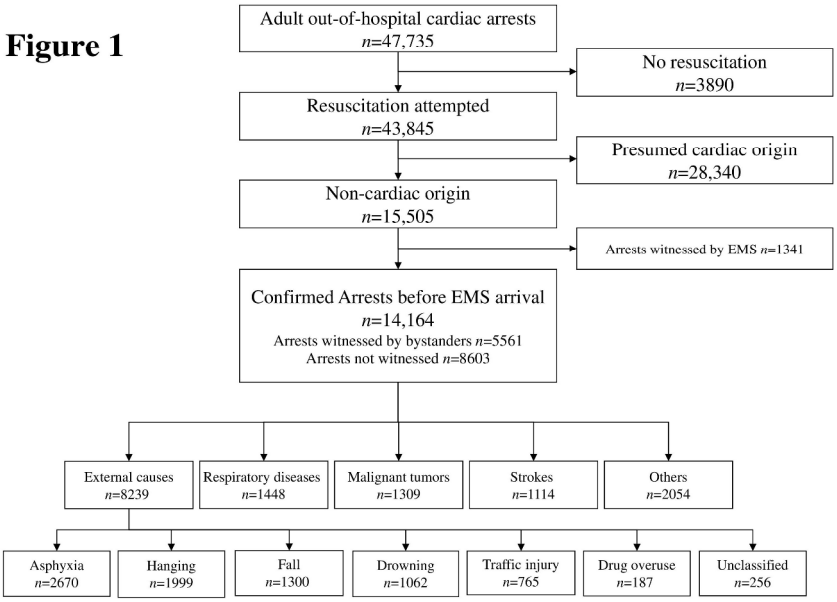
Table 6 Factors associated with outcomes after out-of-Hospital cardiac arrests with non-cardiac origin

	One-month survival				Neurologically favorable outcome			
	Crude OR	(95% CI)	Adjusted OR	(95% CI)	Crude OR	(95% CI)	Adjusted OR	(95% CI)
Adults (versus elderly)	0.95	(0.82-1.10)	1.36	(1.12-1.65)	1.02	(0.76-1.37)	1.52	(1.07-2.15)
Men	0.75	(0.64-0.88)	0.99	(0.84-1.16)	1.09	(0.81-1.46)	0.91	(0.67-1.24)
Witnessed by bystanders	4.41	(3.74-5.19)	4.13	(3.35-5.09)	4.48	(3.23-6.21)	4.83	(3.21-7.29)
Good activities of daily living	0.93	(0.80-1.08)	1.23	(1.03-1.47)	1.39	(1.02-1.88)	1.43	(1.02-2.02)
VF	2.74	(1.96-3.82)	2.04	(1.42-2.92)	7.72	(5.05-11.79)	5.40	(3.40-8.59)
Type of bystander CPR								
No CPR	Reference		Reference		Reference		Reference	
Chest compression-only CPR	0.97	(0.81-1.16)	0.80	(0.66-0.98)	0.95	(0.67-1.35)	0.92	(0.64-1.33)
Conventional CPR with rescue breathing	1.47	(1.20-1.79)	1.07	(0.86-1.34)	1.01	(0.65-1.55)	0.89	(0.56-1.42)
Type of non-cardiac origin								
Respiratory diseases	0.42	(0.33-0.53)	0.51	(0.40-0.65)	0.70	(0.44-1.09)	0.76	(0.48-1.21)
Malignant tumors	0.05	(0.03-0.09)	0.06	(0.03-0.11)	0.06	(0.01-0.23)	0.06	(0.01-0.23)
Strokes	0.31	(0.23-0.42)	0.27	(0.20-0.38)	0.57	(0.33-0.97)	0.34	(0.19-0.61)
Asphyxia	Reference		Reference		Reference		Reference	
Hanging	0.26	(0.21-0.34)	0.56	(0.41-0.77)	0.31	(0.18-0.53)	0.55	(0.28-1.07)
Fall	0.04	(0.02-0.08)	0.03	(0.01-0.06)	0.03	(0.004-0.20)	0.01	(0.002-0.11)
Drowning	0.07	(0.04-0.12)	0.16	(0.09-0.29)	0.14	(0.05-0.38)	0.31	(0.11-0.90)

Traffic injury	0.10 (0.05-0.17)	0.05 (0.03-0.10)	0.29 (0.13-0.67)	0.10 (0.04-0.26)
Drug overdose	0.23 (0.11-0.50)	0.58 (0.26-1.29)	0.80 (0.29-2.21)	1.74 (0.58-5.19)
Others	0.26 (0.20-0.33)	0.29 (0.22-0.38)	0.67 (0.45-1.00)	0.60 (0.39-0.92)
Unclassified	0.10 (0.04-0.26)	0.10 (0.04-0.28)	0.29 (0.07-1.18)	0.27 (0.06-1.16)
Location of arrest				
Homes	Reference	Reference	Reference	Reference
Public places	0.78 (0.61-0.99)	1.45 (1.10-1.91)	1.11 (0.75-1.65)	1.54 (0.97-2.44)
Workplaces	1.29 (0.83-1.98)	1.40 (0.87-2.23)	1.26 (0.55-2.89)	0.95 (0.39-2.30)
Health care facilities	1.69 (1.38-2.07)	0.88 (0.69-1.12)	0.72 (0.42-1.24)	0.47 (0.26-0.85)
Others	0.70 (0.51-0.94)	1.67 (1.19-2.35)	0.68 (0.38-1.24)	1.35 (0.72-2.54)
Intravascular fluid	1.78 (1.50-2.11)	1.45 (1.14-1.84)	1.34 (0.94-1.91)	1.52 (0.97-2.38)
Intubation	1.62 (1.37-1.92)	1.02 (0.84-1.23)	0.73 (0.48-1.10)	0.50 (0.32-0.77)
Epinephrine	2.32 (1.87-2.88)	0.97 (0.71-1.32)	1.25 (0.74-2.09)	0.60 (0.31-1.17)
EMS response time (for one-increment of minute)	0.93 (0.91-0.96)	0.92 (0.90-0.95)	0.91 (0.86-0.96)	0.90 (0.84-0.95)
Year (for one-increment of year)	1.02 (0.98-1.06)	1.01 (0.97-1.06)	1.02 (0.95-1.09)	1.05 (0.97-1.13)

VF denotes ventricular fibrillation; CPR, cardiopulmonary resuscitation; EMS, emergency medical services; OR, odds ratio; CI, confidence interval.

Figure 1



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Supplemental Table Factors associated with one-month survival after out-of-hospital cardiac arrests with non-cardiac origin by internal and external causes

	One-month survival	
	Internal causes	External causes
	Adjusted OR (95% CI)	Adjusted OR (95% CI)
Adults (versus elderly)	1.01 (0.68 - 1.50)	1.51 (1.17 - 1.96)
Men	0.99 (0.71 - 1.40)	0.91 (0.75 - 1.11)
Witnessed by bystanders	2.86 (1.99 - 4.11)	5.03 (3.71 - 6.81)
Good activities of daily living	1.27 (0.87 - 1.85)	1.34 (1.08 - 1.67)
VF	2.35 (1.30 - 4.24)	0.44 (0.17 - 1.11)
Type of bystander CPR		
No CPR	Reference	Reference
Chest compression-only CPR	0.66 (0.43 - 1.01)	0.79 (0.61 - 1.01)
Conventional CPR with rescue breathing	0.83 (0.51 - 1.36)	1.18 (0.89 - 1.54)
Type of non-cardiac origin		
Respiratory diseases	Reference	– –
Malignant tumors	0.12 (0.06 - 0.23)	– –
Strokes	0.55 (0.37 - 0.82)	– –
Asphyxia	– –	Reference
Hanging	– –	0.60 (0.41 - 0.87)
Fall	– –	0.03 (0.01 - 0.06)
Drowning	– –	0.05 (0.03 - 0.11)
Traffic injury	– –	0.17 (0.09 - 0.31)
Drug overdose	– –	0.60 (0.26 - 1.36)
Location of arrest		
Homes	Reference	Reference
Public places	2.01 (1.21 - 3.36)	1.39 (0.94 - 2.04)
Workplaces	1.88 (0.69 - 5.15)	1.47 (0.77 - 2.80)
Health care facilities	1.00 (0.55 - 1.81)	0.82 (0.62 - 1.09)
Others	2.10 (0.99 - 4.47)	1.72 (1.12 - 2.63)
Intravascular fluid	0.65 (0.33 - 1.29)	1.69 (1.27 - 2.25)
Intubation	0.62 (0.39 - 0.97)	1.21 (0.96 - 1.52)
Epinephrine	1.89 (0.82 - 4.34)	0.93 (0.64 - 1.35)
EMS response time (for one-increment of minute)	0.97 (0.91 - 1.03)	0.93 (0.90 - 0.96)
Year (for one-increment of year)	1.02 (0.94 - 1.11)	1.01 (0.96 - 1.06)

VF denotes ventricular fibrillation; CPR, cardiopulmonary resuscitation; EMS, emergency medical services; OR, odds ratio; CI, confidence interval.

Epidemiology and outcome of adult out-of-hospital cardiac arrest with non-cardiac origin in Osaka: a population-based study

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ABSTRACT

Objectives: To evaluate epidemiological characteristics of out-of-hospital cardiac arrests (OHCAs) by detailed non-cardiac cause and factors associated with the outcomes after OHCAs with non-cardiac origin.

Design: A prospective, population-based observational study.

Setting: The Utstein Osaka Project.

Participants: 14,164 adult patients aged >=20 years old with OHCAs due to non-cardiac origin who were resuscitated by emergency-medical-service personnel or bystanders, and then were transported to medical institutions from January 2005 to December 2011.

Primary outcome measures: One-month survival after OHCA. Multiple logistic regression analysis was used to assess factors that were potentially associated with the outcome.

Results: During the study period, the one-month survival rate was 5.3% (755/14,164). The proportion of one-month survival was 6.2% (510/8239) in external causes, 6.5% (94/1148) in respiratory diseases, 0.8% (11/1309) in malignant tumors, 4.9% (55/1114) in strokes, and 4.1% (85/2054) in others. As for external causes, the proportion of one-month survival was 14.3% (382/2670) in asphyxia, 4.2% (84/1999) in hanging,

0.7% (9/1300) in fall, 1.1% (12/1062) in drowning, 1.6% (12/765) in traffic injury, 3.7% (7/187) in drug overuse, and 1.6% (4/256) in unclassified external causes. In a multivariate analysis, adults aged <65 years old, arrests witnessed by bystanders, good activities of daily living before arrests, ventricular fibrillation arrests, public places, intravenous fluid, and early emergency-medical-service response time were significant predictors for one-month outcome after OHCAs with non-cardiac origin. The proportion of one-month survival of the whole OHCAs with non-cardiac origin did not significantly increase (from 4.3% [86/2023] in 2005 to 4.9% [105/2126] in 2011) and the adjusted odds ratio for one-increment of year was 1.01 (95% confidence interval 0.97-1.06).

Conclusions: From a large OHCA registry in Osaka, we demonstrated that one-month survival after OHCAs with non-cardiac origin was poor and stable.

Strengths and limitations of this study

- This study showed that one-month survival after OHCAs with non-cardiac origin was poor and the survival trends did not improve year-by-year in Osaka during the study period from 2005 to 2011. In addition, the survivals exceedingly differed by detailed non-cardiac origin.
- The category of presumed non-cardiac causes is made clinically, as per the Utstein-style international guidelines for cardiac arrest data reporting.

INTRODUCTION

Out-of-hospital cardiac arrest (OHCA) is one of the leading causes of death in the industrialized world.[1-4] Although improvements in the chain of survival including the development of a public-access defibrillation system and revisions to cardiopulmonary resuscitation (CPR) guidelines have led to increased survival after OHCA with cardiac origin in some communities,[5-7] the outcome after OHCAs with non-cardiac origin remains generally poor.[7-13]

Importantly, 20% to 40% of adult OHCAs were reportedly of non-cardiac origin.[7-13] However, epidemiological characteristics of OHCA with non-cardiac origin have not been sufficiently investigated as much as those of OHCA with cardiac origin. Therefore, the evaluation of characteristics, trends, and outcomes by detailed non-cardiac cause and understanding the factors associated with the outcomes are needed to improve the survival after OHCAs with non-cardiac origin.

The Utstein Osaka Project is a large prospective population-based cohort study of OHCA in Osaka, Japan, covering about 8.8 million residents.[5] During the 7 years from 2005 to 2011, we enrolled approximately 14,000 OHCAs with non-cardiac origin before emergency-medical-service (EMS) arrival. The present study aimed to evaluate the epidemiological characteristics of OHCAs by detailed non-cardiac cause. In

addition, we evaluated factors associated with the outcomes after OHCAs with non-cardiac origin in a multivariate analysis.

METHODS

Study design and setting

The Utstein Osaka Project is a prospective, population-based registry of OHCA that is based on the standardized Utstein style.[14,15] This study enrolled adult patients aged =>20 years suffering OHCAs with non-cardiac origin before EMS arrival, who were resuscitated by EMS personnel or bystanders, and were transported to medical institutions in Osaka Prefecture from January 1, 2005 to December 31, 2011. In this study, we excluded pediatric OHCA patients because characteristics and outcomes from OHCAs differed between children and adults.[16,17]

Cardiac arrest was defined as the cessation of cardiac mechanical activity as confirmed by the absence of signs of circulation.[14,15] In this study, the arrests were classified into those of presumed cardiac origin and non-cardiac origin, the latter resulting from external causes, respiratory diseases, malignant tumors, strokes, and any other non-cardiac causes based on hospital medical records. Furthermore, external causes were divided into the seven categories: asphyxia, hanging, fall, drowning, traffic injury, drug overuse, and unclassified external causes. These diagnoses were made clinically by the physician in charge, working in collaboration with the EMS personnel.

EMS organization in Osaka

Details of the EMS system in Osaka were described previously.[5] Osaka is the second largest prefecture in Japan with a population of approximately 8.8 million inhabitants in an area of 1892 km^2. In Osaka, there are 34 fire stations with emergency dispatch centers. The EMS system is operated by the local fire stations. When called, an ambulance is dispatched from the nearest fire station. Emergency services are provided 24 hours each day by them, which is single-tiered in 32 stations and two-tiered in two stations. The latter uses medics followed by physicians.

Most highly-trained prehospital emergency care providers are called Emergency Life-Saving Technicians (ELSTs). Usually, each ambulance has a crew of three emergency providers including at least one ELST. They were allowed to insert an intravenous line and an adjunct airway, and to use a semi-automated external defibrillator for OHCA patients. Specially trained ELSTs were permitted to tracheal intubation since July 2004 and administer intravenous epinephrine since April 2006.

Do-not-resuscitate (DNR) orders or living wills are not generally accepted in Japan. EMS providers are not permitted to terminate resuscitation in the field. Therefore, almost patients with OHCA who were treated by EMS personnel were transported to a

hospital and enrolled in the Utstein Osaka Project, excluding those with decapitation, incineration, decomposition, rigor mortis, or dependent cyanosis.

CPR and AED training for the general public

The use of an automated external defibrillator (AED) by citizens was permitted legally in July 2004. In Osaka, approximately 14,000 citizens per year participated in the CPR training programs, consisting of conventional CPR including chest compressions, mouth-to-mouth ventilation, and AED usage by local fire departments, the Japan Red Cross, Inc., and the Osaka Life Support Association.[5] All EMS providers perform CPR according to the Japanese CPR guidelines.[4]

Data collection and quality control

Data collection were prospectively conducted using a form that included data recommended in the Utstein-style reporting guidelines for cardiac arrests.[14,15] These data included gender, age, first documented cardiac rhythm, witness status, location of arrests, activity of daily living (ADL) before arrests, time-courses of resuscitation, type of bystander-initiated CPR, public-access AED use, intravascular fluid, tracheal intubation, and intravascular epinephrine as well as prehospital return of spontaneous

circulation (ROSC), total ROSC, one-month survival, and neurological status one month after the event. First documented rhythm was recorded and diagnosed by the EMS personnel with semi-automated defibrillators on the scene, and confirmed by the physician who was responsible for the on-line medical direction. Bystander CPR included chest compression-only CPR and conventional CPR with rescue breathing. A series of EMS times of call receipt, vehicle arrival at the scene, contact with patients, initiation of CPR, defibrillation by EMS, and hospital arrival were recorded automatically at the dispatch center.

The data form was completed by the EMS personnel in cooperation with the physicians in charge of the patients, and the data were integrated into the registry system on the Information Center for Emergency Medical Services of Osaka, and then checked by the investigators. If the data sheet was incomplete, the relevant EMS personnel were contacted and questioned for data completion.

All survivors suffering OHCA were followed up for up to one-month after the event by the EMS personnel in charge. One-month neurological outcomes were determined by the physician responsible for treating the patient, using the cerebral performance category (CPC) scale: category 1, good cerebral performance; category 2, moderate cerebral disability; category 3, severe cerebral disability; category 4, coma or

vegetative state; and category 5, death.[14,15]

Outcome measures

The main outcome measure was one-month survival. Secondary outcome measures included prehospital and total ROSCs, admission to hospital, and one-month survival with neurologically favorable outcome. Neurologically favorable outcome was defined as CPC category 1 or 2.[14,15]

Statistical analysis

In this study, patient and EMS characteristics of OHCAs with non-cardiac origin and their outcomes were compared between the groups using unpaired analysis of variance for numerical variables, and chi-square test or Fisher's exact test for categorical variables by cause of arrest. First, non-cardiac causes were divided into the following five groups; external causes, respiratory diseases, malignant tumors, strokes, and any other non-cardiac causes. Next, external causes were further divided into asphyxia, hanging, fall, drowning, traffic injury, drug overuse, and unclassified external causes. Age-adjusted annual incidence of OHCAs by non-cardiac origin was calculated by the direct method using 2005 census data and 1985 Japanese model population.[18,19]

Poisson regression models for the trends in the incidence and one-month survival rate were used. Multiple logistic regression analysis assessed the factors associated with one-month survival and neurological favorable outcome, and adjusted odds ratios (AORs) and their 95% confidence intervals (CIs) were calculated. As potential confounders, factors that were biologically essential and considered to be associated with clinical outcomes were taken in the multivariable analyses.[7] These variables included age (20-64, >=65 years old), gender (men, women), witness status (none, witnessed by bystanders), ADL before arrests (good, other), first documented rhythm (VF, non-VF), bystander CPR status (none, compression-only CPR, conventional CPR), type of non-cardiac causes (the 11 categories described above), location of arrests (homes, public places, work places, health care facilities, others), intravascular fluid (yes, no), intubation (yes, no), epinephrine (yes, no), EMS response time (call to contact with patients), and year of arrest. In addition, we conducted a multivariate analysis of one-month survival from OHCAs with non-cardiac origin after dividing the two groups: internal (respiratory diseases, malignant tumors, and strokes) and external (asphyxia, hanging, fall, drowning, traffic injury, and drug overuse) causes.

All statistical analyses were performed using the SPSS statistical package ver21.0J (IBM Corp. Armonk, NY). All of the tests were 2-tailed and *P* values of <0.05 were

considered statistically significant.

RESULTS

Figure 1 shows an overview of the study patients based on the Utstein template. A total of 47,735 adult arrests were documented during these seven years. Resuscitation was attempted in 43,845, and 15,505 of them were of non-cardiac origin. Excluding 1341 victims who were witnessed by EMS (arrests after EMS arrival), 14,164 (5561 in bystander-witnessed cases and 8603 in non-witnessed cases) were eligible for our analyses. Among these arrests, 8239 (58.2%) were due to external causes, 1448 (10.2%) respiratory diseases, 1309 (9.2%) malignant tumors, 1114 (7.9%) strokes, and 2054 (14.5%) others. Among external causes, 2670 (16.5%) were of asphyxia, 1999 (14.1%) hanging, 1300 (9.2%) fall, 1062 (7.5%) drowning, 765 (5.4%) traffic injury, and 256 (1.8%) unclassified external cause. We could not obtain information on one-month survival and neurological status for 7 (0.05%) among 14,164 eligible victims.

The age-adjusted annual incidence rates per 100,000 persons by non-cardiac cause were calculated over time (Table 1). The incidence rate of OHCAs with external causes significantly increased from 12.4 in 2005 to 13.3 in 2011 (P for trend=0.024). The incidence rate significantly decreased among OHCA patients with respiratory diseases (from 2.2 in 2005 to 1.6 in 2011, P for trend=0.018) and strokes (from 2.0 in

2005 to 1.3 in 2011, P for trend<0.001). The unadjusted one-month survival rates by non-cardiac cause were almost stable during the study period.

Patient and EMS characteristics of OHCAs with non-cardiac origin according to the cause are shown in Table 2, and their outcomes in Table 4. The mean age of all OHCA patients with non-cardiac origin was 66.8 years and males were 58.0%. The proportion of bystander-witnessed arrests, ADL before arrests, first documented rhythm, type of bystander CPR, and advanced life supports such as intravascular fluid, intubation, and epinephrine exceedingly varied between the five groups. In the whole patients, the rate of one-month survival and neurologically favorable outcome was 5.3% and 1.3%. The proportion of one-month survival was 6.2% in external causes, 6.5% in respiratory diseases, 0.8% in malignant tumors, 4.9% in strokes, and 4.1% in others. Furthermore, patient and EMS characteristics of OHCAs in external causes are shown in Table 3, and their outcomes in Table 5. The characteristics and outcomes varied between the seven groups. The proportion of one-month survival was 14.3% in asphyxia, 4.2% in hanging, 0.7% in fall, 1.1% in submersion, 1.6% in traffic injury, 3.7% in drug overuse, and 1.6% in unclassified external cause. The proportion of bystander chest compression-only CPR and conventional CPR with rescue breathing was 23.2% and 13.1% in whole OHCAs with non-cardiac origin, and 22.1% and 14.3% in

bystander-witnessed OHCAs.

Table 6 shows factors contributing to one-month survival and neurologically favorable outcome after OHCAs with non-cardiac origin. In one-month survival, adults aged <65 years old (AOR 1.36, 95% CI 1.12-1.65), arrests witnessed by bystanders (AOR 4.13, 95% CI 3.35-5.09), good ADL before arrests (AOR 1.23, 95% CI 1.03-1.47), VF as first documented rhythm (AOR 2.04, 95% CI 1.42-2.92), public places (AOR 1.45, 95% CI 1.10-1.91), intravenous fluid (AOR 1.45, 95% CI 1.14-1.84), and early EMS response time (AOR for one-increment of minute 0.92, 95% CI 0.90-.095) were associated with improving outcome. However, type of bystander CPR, intubation, and epinephrine were not associated with better outcome. Compared with asphyxia, the AORs were significantly lower in respiratory diseases (0.51, 95% CI 0.40-0.65), malignant tumors (0.06, 95% CI 0.03-0.11), stroke (0.27, 95% CI 0.20-0.38), hanging (0.56, 95% CI 0.41-0.77), fall (0.03, 95% CI 0.01-0.06), drowning (0.16, 95% CI 0.09-0.29), and traffic injury (0.05, 95% CI 0.03-0.10). The proportion of one-month survival of the whole OHCAs with non-cardiac origin did not significantly increase (from 4.3% [86/2023] in 2005 to 4.9% [105/2126] in 2011) and the AOR for one-increment of year was 1.01 (95% CI 0.97-1.06). The AORs of neurologically favorable outcome after OHCAs with non-cardiac origin were almost

similar to those of one-month survival.

Subgroup analyses after dividing the two groups (internal and external causes) are shown in Supplemental Table. As for internal causes, arrests witnessed by bystanders (AOR 2.86, 95% CI 1.99-4.11), VF as first documented rhythm (AOR 2.35, 95% CI 1.30-4.24), and public places (AOR 2.01, 95% CI 1.21-3.36) were associated with improving outcome. As for external causes, adults (AOR 1.51, 95% CI 1.17-1.96), arrests witnessed by bystanders (AOR 5.03, 95% CI 3.71-6.81), good ADL before arrests (AOR 1.34, 95% CI 1.08-1.67), intravenous fluid (AOR 1.69, 95% CI 1.27-2.25), and early EMS response time (AOR for one-increment of minute 0.93, 95% CI 0.90-0.96) were associated with improving outcome.

DISCUSSION

The extensive OHCA registry in Osaka showed that one-month survival after OHCAs with non-cardiac origin was poor and the survival trends did not improve year-by-year. In addition, the survivals differed by detailed non-cardiac origin. To further improve survival after OHCAs, sufficient attention should be paid to the epidemiological characteristics of OHCAs with non-cardiac origin as much as those of OHCA with cardiac origin, and this study describing the actual situation regarding the incidence and outcome of OHCAs with non-cardiac origin provides valuable information to improve the survival.

Our study observed that the outcomes of OHCAs with non-cardiac origin were poor and stable during the seven years. In a previous study in Japan, neurologically favorable outcome of bystander-witnessed OHCAs with non-cardiac origin increased from 2005 to 2011, but the absolute survival was very low,[7] and this result was similar with ours. Improving the outcome of OHCAs with non-cardiac origin poses an important problem in resuscitation science because 20~40% of adult OHCAs are of non-cardiac origin.[7-13] In addition, the survivals exceedingly differed by detailed non-cardiac origin, which also suggests the need and importance of an origin-specific strategy for improving the outcomes.

We also showed that the OHCA incidence trends differed by detailed non-cardiac origin. For instance, the incidence rate of OHCAs due to strokes significantly decreased during the study period. Although the reasons for the decrement were unclear, better blood pressure control and decreasing smoking rate in recent years of Japan might be one of the possible explanations for this phenomenon.[20] In fact, the numbers of stroke patients in Japan has also been decreasing.[21] On the other hand, the incidence rates of OHCAs with external causes in our region increased and the outcomes after OHCAs with external causes excluding asphyxia were miserable. However, there were regional variations on the incidence and outcome from OHCAs with external causes.[22,23] For example, external OHCAs due to trauma, drug overdose, or hanging in metropolitan area of Australia were more common and the survivals from traumatic and hanging-associated OHCAs were not always futile, and the countermeasures would, therefore, differ by regions. Most importantly, more efforts should focus on prevention of OHCAs with external causes because many of them are preventable.[1-4]

In a multivariable analysis, intravenous fluid administration was associated with better one-month survival after OHCAs with non-cardiac origin. In preceding studies, prehospital intravenous fluid for OHCAs including both cardiac and non-cardiac

origins was not associated with the improved outcome,[24] whereas intravenous access were associated with a reduction in hospital mortality among non-injured, non-cardiac arrest patients.[25] Thus, the effects of fluid administration on prehospital emergency patients were under debate, and further investigations by other cohorts or randomized controlled trials are needed to confirm these associations.

In this study, a multivariate analysis also underscored that either bystander-initiated chest compression-only CPR or conventional CPR with rescue breathing was not effective for OHCAs with non-cardiac origin. From a nationwide study focused on 43,000 bystander-witnessed OHCAs with non-cardiac origin, we demonstrated that conventional CPR with rescue breathing had an incremental benefit for OHCAs with non-cardiac origin, but the impact on the overall survival after OHCA was small.[8] Considering these results, the effectiveness of bystander CPR on OHCAs with non-cardiac origin in our region might be related to the significantly high rates of attempted EMS resuscitation in Japan compared with western countirs.[22,26] However, as recommended in the CPR guidelines,[1-4] bystander CPR plays a key role in the "chain of survival" and increasing the proportion of bystander CPR for OHCA patients is important.

Furthermore, factors such as arrests witnessed by bystanders and earlier EMS

response time were also independent predictors of better outcome after OHCAs with non-cardiac origin in a multivariate analysis. This would indicate the importance of an early EMS activation in the chain of survival[1-4] and suggests that activating the EMS system quickly leads to improving the outcomes after OHCAs with non-cardiac origin. In addition, the verification of the effects on prehospital emergency care as well as in-hospital treatment is essential to improve survival after OHCAs with non-cardiac origin.

The present study has some inherent limitations. First, the category of presumed cardiac or non-cardiac causes is made clinically, as per the Utstein-style international guidelines for cardiac arrest data reporting.[14,15] Second, information on post-arrest care is lacking. In-hospital treatment (e.g., hemodynamic support, cardiovascular intervention, induced hypothermia) might affect survival after OHCA.[27] Third, unmeasured confounding factors may have influenced the association between OHCAs with non-cardiac origin and the outcome.

CONCLUSION

The large OHCA registry in Osaka demonstrated that one-month survival after OHCAs with non-cardiac origin was poor, the survival trends did not improve year-by-year, and

the survivals differed by detailed non-cardiac origin. Further monitoring and discussion for epidemiology and outcome of OHCAs with non-cardiac origin are warranted to improve survival after OHCA in this group.

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Contributors

All authors (TK, KK, TS, TI, CN, KK, TN, YH, YK, KY, and TS) participated in the study conception and design, acquisition of data, analysis and interpretation of data, drafting the article and revising it critically for important intellectual content, and final approval of the manuscript.

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Competing interests

None.

Ethics approval

The study was approved by the institutional review board of Osaka University with the assent of the EMS authorities of the local governments in Osaka Prefecture.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data sharing statement

TK had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Figure Legends

Figure 1 Overview of EMS-treated cardiac arrests with an abridged Utstein template from January 1, 2005 to December 31, 2011. EMS, emergency medical service.

Table 1 Age-adjusted incidences and unadjusted one-month survival rate of out-of-hospital cardiac arrests with non-cardiac origin according to the cause over time

	2005	2006	2007	2008	2009	2010	2011	P for trend
Age-adjusted Incidence per 100,000 persons								
External causes	12.4	12.3	13.2	12.8	13.2	13.3	13.3	0.024
Asphyxia	2.7	3.0	2.8	3.4	3.1	2.9	2.9	0.726
Hanging	3.4	3.4	4.1	3.4	3.7	3.9	3.9	0.158
Fall	2.4	2.5	3.1	2.4	2.9	3.0	2.7	0.396
Drowning	1.2	1.1	1.2	1.4	1.2	1.3	1.6	0.065
Traffic injury	1.6	1.5	1.4	1.4	1.4	1.5	1.4	0.229
Drug overdose	0.5	0.4	0.2	0.4	0.4	0.4	0.3	0.304
Unclassified	0.5	0.5	0.4	0.3	0.5	0.4	0.5	0.447
Respiratory diseases	2.2	1.8	1.8	1.7	1.3	1.3	1.6	0.018
Malignant tumors	1.6	1.8	1.8	1.7	1.5	1.3	1.6	0.109
Strokes	2.0	1.8	1.8	1.6	1.4	1.2	1.3	< 0.001
Others	2.7	3.3	3.1	2.9	2.7	2.5	2.4	0.087
Unadjusted one-month survival, % (n/N)								
External causes	4.8 (53/1100)	6.8 (72/1059)	5.7 (66/1164)	7.2 (85/1184)	7.1 (86/1207)	6.1 (75/1225)	5.6 (73/1300)	0.736
Asphyxia	10.4 (35/337)	15.4 (53/344)	13.0 (44/338)	15.6 (67/430)	16.3 (66/406)	14.8 (58/393)	14.0 (59/422)	0.374
Hanging	4.6 (12/261)	4.7 (12/255)	5 (16/318)	4.8 (13/273)	4.9 (14/287)	3.3 (10/301)	2.3 (7/304)	0.101
Fall	0.6 (1/159)	0.6 (1/169)	0.9 (2/219)	1.2 (2/165)	0.0 (0/197)	0.5 (1/208)	1.1 (2/183)	NA
Drowning	1.3 (2/151)	3.3 (4/120)	0.0 (0/128)	1.3 (2/159)	2.1 (3/144)	0.7 (1/148)	0.0 (0/212)	NA
Traffic injury	0.9 (1/116)	1.0 (1/101)	1.8 (2/109)	0.9 (1/106)	1.9 (2/103)	1.7 (2/115)	2.6 (3/115)	0.027

Drug overdose	3.0 (1/33)	0.0 (0/29)	5.6 (1/18)	0.0 (0/25)	3.3 (1/30)	11.1 (3/27)	4.0 (1/25)	NA
Unclassified	2.3 (1/43)	2.4 (1/41)	2.9 (1/34)	0.0 (0/26)	0.0 (0/40)	0.0 (0/33)	2.6 (1/39)	NA
Respiratory diseases	6.4 (17/267)	3.9 (8/206)	8.0 (17/212)	9.8 (21/214)	6.7 (11/165)	4.7 (8/169)	5.6 (12/215)	0.875
Malignant tumors	0.5 (1/186)	0.5 (1/194)	1.0 (2/202)	1.0 (2/196)	0.0 (0/178)	2.5 (4/159)	0.5 (1/194)	NA
Strokes	3.6 (7/196)	6.1 (11/179)	4.5 (8/176)	3.2 (5/154)	4.9 (7/143)	6.0 (8/134)	6.8 (9/132)	0.241
Others	2.9 (8/277)	7.0 (22/314)	1.3 (4/308)	4.5 (14/311)	4.3 (12/278)	5.3 (15/281)	3.5 (10/285)	0.808

NA indicates not analyzed.

Table 2 Patient and EMS characteristics of out-of-hospital cardiac arrests with non-cardiac origin according to the cause

	Total (n =14,164)		External causes (n = 8239)		Respiratory diseases (n =1448)		Malignant tumors (n =1309)		Strokes (n =1114)		Others (n =2054)		*P* value*
Age, yr, mean (SD)	66.8	(19.0)	63.5	(20.5)	76.1	(14.2)	71.9	(12.0)	67.7	(14.7)	69.8	(17.6)	< 0.001
Age group, n (%)													< 0.001
Adults aged 20-64 years	5513	(38.9)	3826	(46.4)	229	(15.8)	345	(26.4)	447	(40.1)	666	(32.4)	
Elderly aged >=65 years	8651	(61.1)	4413	(53.6)	1219	(84.2)	964	(73.6)	667	(59.9)	1388	(67.6)	
Men, n (%)	8215	(58.0)	4789	(58.1)	844	(58.3)	881	(67.3)	559	(50.2)	1142	(55.6)	< 0.001
Arrests witnessed by bystanders, n (%)	5561	(39.3)	2952	(35.8)	682	(47.1)	639	(48.8)	493	(44.3)	795	(38.7)	< 0.001
Good activities of daily living, n (%)	8522	(60.2)	5213	(63.3)	653	(45.1)	443	(33.8)	896	(80.4)	1317	(64.1)	< 0.001
First documented rhythm, n (%)													< 0.001
VF	324	(2.3)	119	(1.4)	35	(2.4)	26	(2.0)	69	(6.2)	75	(3.7)	
PEA	3356	(23.7)	1853	(22.5)	394	(27.2)	262	(20.0)	329	(29.5)	518	(25.2)	
Asystole	10196	(72.0)	6124	(74.3)	983	(67.9)	1008	(77.0)	647	(58.1)	1434	(69.8)	
Others	288	(2.0)	143	(1.7)	36	(2.5)	13	(1.0)	69	(6.2)	27	(1.3)	
Location of arrest, n (%)													< 0.001
Homes	9010	(63.6)	4435	(53.8)	1098	(75.8)	1217	(93.0)	801	(71.9)	1459	(71.0)	
Public places	2035	(14.4)	1608	(19.5)	59	(4.1)	24	(1.8)	156	(14.0)	188	(9.2)	
Work places	346	(2.4)	223	(2.7)	7	(0.5)	4	(0.3)	48	(4.3)	64	(3.1)	
Health care facilities	1505	(10.6)	904	(11.0)	248	(17.1)	55	(4.2)	63	(5.7)	235	(11.4)	
Others	1268	(9.0)	1069	(13.0)	36	(2.5)	9	(0.7)	46	(4.1)	108	(5.3)	
Public-access AED use, n (%)	13	(0.1)	4	(0.05)	2	(0.1)	0	(0.0)	5	(0.4)	2	(0.1)	0.001
Type of Bystander CPR, n (%)													< 0.001
No CPR	9023	(63.7)	5383	(65.3)	836	(57.7)	889	(67.9)	633	(56.8)	1282	(62.4)	
Chest compression-only CPR	3288	(23.2)	1811	(22.0)	408	(28.2)	297	(22.7)	283	(25.4)	489	(23.8)	

Conventional CPR with rescue breathing	1853	(13.1)	1045	(12.7)	204	(14.1)	123	(9.4)	198	(17.8)	283	(13.8)		
Intravascular fluid, n (%)	2320	(16.4)	1458	(17.7)	202	(14.0)	113	(8.6)	230	(20.6)	317	(15.4)	<	0.001
Intubation, n (%)	2639	(18.6)	1364	(16.6)	338	(23.3)	242	(18.5)	257	(23.1)	438	(21.3)	<	0.001
Epinephrine, n (%)	987	(7.0)	572	(6.9)	88	(6.1)	49	(3.7)	125	(11.2)	153	(7.4)	<	0.001
Call to contact with a patient by EMS (EMS response time), min, mean (SD)	7.9	(4.1)	8.0	(4.6)	7.7	(3.0)	7.7	(2.7)	7.7	(2.8)	7.9	(3.8)		0.003
Call to CPR by EMS, min, mean (SD)	8.5	(4.5)	8.8	(5.1)	8.1	(3.1)	8.1	(2.8)	8.2	(2.9)	8.4	(4.2)	<	0.001
Call to hospital arrival, min, mean (SD)	28.2	(8.6)	28.4	(8.6)	27.3	(8.2)	28.0	(8.9)	28.2	(8.4)	28.1	(8.7)		0.001

*P values are calculated to test the homogeneity among the 5 cause groups.

EMS indicates emergency medical services; CPR, cardiopulmonary resuscitation; VF, ventricular fibrillation; PEA, pulseless electrical activity; AED, automated external defibrillator; SD, standard deviation.

Data on the times from call to contact with a patient, CPR by EMS, and hospital arrival were missing for 33, 40, and 166 victims, respectively.

Table 3 Patient and EMS characteristics of out-of-hospital cardiac arrests with external causes according to the cause

	Asphyxia (n = 2670)	Hanging (n = 1999)	Fall (n = 1300)	Drowning (n = 1062)	Traffic injury (n = 765)	Drug overdose (n = 187)	Unclassified (n = 256)	*P* value*
Age, yr, mean (SD)	77.9 (14.4)	55.6 (17.4)	47.4 (17.4)	73.1 (14.8)	52.6 (19.0)	49.9 (19.5)	58.1 (19.3)	< 0.001
Age group, n (%)								< 0.001
Adults aged 20-64 years	403 (15.1)	1136 (66.8)	1055 (81.2)	210 (19.8)	523 (68.4)	141 (75.4)	158 (61.7)	
Elderly aged >=65 years	2267 (84.9)	663 (33.2)	245 (18.8)	852 (80.2)	242 (31.6)	46 (24.6)	98 (38.3)	
Men, n (%)	1345 (50.4)	1290 (64.5)	781 (60.1)	530 (49.9)	558 (72.9)	117 (62.6)	168 (65.6)	< 0.001
Arrests witnessed by bystanders, n (%)	1801 (67.5)	27 (1.4)	510 (39.2)	56 (5.3)	476 (62.2)	10 (5.3)	72 (28.1)	< 0.001
Good activities of daily living, n (%)	1099 (41.2)	1769 (88.5)	685 (52.7)	854 (80.4)	517 (67.6)	133 (71.1)	156 (60.9)	< 0.001
First documented rhythm, n (%)								< 0.001
VF	56 (2.1)	13 (0.7)	19 (1.5)	12 (1.1)	14 (1.8)	1 (0.5)	4 (1.6)	
PEA	960 (36.0)	198 (9.9)	274 (21.1)	72 (6.8)	259 (33.9)	20 (10.7)	70 (27.3)	
Asystole	1589 (59.5)	1775 (88.8)	985 (75.8)	970 (91.3)	469 (61.3)	160 (85.6)	176 (68.8)	
Others	65 (2.4)	13 (0.7)	22 (1.7)	8 (0.8)	23 (3.0)	6 (3.2)	6 (2.3)	
Location of arrest, n (%)								< 0.001
Homes	1596 (59.8)	1667 (83.4)	139 (10.7)	770 (72.5)	2 (0.3)	150 (80.2)	111 (43.4)	
Public places	139 (5.2)	86 (4.3)	553 (42.5)	83 (7.8)	677 (88.5)	14 (7.5)	56 (21.9)	
Workplaces	35 (1.3)	94 (4.7)	44 (3.4)	3 (0.3)	7 (0.9)	7 (3.7)	33 (12.9)	
Health care facilities	835 (31.3)	27 (1.4)	12 (0.9)	14 (1.3)	1 (0.1)	0 (0.0)	15 (5.9)	
Others	65 (2.4)	125 (6.3)	552 (42.5)	192 (18.1)	78 (10.2)	16 (8.6)	41 (16.0)	

Public-access AED use, n (%)	4	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0.214
Type of Bystander CPR, n (%)															< 0.001
No CPR	1386	(51.9)	1174	(58.7)	1191	(91.6)	608	(57.3)	673	(88.0)	154	(82.4)	197	(77.0)	
Chest compression-only CPR	748	(28.0)	549	(27.5)	93	(7.2)	281	(26.5)	74	(9.7)	23	(12.3)	43	(16.8)	
Conventional CPR with rescue breathing	536	(20.1)	276	(13.8)	16	(1.2)	173	(16.3)	18	(2.4)	10	(5.3)	16	(6.2)	
Intravascular fluid, n (%)	540	(20.2)	393	(19.7)	107	(8.2)	281	(26.5)	76	(9.9)	27	(14.4)	34	(13.3)	< 0.001
Intubation, n (%)	800	(30.0)	167	(8.4)	41	(3.2)	251	(23.6)	31	(4.1)	33	(17.6)	41	(16.0)	< 0.001
Epinephrine, n (%)	326	(12.2)	83	(4.2)	41	(3.2)	68	(6.4)	37	(4.8)	6	(3.2)	11	(4.3)	< 0.001
Call to contact with a patient by EMS (EMS response time), min, mean (SD)	7.6	(2.9)	7.8	(3.3)	7.4	(3.3)	9.4	(7.6)	7.6	(4.2)	14.2	(10.7)	9.4	(7.3)	< 0.001
Call to CPR by EMS personnel, min, mean (SD)	7.9	(3.1)	8.6	(3.9)	8.2	(3.8)	10.0	(7.5)	9.3	(5.9)	14.4	(10.0)	11.0	(8.7)	< 0.001
Call to hospital arrival, min, mean (SD)	28.6	(8.6)	28.2	(7.9)	27.5	(8.3)	29.1	(9.3)	27.1	(8.8)	32.1	(11.1)	29.5	(9.4)	< 0.001

*P values are calculated to test the homogeneity among the 7 cause groups.

EMS indicates emergency medical services; CPR, cardiopulmonary resuscitation; VF, ventricular fibrillation; PEA, pulseless electrical activity; AED, automated external defibrillator; SD, standard deviation.

Table 4 Outcomes after out-of-hospital cardiac arrests with non-cardiac origin according to the cause

	Total (n = 1,4164)	External causes (n = 8239)	Respiratory diseases (n = 1448)	Malignant tumors (n = 1309)	Strokes (n = 1114)	Others (n =2054)	*P* value*
Prehospital ROSC, n (%)	1229 (8.7)	703 (8.5)	114 (7.9)	57 (4.4)	216 (19.4)	139 (6.8)	< 0.001
Total ROSC, n (%)	4744 (33.5)	2638 (32.0)	620 (42.8)	234 (17.9)	650 (58.3)	602 (29.3)	< 0.001
Hospital admission, n (%)	4142 (29.2)	2356 (28.6)	530 (36.6)	173 (13.2)	585 (52.5)	498 (24.2)	< 0.001
One-month survival, n (%)	755 (5.3)	510 (6.2)	94 (6.5)	11 (0.8)	55 (4.9)	85 (4.1)	< 0.001
Neurologically favorable outcome, n (%)	188 (1.3)	105 (1.3)	27 (1.9)	2 (0.2)	17 (1.5)	37 (1.8)	< 0.001

*P values are calculated to test the homogeneity among the 5 cause groups.

ROSC indicates return of spontaneous circulation.

Data on one-month survival and neurological status were missing for 7 victims.

Table 5 Outcomes after out-of-hospital cardiac arrests with external causes according to the cause

	Asphyxia (n = 2670)	Hanging (n = 1999)	Fall (n = 1300)	Drowning (n = 1062)	Traffic injury (n = 765)	Drug overdose (n = 187)	Unclassified (n = 256)	*P* value*
Prehospital ROSC, n (%)	463 (17.3)	144 (7.2)	22 (1.7)	36 (3.4)	28 (3.7)	4 (2.1)	6 (2.3)	< 0.001
Total ROSC, n (%)	1003 (37.6)	1500 (75.0)	1213 (93.3)	894 (84.2)	637 (83.3)	143 (76.5)	211 (82.4)	< 0.001
Hospital admission, n (%)	1529 (57.3)	453 (22.7)	62 (4.8)	147 (13.8)	92 (12.0)	40 (21.4)	33 (12.9)	< 0.001
One-month survival, n (%)	382 (14.3)	84 (4.2)	9 (0.7)	12 (1.1)	12 (1.6)	7 (3.7)	4 (1.6)	< 0.001
Neurologically favorable outcome, n (%)	71 (2.7)	17 (0.9)	1 (0.1)	4 (0.4)	6 (0.8)	4 (2.1)	2 (0.8)	< 0.001

*P values are calculated to test the homogeneity among the 7 cause groups.

ROSC indicates return of spontaneous circulation.

Table 6 Factors associated with outcomes after out-of-Hospital cardiac arrests with non-cardiac origin

	One-month survival				Neurologically favorable outcome			
	Crude OR	(95% CI)	Adjusted OR	(95% CI)	Crude OR	(95% CI)	Adjusted OR	(95% CI)
Adults (versus elderly)	0.95	(0.82-1.10)	1.36	(1.12-1.65)	1.02	(0.76-1.37)	1.52	(1.07-2.15)
Men	0.75	(0.64-0.88)	0.99	(0.84-1.16)	1.09	(0.81-1.46)	0.91	(0.67-1.24)
Witnessed by bystanders	4.41	(3.74-5.19)	4.13	(3.35-5.09)	4.48	(3.23-6.21)	4.83	(3.21-7.29)
Good activities of daily living	0.93	(0.80-1.08)	1.23	(1.03-1.47)	1.39	(1.02-1.88)	1.43	(1.02-2.02)
VF	2.74	(1.96-3.82)	2.04	(1.42-2.92)	7.72	(5.05-11.79)	5.40	(3.40-8.59)
Type of bystander CPR								
No CPR	Reference		Reference		Reference		Reference	
Chest compression-only CPR	0.97	(0.81-1.16)	0.80	(0.66-0.98)	0.95	(0.67-1.35)	0.92	(0.64-1.33)
Conventional CPR with rescue breathing	1.47	(1.20-1.79)	1.07	(0.86-1.34)	1.01	(0.65-1.55)	0.89	(0.56-1.42)
Type of non-cardiac origin								
Respiratory diseases	0.42	(0.33-0.53)	0.51	(0.40-0.65)	0.70	(0.44-1.09)	0.76	(0.48-1.21)
Malignant tumors	0.05	(0.03-0.09)	0.06	(0.03-0.11)	0.06	(0.01-0.23)	0.06	(0.01-0.23)
Strokes	0.31	(0.23-0.42)	0.27	(0.20-0.38)	0.57	(0.33-0.97)	0.34	(0.19-0.61)
Asphyxia	Reference		Reference		Reference		Reference	
Hanging	0.26	(0.21-0.34)	0.56	(0.41-0.77)	0.31	(0.18-0.53)	0.55	(0.28-1.07)
Fall	0.04	(0.02-0.08)	0.03	(0.01-0.06)	0.03	(0.004-0.20)	0.01	(0.002-0.11)
Drowning	0.07	(0.04-0.12)	0.16	(0.09-0.29)	0.14	(0.05-0.38)	0.31	(0.11-0.90)

Traffic injury	0.10	(0.05-0.17)	0.05	(0.03-0.10)	0.29	(0.13-0.67)	0.10	(0.04-0.26)
Drug overdose	0.23	(0.11-0.50)	0.58	(0.26-1.29)	0.80	(0.29-2.21)	1.74	(0.58-5.19)
Others	0.26	(0.20-0.33)	0.29	(0.22-0.38)	0.67	(0.45-1.00)	0.60	(0.39-0.92)
Unclassified	0.10	(0.04-0.26)	0.10	(0.04-0.28)	0.29	(0.07-1.18)	0.27	(0.06-1.16)
Location of arrest								
Homes	Reference		Reference		Reference		Reference	
Public places	0.78	(0.61-0.99)	1.45	(1.10-1.91)	1.11	(0.75-1.65)	1.54	(0.97-2.44)
Workplaces	1.29	(0.83-1.98)	1.40	(0.87-2.23)	1.26	(0.55-2.89)	0.95	(0.39-2.30)
Health care facilities	1.69	(1.38-2.07)	0.88	(0.69-1.12)	0.72	(0.42-1.24)	0.47	(0.26-0.85)
Others	0.70	(0.51-0.94)	1.67	(1.19-2.35)	0.68	(0.38-1.24)	1.35	(0.72-2.54)
Intravascular fluid	1.78	(1.50-2.11)	1.45	(1.14-1.84)	1.34	(0.94-1.91)	1.52	(0.97-2.38)
Intubation	1.62	(1.37-1.92)	1.02	(0.84-1.23)	0.73	(0.48-1.10)	0.50	(0.32-0.77)
Epinephrine	2.32	(1.87-2.88)	0.97	(0.71-1.32)	1.25	(0.74-2.09)	0.60	(0.31-1.17)
EMS response time (for one-increment of minute)	0.93	(0.91-0.96)	0.92	(0.90-0.95)	0.91	(0.86-0.96)	0.90	(0.84-0.95)
Year (for one-increment of year)	1.02	(0.98-1.06)	1.01	(0.97-1.06)	1.02	(0.95-1.09)	1.05	(0.97-1.13)

VF denotes ventricular fibrillation; CPR, cardiopulmonary resuscitation; EMS, emergency medical services; OR, odds ratio; CI, confidence interval.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.