for survival after OHCAs, as suggested by Herlitz et al.[4]

Consistent with many previous studies, outcomes after OHCAs were poor for infants.[5,13,19] Only 8% of infant OHCAs were witnessed by bystanders, and presumably many of the unwitnessed arrests were attributable to sudden infant death syndrome (SIDS).[20] Notably, previous investigations showed that one-third to one-half of cardiac arrests among infants are attributable to SIDS.[21,22] Because children with SIDS typically have had no blood flow for a prolonged time before a parent realizes that the infant is experiencing cardiac arrest, it is not surprising that the outcomes are so poor. It was reported that outcomes after in-hospital cardiac arrests were better among infants and younger children, compared with older children and adults.[23] Those authors speculated that infants might have superior CPR hemodynamics because of better transmission of chest compression forces through their more-compliant chest walls. In contrast to infants with OHCAs, 83% of infants with in-hospital cardiac arrests were being observed and monitored. Therefore, the infants with in-hospital cardiac arrests could receive CPR promptly, with superior hemodynamics and with resultant return of spontaneous circulation, whereas infants with OHCAs usually do not have the same opportunity. Not surprisingly, a proactive prevention campaign[24–27] is more important than advanced life support programs for reducing mortality rates in this age group.[22]

As expected, we observed different incidence patterns of OHCAs among the different age groups. The incidence was much higher among infants than among younger children, older children, and adolescents. Interestingly, the incidence among infants was similar to the incidence among adults, consistent with previous reports.[5] The population-based annual incidences of nontraumatic pediatric OHCAs in Osaka (7.3 cases per 100 000 person-years for 0- to 17-year-old patients and 65.5 cases per 100 000 person-years for infants) were quite similar to those in North America (8.0 cases per 100 000 person-years for 0- to 19-year-old patients and 72.7 cases per 100 000 person-years for infants).[5] In contrast, the annual incidence of adult cardiac arrests in North America (126.5 cases per 100 000 person-years)[5] was almost double that in Osaka (64.7 cases per 100 000 person-years). These differences in annual incidences among adults might be explained by differences in lifestyle and environmental factors.[28]

An important finding is that the rates of survival with favorable neurologic outcomes in the present study were quite low for all pediatric and adult age groups except adolescents. There are some possible explanations for these poor outcomes. Overall, 76% of these nontraumatic pediatric OHCAs were not witnessed and only 4% had shockable rhythms. In addition, the Japanese emergency physicians, nurses, and EMS personnel had limited pediatric training, equipment, and experience. Furthermore, regionalized care for critically ill children was, and is, lacking and most children with OHCAs were sent to adult tertiary emergency facilities[29] or hospitals with relatively small pediatric services, without a PICU.[30] With greater national emphasis on the recognition and treatment of OHCAs, increased attention to lay CPR training, the addition of telephone dispatcher assistance with CPR, superior EMS basic and advanced life support training for OHCAs,[27] and improvements in postarrest care,[31] outcomes of adult OHCAs have improved over the past several years.[8,14] Perhaps improvements in outcomes also are occurring for pediatric OHCAs, although the small number of pediatric OHCAs precludes meaningful year-by-year analysis. Nevertheless, outcomes after pediatric OHCAs were better than adult outcomes.

An important limitation of this study is that we enrolled only children who were noted by EMS providers to have an absence of signs of circulation. Animal and clinical investigations of pediatric OHCAs indicated that CPR could be quite effective when provided promptly by a simulated bystander and return of spontaneous circulation might occur within a few minutes (ie, before the EMS personnel would arrive).[2,32,33] Such pediatric OHCAs with potentially good outcomes would have been excluded from this study. Therefore, it is likely that the incidence of pediatric OHCAs in this population was actually higher and the outcomes were better than documented in this investigation.

This observational study has several other limitations. We were able to evaluate neurologic status only at 1 month after the OHCA, because longer follow-up data were not available. It is possible that neurologic status might have improved over time for some children. Furthermore, the Glasgow-Pittsburgh Cerebral Performance Category scale available in our data collection system was derived for adults and may be less useful for infants and children. In addition, the category of presumed cardiac cause of arrest is a diagnosis of exclusion (ie, there was simply no evidence of a noncardiac cause), according to the international Utstein-style guidelines for cardiac arrest data reporting. For children, the presumption that cardiac arrests with an undiagnosed cause should be attributed to a cardiac cause may be problematic. For example, infants with SIDS might be included in the cardiac group.

Nevertheless, we used this classification system because it is the consensus, international, Utstein-style classification system in the literature.[5,7,10,12,15,17] As with all observational studies, data integrity, validity, and ascertainment bias are potential limitations. The use of uniform data collection on the basis of Utstein-style guidelines for reporting of cardiac arrests, the large sample size, and the population-based design were intended to minimize these potential sources of biases.

CONCLUSIONS

In this study, children had better 1-month survival rates and better neurologic outcomes, compared with adults, after OHCAs. In addition, patient characteristics and outcomes of pediatric OHCAs differed among age groups. Age-specific approaches should be considered to reduce the rates of deaths attributable to OHCAs among children.

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Clinical paper

Association of out-of-hospital cardiac arrest with prior activity and ambient temperature☆

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ABSTRACT

Objective: Little is known about triggers of sudden cardiac arrest. This study aimed to analyze the association of the occurrence of out-of-hospital cardiac arrest (OHCA) with patient activities just before the arrest and ambient temperature as one of the major environmental factors.
Methods: This prospective, population-based cohort study enrolled all person aged 18 years or older with OHCA of presumed cardiac origin in Osaka Prefecture, Japan, from 2005 through 2007. Patient activities before arrest were divided into six categories: sleeping, bathing, working, exercising, non-specific activities, and unknown. Age-adjusted annual incidence rate of OHCA according to their prior activity and an hourly event rate in each activity by temperature were calculated.
Results: Among 19,303 OHCAs, 10,723 were presumed to be of cardiac etiology. The event rate of OHCA was 6.22, 54.49, 1.15, and 10.11 per 10,000,000 population per hour for sleeping, bathing, working, and exercising, respectively. Among patients who suffered OHCA during bathing, the event rate of OHCA per 10,000,000 per hour increased with decreasing temperature from 18.27 (≥25.1 °C) to 111.42 (≤5.0 °C) (odds ratio [OR] for 1 °C increase in temperature, 0.915; 95% confidence interval [CI], 0.907–0.923), while it was almost constant among those who were working (OR for 1 °C increase, 0.994; 95% CI, 0.981–1.007) or exercising (OR for 1 °C increase, 1.004; 95% CI, 0.971–1.038) before arrest.
Conclusion: Both activities before cardiac arrest and ambient temperature were associated with the occurrence of OHCA. Preventive measures against OHCA should be enveloped considering these behavioral and environmental factors.

1. Introduction

Out-of-hospital cardiac arrest (OHCA) is one of the leading causes of death both in Japan and other industrialized countries.[1,2] Approximately 50,000 events occur every year in Japan.[3] Although survival after OHCA is gradually increasing as the chain of survival improves, the absolute value of survival remains low.[4,5] An ongoing challenge to improved survival is that OHCA is often the first manifestation of heart disease.[6] Prevention of OHCA is, therefore, an urgent matter.

OHCA is usually caused by ventricular tachycardia (VT) or fibrillation (VF).[1] Previous reports suggest that VF is triggered by heavy physical exertion,[7,8] and severe emotional,[9] or working stress.[10] Environmental factors are also associated with occurrence of OHCA as coldness is well known to trigger OHCAs.[11] However, the relationships between ambient temperature and OHCA by activities had been poorly understood.

The Utstein Osaka Project, launched in 1998, is an ongoing large, prospective, population-based cohort study of OHCA in Osaka, Japan that covers 8.8 million people.[2,5] During the three-year study period, there were over 10,000 emergency medical service (EMS)-resuscitated OHCAs of presumed cardiac etiology. The objective of this study was to analyze the associations of the occurrence of OHCA with the patient activities just before the arrest and the ambient temperature on the day that the episode occurred.

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2. Methods

2.1. Study design, population, and setting

Data were extracted for this study from the Utstein Osaka Project which is a prospective, population-based cohort study of all persons with OHCA that were treated by EMS in Osaka Prefecture, Japan. Osaka is the second largest prefecture in Japan with a population of 8,817,166 (in 2005) inhabitants in an area of 1892 km^2 and located at 135° east longitude, and at 34° north latitude. All OHCA patients aged 18 years or older from January 1, 2005, through December 31, 2007, and were presumed to be cardiac origin were enrolled for this study.

Cardiac arrest was defined as the cessation of cardiac mechanical activities as confirmed by the absence of signs of circulation.[12] The arrest was presumed to be of cardiac etiology unless it was caused by trauma, drowning, drug overdose, asphyxia, exsanguination, or any other non-cardiac causes determined by a physician in charge in collaboration with the EMS rescuers.

This study was approved by the institutional review board of Osaka University, with the assent of the EMS authorities and municipal governments in Osaka Prefecture, Japan.

2.2. The emergency medical service system in Osaka

In Osaka prefecture, there are 34 fire stations with a corresponding number of emergency dispatch centers in 2007. Emergency life support is provided 24 h every day by single-tiered system in 32 stations and two-tiered system in 2 stations. The most highly trained pre-hospital emergency care providers are the Emergency Life-Saving Technicians (ELSTs). Each ambulance has three providers and most of them have at least one ELST. Public access defibrillation (PAD) programs were started in July 2004. Details of the EMS system in Osaka were described elsewhere.[2,5]

2.3. Data collection

Data were prospectively collected using a form that included all core data recommended in the Utstein-style reporting guidelines for cardiac arrests,[12] such as sex, age, location, activities of daily living before arrest, initial cardiac rhythm, time-course of resuscitation, type of bystander-initiated cardiopulmonary resuscitation (CPR), return of spontaneous circulation (ROSC), hospital admission, one-month survival, and neurological status one month after the event. The patient activity before arrest was divided into six categories: sleeping, bathing, working, exercising, non-specific activities, and unknown. The data form was filled out by the EMS personnel in cooperation with the physicians in charge of the patient, transferred to 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, and the data sheet was completed.

All survivors were followed for up to one month after the event by the EMS personnel in charge. One-month neurological outcome was determined by physician in charge, 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.[12]

Data on mean ambient temperature of the day of event were obtained from the Osaka District Meteorological Observatory database through the Internet.[13]

2.4. Statistical analysis

Age-adjusted annual incidence rates of OHCA according to their activity before arrest were calculated by the direct method using the census 2005 data and the Japanese model population 1985. Event rate of OHCA per hour for each activity by month and ambient temperature (≤5.0, 5.1–10.0, 10.1–15.0, 15.1–20.0, 20.1–25.0, and ≥25.1 °C) was calculated referring data on time-consumption in daily life among Japanese.[14,15] According to the database,[14,15] the mean time consumed for sleeping, bathing, working, and exercising among Japanese was 7.4, 0.35, 7.5, and 0.13 h a day, respectively. ROSC, admission to hospital, one-month survival, and one-month survival with favorable neurological outcomes (i.e., CPC category 1 or 2) were also compared by the patient activity.

The data were compared across groups using chi-square test or Fisher's exact test for categorical variables and ANOVA for continuous variables. Poisson regression was applied to the temperature dependency of the event rates. Odds ratio (ORs) for 1 °C increase in temperature and its 95% confidence intervals (CIs) were calculated. Analyses were performed using SPSS Ver.15 (SPSS, Inc., Chicago, IL). A two-tailed value of $P < 0.05$ was considered statistically significant.

3. Results

3.1. Incidence of OHCA and characteristics according to prior activity

A total of 19,303 OHCA cases with an age of 18 years or more were documented during this study period. Among such cases, resuscitation was attempted for 17,349 and 10,723 of them were presumed to be of cardiac etiology. Before the arrest, 2,355 (22.0%) patients were sleeping, 985 (9.2%) bathing, 325 (3.0%) working, 51 (0.5%) exercising and 5447 (50.8%) non-specific activities. There were no missing data on activities but 1560 (14.5%) were classified into "unknown" category. The age-adjusted annual incidence rate was 7.0, 2.9, 1.3, 0.2, 17.0, and 5.0 per 100,000 population for sleeping, bathing, working, exercising, non-specific activities, and unknown, respectively. Event rate of OHCA was 6.22, 54.49, 1.15, and 10.11 per 10,000,000 population per hour for sleeping, bathing, working, and exercising, respectively.

Table 1 shows the patient and resuscitation characteristics according to the activities before OHCA. Among patients who had worked and exercised, male sex was more frequent (88.3% and 76.5%, respectively) and age was lower (60.0 years and 61.5 years, respectively) than the others. Good activities of daily living before arrest (91.7% and 98.0%) and witnessed arrest (54.8% and 82.4%) were also more frequent among the working and excising patients. Noteworthy, 35.7% and 47.1% patients engaged in working and exercising were more like to have VF as initial rhythm. Time interval from collapse to call during sleeping, bathing, working, and exercising was 3 (interquartile range [IQR], 1–7), 3 (IQR, 1–5), 2 (IQR, 1–4), and 2 (IQR, 1–5), respectively.

3.2. Event rate of OHCA per hour for activity before arrest by month

The age-adjusted monthly variation of event rate of OHCA was different among the activities before arrest (Fig. 1). The age-adjusted event rate per hour during bathing increased in winter season (34.34 in January), which was approximately 10 times more frequent than in summer season (3.56 in August and September). In contrast, the event rate was almost constant by month for sleeping, working and exercising activities.

Table 1
Patient and resuscitation characteristics according to the activity before out-of-hospital cardiac arrest.

	Sleeping n=2355	Bathing n=985	Working n=325	Exercising n=51	Non-specific activities n=5447	Unknown n=1560	*P*-value
Men, *n* (%)	1234(52.4)	551(55.9)	287(88.3)	39(76.5)	3193(58.6)	853(54.3)	<0.001
Age, year, mean (SD)	76.1 (15.4)	76.0 (11.4)	60.0 (13.6)	61.5 (18.6)	73.1 (14.5)	71.6 (14.1)	<0.001
Activities of daily living before arrest, Good, *n* (%)	1176(49.9)	845(85.8)	298(91.7)	50(98.0)	3348(70.6)	1056(67.7)	<0.001
Location, *n* (%)							<0.001
Home	1893(80.4)	830(84.3)	44(13.5)	3(5.9)	3366(61.8)	1126(72.2)	
Public spaces	12(0.5)	127(12.9)	55(16.9)	34(66.7)	790(14.5)	217(13.9)	
Work places	2(0.1)	0	183(56.3)	0	39(0.7)	13(0.8)	
Healthcare facilities[a]	437(18.6)	12(1.2)	8(2.5)	0	524(9.6)	125(8.0)	
Others	11(0.5)	16(1.6)	35(10.8)	14(27.5)	728(13.4)	79(5.1)	
Witnessed, *n* (%)	618(26.2)	80(8.1)	178(54.8)	42(82.4)	3344(61.4)	133(8.5)	<0.001
Bystander CPR, n (%)	982(41.7)	378(38.4)	115(35.4)	26(51.0)	1649(30.3)	513(32.9)	<0.001
VF as initial rhythm, *n* (%)	148(6.3)	19(1.9)	116(35.7)	24(47.1)	864(15.9)	93(6.0)	<0.001
Collapse to call, min, median (IQR)[b]	3(1–7)	3(1–5)	2(1–4)	2(1–5)	2(1–5)	2(1–5)	0.002
Call to EMS's CPR, min, median (IQR)	8(6–9)	8(6–9)	7(6–9)	7(5–9)	8(6–10)	7(6–9)	0.215

CPR, cardiopulmonary resuscitation; VF, ventricular fibrillation; EMS, emergency medical service; IQR, interquartile range.
[a] Includes nursing home and medical offices.
[b] Data are available for those with witnessed status.

3.3. *Event rate of OHCA per hour for activity before arrest by ambient temperature*

The monthly variation of event rate could be interpreted as ambient temperature dependency (Table 2). The age-adjusted event rate of OHCA per 10,000,000 per hour during bathing increased with a decreasing temperature from 18.27 (≥25.1 °C) to 111.42 (≤5.0 °C) and OR of occurrence of OHCA for 1 °C increase in temperature was 0.915 (95% CI 0.907–0.923). Temperature-dependent variation in event rate during other activities was rather small. Their ORs for 1 °C increase in temperature were 0.994 (95% CI 0.981–1.007) during working, and 1.004 (95% CI 0.971–1.038) during exercising.

3.4. *Outcome according to activity before arrest*

One-month survival with favorable neurological outcome differed by activities before OHCA (Table 3). More than 10% of patients arrested during exercising and working survived in good neurological condition, while only about 1% of patients arrested during sleeping and bathing survived well ($P < 0.001$). ROSC, hospital admission, and one-month survival were also poor for OHCAs during sleeping and bathing compared with other activities.

4. Discussion

This large, population-based, prospective study clearly demonstrated the association between the occurrence of OHCAs and their prior activities. Our study was far superior to previous studies,[16–18] in complete follow-up and large sample size. Activity-dependence of OHCA was consistent with previous studies[17,18] regardless of different settings, and the results would be quite robust.

In addition to prior activities, this study indicated the impact of low ambient temperature on the occurrence of OHCA. Interestingly, the influence of temperature on occurrence of OHCA differed by the prior activities. Low temperature had a much stronger asso-

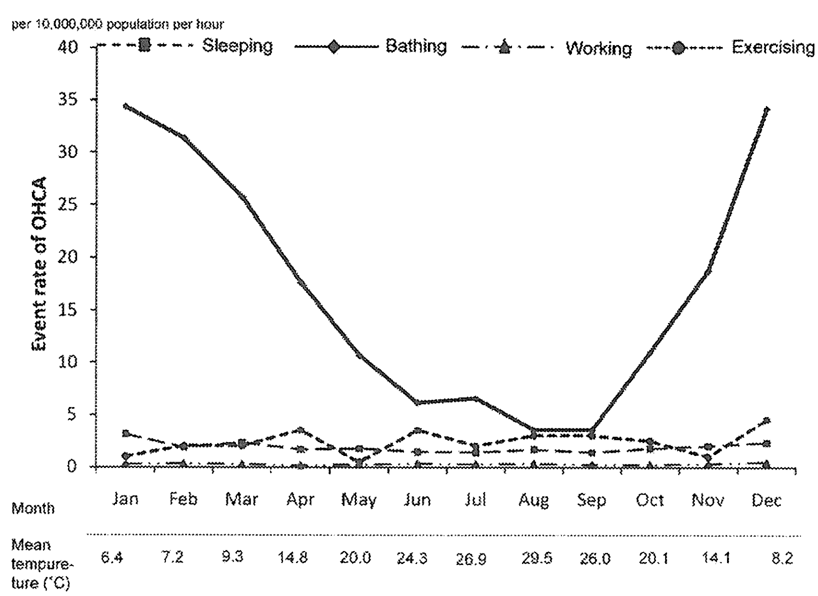

Fig. 1. Age-adjusted event rate of out-of-hospital cardiac arrest per 10,000,000 per hour for activity before out-of-hospital cardiac arrest by month.

Table 2
Event rate of out-of-hospital cardiac arrest per 10,000,000 per hour for activity before arrest by temperature.

Temperature (°C)	Sleeping n=2355	Bathing n=985	Working n=325	Exercising n=51
≤5.0	8.49	111.42	0.90	3.84
5.1–10.0	8.22	96.79	1.70	13.70
10.1–15.0	6.77	65.75	1.40	8.77
15.1–20.0	5.29	49.32	0.90	12.27
20.1–25.0	6.03	21.92	0.99	10.08
≥25.1	5.01	18.27	1.40	11.95
OR[a] (95% CI)	0.977 (0.972–0.982)	0.915 (0.907–0.923)	0.994 (0.981–1.007)	1.004 (0.971–1.038)

OR, odds ratio; CI, confidence intervals.
[a] OR for 1 °C increase in temperature.

Table 3
Outcome of out-of-hospital cardiac arrest according to activity before arrest.

	Sleeping n=2355	Bathing n=985	Working n=325	Exercising n=51	P-value
ROSC, n (%)	467(19.8)	129(13.1)	119(36.6)	22(43.1)	<0.001
Hospital admission, n (%)	346(14.7)	110(11.2)	108(33.2)	17(33.3)	<0.001
One-month survival, n (%)	67(2.8)	10(1.0)	60(18.5)	8(15.7)	<0.001
Neurologically favorable one-month survival, n (%)	28(1.2)	2(0.2)	36(11.1)	6(11.8)	<0.001

ROSC denotes return of spontaneous circulation.

ciation with OHCA during bathing than during exercise. It is well known that lower temperature increases sympathetic nerve tone and catecholamine release, which increase heart rate, ventricular contractility, vascular resistance, and blood pressure.[19,20] Besides, a rapid increase in body temperature by bathing causes a rapid fall in blood pressure with consequent increasing risk of OHCA.[21,22] In Japan, most people take a deep hot bath, since traditional Japanese homes are not well-insulated as in the west, and central heating is quite uncommon. The temperature differences between the inside and outside the bathtub/bathroom would be substantially large in winter season, which might cause acute hemodynamic changes resulting in a sine-curve monthly variation of OHCA incidence during bathing. Since OHCA during bathing was less likely to be witnessed or survived, preventive approaches such as warming a bathroom and a hallway or refraining from taking a deep hot bath could be important for high risk people.

Our results implied that risk of OHCA is relatively higher during bathing and exercising compared with other activities. It was reported that the risk of cardiac arrest was transiently elevated during or just after vigorous exertion.[8] However, the risk of OHCA during excising was less frequent than expected and far less than bathing. Although we did not obtain the detailed information about the intensity of physical activities, an estimated metabolic equivalent (MET) levels were >3 for exercise activity and from 1.5 to 2.0 for bathing.[23] The higher incidence of OHCA during bathing compared with exercising suggests factors other than exercise intensity including the temperature changes would account for the finding.

In this study, we could not identify any seasonal variations surpassing temperature, although some study reported the influence of social factors such as holidays or fiscal year term on cardiac deaths.[24–26] The higher proportion of the elderly OHCA patients in this study cohort might underlie the results because the aged people are less exposed to social stress. The deterioration of homeostasis among elderly people might make them be susceptible to temperature change and also affect this result.[27]

VF was more frequently observed among OHCA during excising and working compared with other activities. This high proportion of VF among OHCA during excising and working could be partially explained by their higher proportion of witnessed arrests, quick bystander CPR, and other earlier response. It has been reported that the effect of public access defibrillation (PAD) program would depend on the situation or location.[28–30] PAD programs are more effective in these situations where VF is frequently observed. An intensive placement of AED combined with aggressive CPR training for work places or sports facilities might be effective.

This study has some limitations. First, unfortunately, we have no information about patients' medical or behavioral status and natural or social environment except for ambient temperature. Medication, emotional upset, smoking, and sexual activity might overwhelm the activities discussed here.[31] Second, we only obtained outside temperature data, and no indoor (e.g., bathroom) temperature data were available. Low outdoor temperatures may not reflect the exposure of the patient inside the home. Third, population-attributable risk could not be estimated accurately because the actual number of people who were engaged in each activity is unknown. However, all people should sleep and most people take a bath, and the absolute activity-related excess risk of OHCA would be great. Fourth, many patients were engaged in non-specific and unknown activities. We, therefore, might miss some important activities at high risk of OHCA. Further efforts should be needed to identify such specific activities. Final, we could not take the intensity of physical activities[16] into consideration due to the lack of this information. Since prospective studies are virtually impossible, then a retrospective study with case-crossover design would be warranted to assess the relationships between physical activity and OHCA.

5. Conclusions

Data from a large scale population-based cohort indicated that both the activity and temperature were associated with the occurrence of OHCA and their interaction was also found. We need to explore a strategy to decrease deaths from OHCA considering activities before arrest and environmental factors.

Conflict of interest statement

There are no conflicts of interest to declare.

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Clinical paper

Prognostic indicators and outcome prediction model for patients with return of spontaneous circulation from cardiopulmonary arrest: The Utstein Osaka Project☆

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ABSTRACT

Objective: To determine the most important indicators of prognosis in patients with return of spontaneous circulation (ROSC) following out-of-hospital cardiopulmonary arrest (OHCA) and to develop a best outcome prediction model.

Design and patients: All patients were prospectively recorded based on the Utstein Style in Osaka over a period of 3 years (2005–2007). Criteria for inclusion were a witnessed cardiac arrest, age greater than 17 years, presumed cardiac origin of the arrest, and successful ROSC. Multivariate logistic regression (MLR) analysis was used to develop the best prediction model. The dependent variables were favourable outcome (cerebral-performance category [CPC]: 1–2) and poor outcome (CPC: 3–5) at 1 month after the event. Eight explanatory pre-hospital variables were used concerning patient characteristics and resuscitation. External validation was performed on an independent set of Utstein data in 2007.

Results: Subjects comprised 285 patients in VF and 577 patients with pulseless electrical activity (PEA)/asystole. The percentage of favourable outcomes was 31.9% (91/285) in VF and 5.7% (33/577) in PEA/asystole. The most important prognostic indicators of favourable outcome found by MLR were age ($p = 0.10$), time from collapse to ROSC (TROSC) ($p < 0.01$), and presence of pre-hospital ROSC (PROSC) ($p = 0.15$) for VF and age ($p = 0.03$), TROSC ($p < 0.01$), PROSC ($p < 0.01$), and conversion to VF ($p = 0.01$) for PEA/asystole. For external validation data, areas under the receiver-operating characteristic curve were 0.867 for VF and 0.873 for PEA/asystole.

Conclusions: A model based on four selected indicators showed a high predictive value for favourable outcome in OHCA patients with ROSC.

1. Introduction

Although increasing numbers of patients return to spontaneous circulation following out-of-hospital cardiac arrest (OHCA), by prevalence of the chain of survival, the rate of patients surviving without neurological deficit remains low. The Utstein Osaka Project, begun in 1998, is an ongoing, large, prospective, population-based cohort study of OHCA in Osaka, Japan, that covers 8.8 million people.[1] In the data, 35.6% of patients with witnessed OHCAs due to cardiac aetiology had return of spontaneous circulation (ROSC), whereas only 3.4% of patients had a favourable outcome at 1 month after OHCA. Recently, therapeutic hypothermia and percutaneous cardiopulmonary support (PCPS) therapy with coronary intervention were reported to improve neurological outcomes in a specific patient group.[2–4] Such intensive treatment is, however, costly and time-consuming. Accurate prediction of

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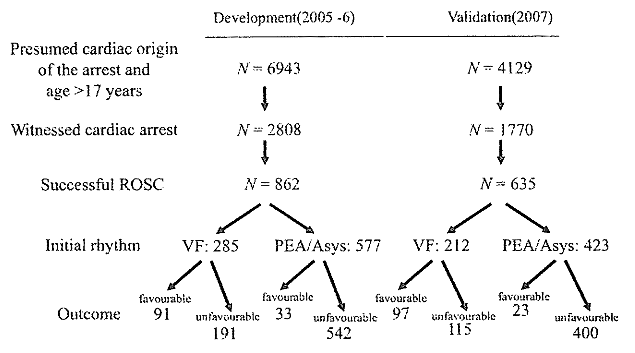

Fig. 1. Patient numbers and outcomes. VF, initial rhythm of ventricular fibrillation; PEA/Asys, initial rhythm of pulseless electrical activity or asystole.

neurological outcome at the time of initial hospital admission will be helpful when considering indications for these intensive therapies or to stratify patients for precise clinical research. Although some prognostic indicators for patients with OHCA have been proposed,[5–7] a mathematical model with high predictive value for neurological outcomes has not been established. The purpose of the present study was to determine the most important indicators of prognosis in patients with ROSC from cardiopulmonary arrest (CPA) and to develop a best outcome prediction model using data from the Utstein Osaka project.

2. Methods

2.1. Patient sample

All patients were prospectively recorded based on the Utstein Style in Osaka over a 3-year period (2005–2007). Inclusion criteria were a witnessed cardiac arrest, patient age >17 years, presumed cardiac origin of the arrest, and successful ROSC as shown in Fig. 1. Successful ROSC was defined as ROSC, even if just once during resuscitation. Only the patients with successful ROSC were analyzed in the present study. Excluded were patients with untreated OHCA, those with clear signs of death such as presence of decomposition or rigor mortis, or compelling reasons that included extensive history of terminal illness or intractable disease and/or a "do not resuscitate" order.

Cardiac arrest was defined as the cessation of cardiac mechanical activity, as confirmed by the absence of signs of circulation. The arrest was presumed to be of cardiac origin unless caused by trauma, drowning, drug overdose, asphyxia, exsanguination, or any other non-cardiac causes as determined by a physician in charge and collaborated by the emergency medical service (EMS) rescuers. Patients registered in the first 2 years were used for model development, and those registered in 2007 were used for external validation. The research protocol was approved by the institutional review board of Osaka University, with the assent of the EMS authorities and local governments in Osaka prefecture.

2.2. Osaka EMS system

Osaka prefecture, with an area of 1892 km^2, is home to approximately 8.8 million people. There are 35 fire stations with a corresponding number of emergency dispatch centers. The EMS system is operated by the local fire stations, and life support is provided 24 h/day via a single-tier system in 33 stations and a 2-tier system in 2 stations. The latter stations use medics followed by physicians responding by vehicle. All EMS providers performed cardiopulmonary resuscitation (CPR) according to Japanese CPR guidelines based on the AHA guidelines. The most highly trained pre-hospital emergency care providers are the Emergency Life-Saving Technicians (ELST). Each ambulance has 3 providers, and most have at least 1 ELST. The ELST must be qualified by national exam and trained in a teaching hospital. The ELST system was started in 1991, but before 2003, ELST were only allowed to insert an intravenous line and an adjunct airway and to use a semiautomated external defibrillator for OHCA patients under the online medical direction of a physician. ELST have been allowed to deliver shocks without online medical direction since April 2003, and trained ELST have been allowed to insert tracheal tubes since July 2004 and to use epinephrine intravenously since April 2006.

2.3. Data collection

Data were collected prospectively with a data form that included all core data recommended in the Utstein-Style reporting guideline for cardiac arrest, such as sex, age, initial cardiac rhythm on ambulance arrival, time course of resuscitation, presence of witnesses and by-stander CPR, ROSC, hospital admission, 1-month survival, and neurological status 1 month post event. The time course of resuscitation was determined as follows. Time of EMS call receipt and time of vehicle arrival at the scene were recorded automatically at the dispatch center. Times of collapse and initiation of bystander CPR were obtained by EMS interview of bystanders before leaving the scene. Time of defibrillation was recorded by the semiautomated defibrillator. The watches of the EMS personnel were synchronised with the clock at their dispatch center. Time intervals from collapse to CPR and collapse to shock were defined as the shorter of the times obtained from the bystanders and the EMS personnel. Time from the collapse to ROSC (TROSC) was calculated as the time from presumed arrest to the time of the first ROSC during resuscitation, irrespective of whether ROSC was achieved on scene, during transport or after hospital arrival. PROSC was defined as ROSC prior to arrival to the hospital under prehospital conditions.

All survivors were followed up for up to 1 month post event by EMS personnel. Neurological outcome was accessed by telephone interview 1 month after successful resuscitation with the Cerebral Performance Category scale (CPC): 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.

2.4. Statistical analysis

Continuous variables are presented as median value with interquartile range, and categorical variables are presented as percentage of the total. Multivariate logistic regression analysis was used to identify factors for good outcome and was separately performed for ventricular fibrillation (VF) and pulseless electrical activity/asystole (PEA/Asys) (2005–2006), where the responses were favourable outcome (CPC: 1–2) and poor outcome (CPC: 3–5) at 1 month post event. Eight explanatory pre-hospital variables related to patient characteristics and resuscitation were used: age, sex, presence of bystander CPR, TROSC, time from collapse to the first attempt at resuscitation by the ambulance crew, time from collapse to arrival of the ambulance at the hospital, PROSC, and time from collapse to first defibrillation (in VF only) or presence of conversion to VF (in PEA/Asys only). A full model was made that included all candidate predictors. This model was simplified according to statistical and clinical criteria. Variable selection used for the research was "best subset selection" with Akaike Information Criterion (AIC) because stepwise selection might fail to identify variables known or not known to be important.[8] The best subset selection with AIC run through all combinations of variables, penalises models with large numbers of parameters and then provides the best "goodness of fit" subset of variables for the prediction.

Table 1A
Characteristics of patient with initial rhythm of ventricular fibrillation.

	Development data (n = 285)	Validation data (n = 212)	p value
Age (years)	65.0 (56.0–73.0)	65.0 (56.3–73.8)	0.53
Male (%)	225 (78.9)	160 (75.5)	0.36
Bystander CPR (%)	115 (40.4)	100 (47.2)	0.13
EMS witnessed arrest (%)	5 (1.8)	5 (2.4)	0.75
Time from collapse to the first attempt at resuscitation by ambulance crew (min)	6.0 (5.0–9.0) (n = 280)	6.0 (4.0–8.0) (n = 207)	0.91
Time from collapse to arrival of ambulance at the hospital (min)	26.0 (20.0–31.0)	27.0 (22.0–33.0)	0.06
TROSC (min)	23.0 (13.0–37.0) (n = 274)	21.5 (13.8–36.3) (n = 210)	0.94
PROSC (%)	152 (53.3)	119 (56.1)	0.54
Time from collapse to the first defibrillation (min)	9.0 (7.0–11.8) (n = 272)	9.0 (7.0–11.0) (n = 206)	0.99
CPC			0.03
CPC1 (%)	71 (24.9)	82 (38.7)	
CPC2 (%)	20 (7.0)	15 (7.1)	
CPC3 (%)	24 (8.4)	12 (5.7)	
CPC4 (%)	40 (14.0)	23 (10.8)	
CPC5 (%)	127 (44.6)	80 (37.7)	

EMS, emergency medical service; TROSC, time from collapse to return of spontaneous circulation; PROSC, presence of return of spontaneous circulation under pre-hospital conditions; CPC, Cerebral Performance Category scale.

It is well-known that use of the traditional significance level (0.05) for model selection may fail to identify variables not known to be important; thus, a level of 0.20 was used for model building in the present study. The variables included in our final model were evaluated and determined from both statistical and clinical viewpoints.

We assessed the correlation between the candidate variables included in the model selection for co-linearity in the initial analysis of data. In addition, in the fitted model, we assessed the signs of the regression coefficients of the variables because a change in the sign indicates a co-linearity-like situation. Furthermore, we assessed variance inflation factors of the included variables to determine if there was significant co-linearity.

External validity of the model was assessed by an independent data set of Utstein data collected from January 1 to December 31, 2007. To assess performance of model discrimination, receiver-operating characteristic (ROC) curves were calculated and quantified by the integrals of the curve (area under the curve [AUC]), plotting the dependency of specificity on sensitivity. All p values were two-sided and $p < 0.05$ was considered to be statistically significant. All analyses were done with SAS for Windows Ver. 9.1 (SAS Institute, Inc., Cary, NC) and SPSS for Windows Ver. 15.0 (SPSS, Inc., Chicago, IL).

3. Results

3.1. Patient characteristics

Patient characteristics from the model development and validation data sets are shown in Tables 1A and 1B. In the study with VF as the initial rhythm, 285 patients were included in the development data (DD) and 212 patients were included in the validation data (VD). Although there was no significant difference in almost any characteristic between the two groups, the percentage of patients classified as CPC1 was significantly greater in the VD group. In the study with PEA/Asys as the initial rhythm, 577 patients were included in the DD and 423 patients were included in the VD (Table 1B). Time from patient collapse to ambulance arrival at the hospital was slightly but significantly longer in the VD group.

3.2. Predictive model for good neurological outcome

Multivariate logistic regression analysis carried out according to AIC found the most important prognostic indicators to be age (p = 0.10), TROSC (p < 0.01), and PROSC (p = 0.15) in VF (Table 2A) and age (p = 0.03), TROSC (p < 0.01), PROSC (p < 0.01), and conver-

Table 1B
Characteristics of patients with an initial rhythm of pulseless electrical activity/asystole.

	Development data (n = 577)	Validation data (n = 423)	p value
Age (years)	75.0 (67.0–83.0)	76.0 (67.0–84.0)	0.98
Male (%)	332 (57.5)	241 (57.0)	0.86
Bystander CPR (%)	200 (34.7)	161 (38.1)	0.27
EMS witnessed arrest (%)	16 (2.8)	12 (2.8)	1.0
Time from collapse to first attempt at resuscitation by ambulance crew (min)	7.0 (4.0–11.0) (n = 573)	7.0 (4.0–11.0) (n = 421)	0.55
Time from collapse to arrival of ambulance at the hospital (min)	27.0 (22.0–34.0)	28.0 (23.0–36.0)	0.01
TROSC (min)	38.0 (30.0–49.0) (n = 567)	37.0 (29.0–49.5) (n = 417)	0.61
PROSC (%)	99 (17.2)	85 (20.1)	0.24
Presence of conversion to ventricular fibrillation (%)	50 (8.7)	38 (9.0)	0.76
CPC			0.77
CPC1 (%)	24 (4.2)	15 (3.5)	
CPC2 (%)	9 (1.6)	8 (1.9)	
CPC3 (%)	21 (3.6)	10 (2.4)	
CPC4 (%)	33 (5.7)	26 (6.1)	
CPC5 (%)	488 (84.6)	364 (86.1)	

EMS, emergency medical service; TROSC, time from collapse to return of spontaneous circulation; PROSC, presence of return of spontaneous circulation under pre-hospital conditions; CPC, Cerebral Performance Category scale.

Table 2A
Results of multivariate logistic regression analysis for ventricular fibrillation.

	Odds ratio	95% CI	*p* value
Age	0.98	0.96–1.00	0.10
TROSC	0.90	0.86–0.94	<0.01
PROSC	1.96	0.78–5.00	0.15

95% CI, 95% confidence interval; TROSC, time from collapse to return of spontaneous circulation; PROSC, presence of return of spontaneous circulation under pre-hospital conditions.

Table 2B
Results of multivariate logistic regression analysis for pulseless electrical activity/asystole.

	Odds ratio	95% CI	p value
Age	0.96	0.93–1.00	0.03
TROSC	0.93	0.88–0.97	<0.01
PROSC	5.56	1.69–20.0	<0.01
Conversion to VF	4.35	1.37–14.3	0.01

95% CI, 95% confidence interval; TROSC, time from collapse to return of spontaneous circulation; PROSC, presence of return of spontaneous circulation under pre-hospital conditions; VF, ventricular fibrillation.

sion to VF ($p = 0.01$) in PEA/Asys (Table 2B). A statistical model for outcome prediction was developed according to these results as follows: $Pf = \exp(B)/1 + \exp(B)$, where Pf is the probability of a favourable outcome and $\exp(B)$ is the exponential function of B. For VF, $B = -0.02 \ast \text{age (years)} - 0.109 \ast \text{TROSC (min)} + 0.677 \ast \text{PROSC (1 or 0)} + 2.442$. For PEA/Asys, $B = -0.037 \ast \text{age (years)} - 0.076 \ast \text{TROSC (min)} + 1.735 \ast \text{PROSC (1 or 0)} + 1.462 \ast \text{conversion to VF (1 or 0)} + 1.101$.

Prognostic regression lines are shown in Figs. 2 and 3. Fig. 2 shows that if a 50-year-old person had a cardiac arrest but recovered spontaneous circulation from VF at 30 min after collapse and before arriving at hospital, the probability of a favourable outcome (Pf) 1 month later would be calculated as 24.7%. Pf decreased in cases without PROSC and also decreased as patient age increased. The same trend was observed in patients with an initial rhythm of PEA/Asys. In addition to age, TROSC, and PROSC, conversion to VF was an important prognostic factor in patients with an initial rhythm of PEA/Asys (Fig. 3a and b). Multivariate logistic regression indicated that the odds ratio of conversion to VF was >4.

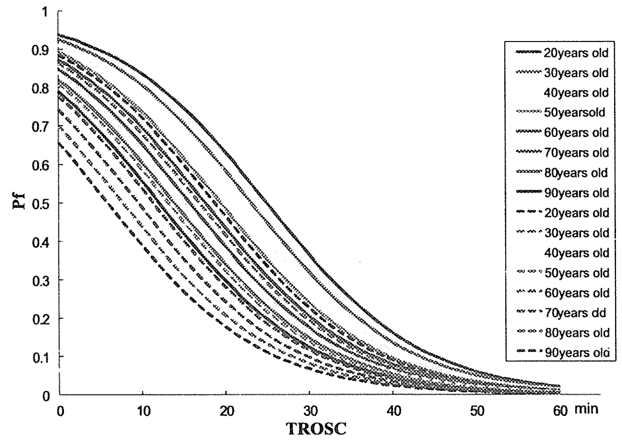

Fig. 2. Prognostic regression line of favourable outcome for VF. Solid lines represent cases with pre-hospital return of spontaneous circulation (PROSC), and dotted lines represent cases without PROSC. Pf, probability of favourable outcome; TROSC, time from collapse to return of spontaneous circulation.

3.3. Validation of the logistic regression model

ROC curves for a favourable outcome in VF patients are shown in Fig. 4. The AUC was 0.851 (95% confidence interval [CI]: 0.804–0.899) for VF in the DD group (Fig. 4a), and the AUC was 0.867 (95% CI: 0.818–0.917) in the VD group (Fig. 4b). If the cut-off value was taken at 0.53, the positive predictive value (PPV) was 69.5% (57/82), the negative predictive value (NPV) was 84.1% (159/189), and the total predictive value (TPV) was 79.7% (216/271). For PEA/Asys, the AUC was 0.890 (95% CI: 0.820–0.959) in the DD group (Fig. 4c) and 0.873 (95% CI: 0.807–0.940) in the VD group (Fig. 4d). If the cutoff value was taken at 0.31, PPV was 58.6% (17/29), NPV was 97.3% (522/536), and TPV was 95.3% (539/565). In both models, there was almost no difference in AUC between DD and VD, which indicated that the models were highly predictive and robust.

4. Discussion

Over the past decades, various studies for prediction of neurological outcomes after CPA have been reported.[5–7,9–24] However,

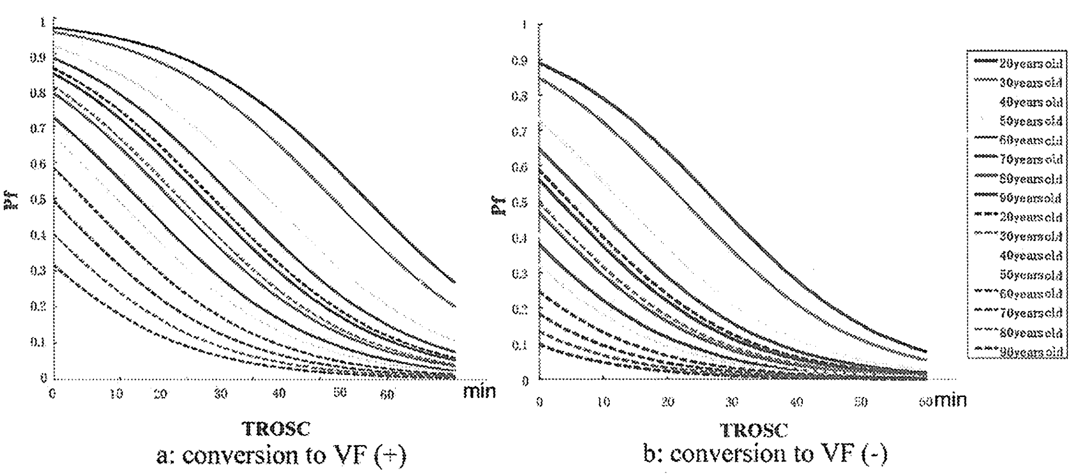

Fig. 3. Prognostic regression line of favourable outcome for PEA/Asys. Solid lines represent cases with pre-hospital return of spontaneous circulation (PROSC) and dotted lines represent cases without PROSC. Pf, probability of favourable outcome, TROSC, time from the collapse to return of spontaneous circulation. Panel a represents cases with conversion to VF, and panel b represents cases without conversion to VF.

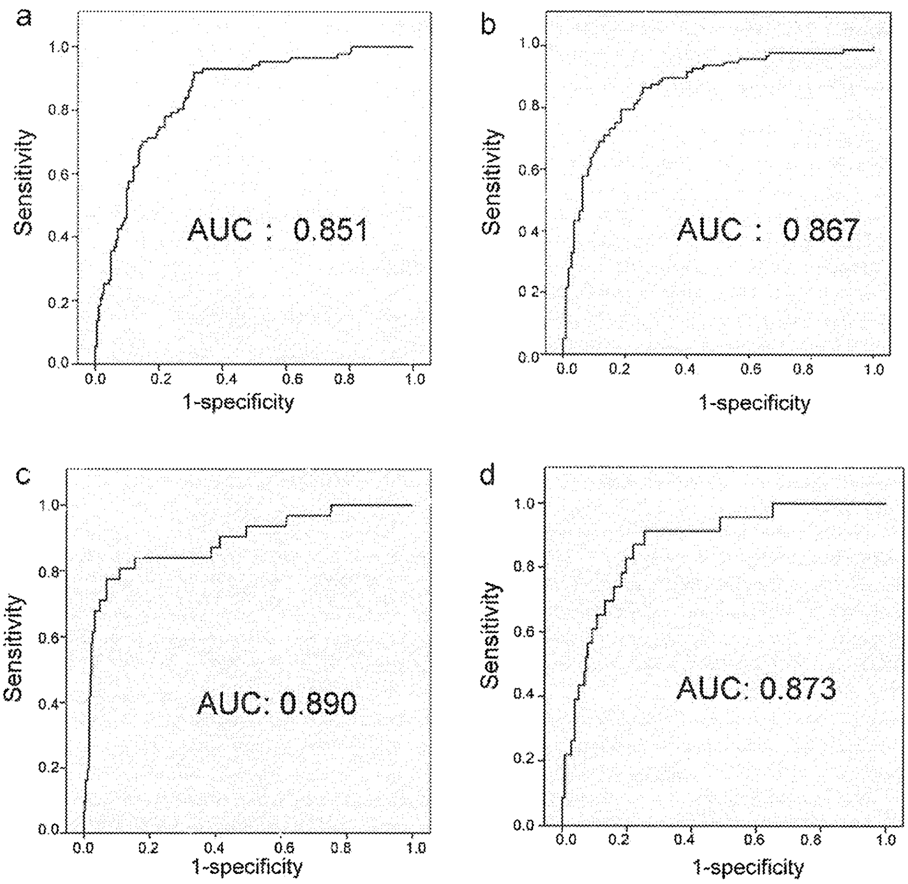

Fig. 4. Area under receiver-operating characteristic curves (AUC). (a) AUC for model development data in VF; (b) AUC for validation data in VF. (c) AUC for model development data in PEA/Asys. (d) AUC for validation data in PEA/Asys. VF, initial rhythm of ventricular fibrillation; PEA/Asys, initial rhythm of pulseless electrical activity or asystole.

most of the predictive indicators were obtained several days after admission. Such data does not allow us to determine whether intensive therapy such as PCPS is indicated. For this reason, we used prehospital prognostic factors in the present study.

We selected patients with cardiac origin of CPA as the subjects of this study because prognosis is very different between CPA of cardiac origin and that of non-cardiac origin such as asphyxia. In addition, we divided the patients into two groups according to the initial rhythm at the time of ambulance arrival to increase the predictive value because there was much difference between patients with VF and those with PEA/Asys.[25,26]

The presence of pre-hospital ROSC was detected as an independent predictor in both VF and PEA/Asys patients in the present study, which indicates that a patient with PROSC would be more likely to have a favourable outcome compared to a patient without PROSC, even if time from collapse to ROSC was the same in both patients. All EMS providers performed CPR according to the Japanese CPR guidelines based on the AHA guidelines. However, trained ELST have only been allowed to insert tracheal tubes and use epinephrine intravenously since April 2006. Moreover, CPR might be paused for breath due to the difficulty of chest compression while transporting the patients. Thus, quality of CPR might be slightly lower than in-hospital CPR. Therefore, ROSC by life support alone during the pre-hospital period might indicate that the patient had preserved better cardiac function.

Although we selected the time from collapse to first defibrillation as an explanatory variable, it was not chosen as an independent predictor. Valenzuela et al. reported that early defibrillation is an independent predictor of survival in CPA patients with VF.[26] We do not think this suggests that early defibrillation is not necessary for a good outcome, but other variables, especially TROSC, for example, might contribute more strongly to good outcomes. In PEA/Asys patients, the presence of conversion to VF was also detected as an independent prognostic indicator in the present study. Although some reports indicate that conversion to VF was associated with poor outcomes,[27] Kajino et al. reported that in OHCA patients with an initial non-shockable rhythm, subsequent VF was associated with a better outcome.[28]

Adrie et al. reported that initial rhythm, estimated no-flow interval and low-flow interval, blood lactate, and creatinine levels at admission were independently associated with poor outcome at discharge, and their prediction model for poor outcome has a high predictive value equivalent to that of our data.[5] Our study was different from their study in 3 ways. First, our study was a large population-based study covering 8.8 million people, whereas their study consisted of data from 4 hospitals. Second, the outcome data in our study were gathered 1 month after OHCA. Finally, all data in our study were pre-hospital data and laboratory analysis was not necessary for the model. We sometimes have to decide to use PCPS immediately after admission. Our prediction model is applicable even in such situations.

4.1. Limitations

We acknowledge several limitations in the present study. A change was made in EMS practices during the study period where only trained ELST were allowed to use epinephrine intravenously since April 2006. This might have influenced the results. However, the AUC of the mathematical model developed from 2005 to 2006 data did not change very much when the model was applied to data from 2007 in both VF and PEA/Asys. This suggests that the impact of the change was not great.

There were a limited number of patients with PEA/Asys who had a favourable outcome (DD group, $n = 33$; VD group, $n = 23$), and this might have widened the odds ratios. Although our model provided good prediction for validated data, we still need a large number of patients to establish a highly-reliable prediction model.

Life support therapy allowed by each EMS is different in different countries. During the study period, only trained ELST have been allowed to insert tracheal tubes and used epinephrine intravenously, so the other ELST used adjunct airway with/without epinephrine. As a result, some patients received BLS and some ACLS. Although our prediction model revealed a high predictive value in the present study, different approaches to pre-hospital resuscitation might affect the predictive value when the model is applied to patients in different countries, so the model may need to be calibrated for each specific EMS.

TROSC is naturally associated with neurological outcomes. However, in the clinical setting, we cannot always detect the time of collapse in CPA patients, so the application of this model was limited to a specific group of patients. To develop a predictive model that is more widely applicable for decision making in intensive care, development of a model based on laboratory data such as lactate on admission may be required.

Finally, Oksanen et al. reported that among patients with OHCA and VF as the initial rhythm who were treated with therapeutic hypothermia, pre-hospital variables did not influence outcome, and the OHCA score did not reliably predict outcome.[12] Utstein data in the present study did not include information concerning the use of PCPS or therapeutic hypothermia, so our model may be influenced by wider use of these modalities. During the study, hypothermia was used for patients quickly resuscitated from VF, and PCPS was only used in patients likely to have a favourable outcome, but we have no detailed data on this. The effects of these therapies on outcome require clarification in future studies.

5. Conclusions

The most important prognostic indicators of patients with ROSC from VF were age, TROSC, and PROSC, whereas those from PEA/Asys were age, TROSC, PROSC, and conversion to VF. A model based on these indicators showed a high predictive value for favourable outcome in CPA patients with ROSC and would be useful for decision making, family counseling, and review of treatment in cases of CPA. The model should be tested on another material from another system or country.

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Conflict of interest statement

There are no conflicts of interest to declare.

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Clinical paper

Time-dependent effectiveness of chest compression-only and conventional cardiopulmonary resuscitation for out-of-hospital cardiac arrest of cardiac origin☆

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ABSTRACT

Background: Little is known about the effect of the type of bystander-initiated cardiopulmonary resuscitation (CPR) for prolonged out-of-hospital cardiac arrest (OHCA).
Objectives: To evaluate the time-dependent effectiveness of chest compression-only and conventional CPR with rescue breathing for witnessed adult OHCA of cardiac origin.
Methods: A nationwide, prospective, population-based, observational study of the whole population of Japan included consecutive OHCA patients with emergency responder resuscitation attempts from 1 January 2005 to 31 December 2007. Multiple logistic regression analysis was performed to assess the contribution of the bystander-initiated CPR technique to favourable neurological outcomes.
Results: Among 55 014 bystander-witnessed OHCA of cardiac origin, 12 165 (22.1%) received chest compression-only CPR and 10 851 (19.7%) received conventional CPR. For short-duration OHCA (0–15 min after collapse), compression-only CPR had a higher rate of survival with favourable neurological outcome than no CPR (6.4% vs. 3.8%; adjusted odds ratio (OR), 1.55; 95% confidence interval (CI), 1.38–1.74), and conventional CPR showed similar effectiveness (7.1% vs. 3.8%; adjusted OR, 1.78; 95% CI, 1.58–2.01). For the long-duration arrests (>15 min), conventional CPR showed a significantly higher rate of survival with favourable neurological outcome than both no CPR (2.0% vs. 0.7%; adjusted OR, 1.93; 95% CI, 1.27–2.93) and compression-only CPR (2.0% vs. 1.3%; adjusted OR, 1.56; 95% CI, 1.02–2.44).
Conclusions: For prolonged OHCA of cardiac origin, conventional CPR with rescue breathing provided incremental benefit compared with either no CPR or compression-only CPR, but the absolute survival was low regardless of type of CPR.

Sudden cardiac arrest is a major public health problem in the industrialised world.[1] Because of improvements in the chain of survival, outcomes from out-of-hospital cardiac arrest (OHCA) have been improving in some communities.[1–3] Importantly, bystander-initiated cardiopulmonary resuscitation (CPR) substantially improves survival.[2–6]

We previously showed that bystander-initiated chest compression-only CPR increased neurologically favourable survival after adult OHCA of presumed cardiac origin when the interval from collapse to the initiation of emergency medical service (EMS) CPR was <15 min.[6] In addition, several other studies also showed that both bystander-initiated chest compression-only and conventional CPR with chest compressions and rescue breathing improved outcomes following OHCAs.[7–12] Based on these data, the

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American Heart Association (AHA) recommends that laypersons, who witness adult sudden collapse, should provide either continuous chest compressions without rescue breathing or conventional CPR.[13] However, some reports demonstrated the effectiveness of rescue breathing for cardiac arrests in situations such as those of non-cardiac origin.[14–16] It is also possible that the addition of rescue breathing may improve outcomes of OHCA, when the duration of the arrest is prolonged.[13,17] Notably, some experts have stated that conventional CPR with the 2005 Guidelines (30:2 ratio of compressions-to-ventilations rather than 15:2) may result in better outcomes than compression-only CPR.[13,17]

The Fire and Disaster Management Agency (FDMA) of Japan launched a prospective, nationwide, population-based cohort study of OHCA victims and collected approximately 55 000 bystander-witnessed OHCAs of presumed cardiac origin. Our hypothesis was that bystander-initiated conventional CPR would result in higher rates of survival with favourable neurological outcomes following adult-witnessed OHCAs with cardiac origin of prolonged duration (>15 min from collapse to the initiation of EMS CPR) compared with either no CPR or compression-only CPR. We further hypothesised that both compression-only CPR and conventional CPR would be similarly effective for adult-witnessed OHCAs with cardiac origin of shorter duration, even after implementation of 2005 Guidelines with conventional CPR of 30:2 compressions-to-ventilations.

1. Methods

1.1. Study design and setting

The All-Japan Utstein Registry of the FDMA is a prospective, nationwide, population-based registry system of OHCA based on the Utstein style.[18,19] This observational study enrolled adult patients aged ≥18 years suffering OHCA, who were treated by EMS personnel and then transported to medical institutions from 1 January 2005 through 31 December 2007. The implementation working group for All-Japan Utstein Registry of the FDMA designed the study protocol, the FDMA collected and managed the data and the authors analysed the data and wrote the manuscript. The protocol for analyses was approved by the Ethics Committee of Kyoto University Graduate School of Medicine. The requirement of informed consent was waived.

Cardiac arrest was defined as the cessation of cardiac mechanical activity as confirmed by the absence of signs of circulation.[18,19] The arrest was presumed to be of cardiac origin unless it was caused by cerebrovascular diseases, respiratory diseases, malignant tumours, external causes including trauma, hanging, drowning, drug overdose and asphyxia, or any other non-cardiac causes. These diagnoses of cardiac or non-cardiac origin were determined by the physicians in charge, in collaboration with the EMS personnel.

1.2. EMS systems in Japan

Japan has an area of approximately 378 000 km^2, including both urban and rural communities, and its population was 127 767 994 in 2005, and 106 426 048 were ≥18 years old.[20] There were 807 fire stations with dispatch centres in 2007, and all EMS was provided by the municipal governments. Usually, each ambulance had a crew of three emergency providers, including at least one Emergency Life-Saving Technician (ELST), a highly trained prehospital emergency care provider. ELSTs were allowed to insert an intravenous line and an adjunct airway, and to use semi-automated external defibrillators for OHCA patients. Specially trained ELSTs were permitted to insert tracheal tubes since July 2004 and to administer intravenous epinephrine since April 2006. Citizen use of an automated external defibrillator (AED) has been legally permitted since July 2004 in Japan. EMS providers were not permitted to terminate resuscitation in the field. Therefore, most patients with OHCA, who were treated by EMS personnel, were transported to hospitals and registered in this study, excluding cases of decapitation, incineration, decomposition, rigor mortis or dependent cyanosis.

1.3. Guideline alteration and systemic training for the general public

All EMS providers had performed and taught CPR, according to the Japanese CPR Guidelines based on the AHA and the International Liaison Committee on Resuscitation (ILCOR) Guidelines 2000 until September 2006 and the respective 2005 Guidelines thereafter.[1,21–23] In Japan, approximately 1.4 million citizens per year participated in the CPR training programmes, consisting of conventional CPR including chest compressions, mouth-to-mouth ventilation and AED usage (generally provided by local fire departments).[24] Compression-only CPR had not been taught as the recommended technique in any resuscitation training programme during the study period, but it was first recommended as 'acceptable' for those who could not or did not wish to perform rescue breathing with the 2005 CPR Guidelines.[1,21–23] The emergency-telephone dispatchers in Japan are basically trained and ordered to give CPR instructions with conventional CPR before the arrival of the EMS. However, it is permitted to encourage bystanders to provide chest compression-only CPR, if it is difficult for them to administer rescue breathing.

1.4. Data collection and quality control

Data were prospectively collected using a form based on the Utstein-style reporting guidelines for OHCA, including gender, age, type of bystander-witnessed status, initial cardiac rhythm, time course of resuscitation, type of bystander-initiated CPR, type of advanced airway management, intravenous fluids and epinephrine, as well as 1-month survival and neurological status 1 month after the event. 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 based on the clock used by each EMS system. Data about the initiation and type of bystander CPR were obtained by EMS interview with the bystander before leaving the scene. All survivors were evaluated at 1 month after the event by the EMS personnel in charge.

The data form was filled out by the EMS personnel in co-operation with the physicians in charge of the patients, and the data were integrated into the registry system on the FDMA database server. They were logically checked by the computer system and were confirmed by the implementation working group. If the data form was incomplete, the FDMA returned it to the respective fire station and the data were completed.

1.5. Main outcome measure

Neurological outcome was determined by a follow-up interview 1 month after successful resuscitation, 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.[18,19] The primary outcome measure was 1-month survival with favourable neurological outcome, defined as CPC category 1 or 2.[18,19]

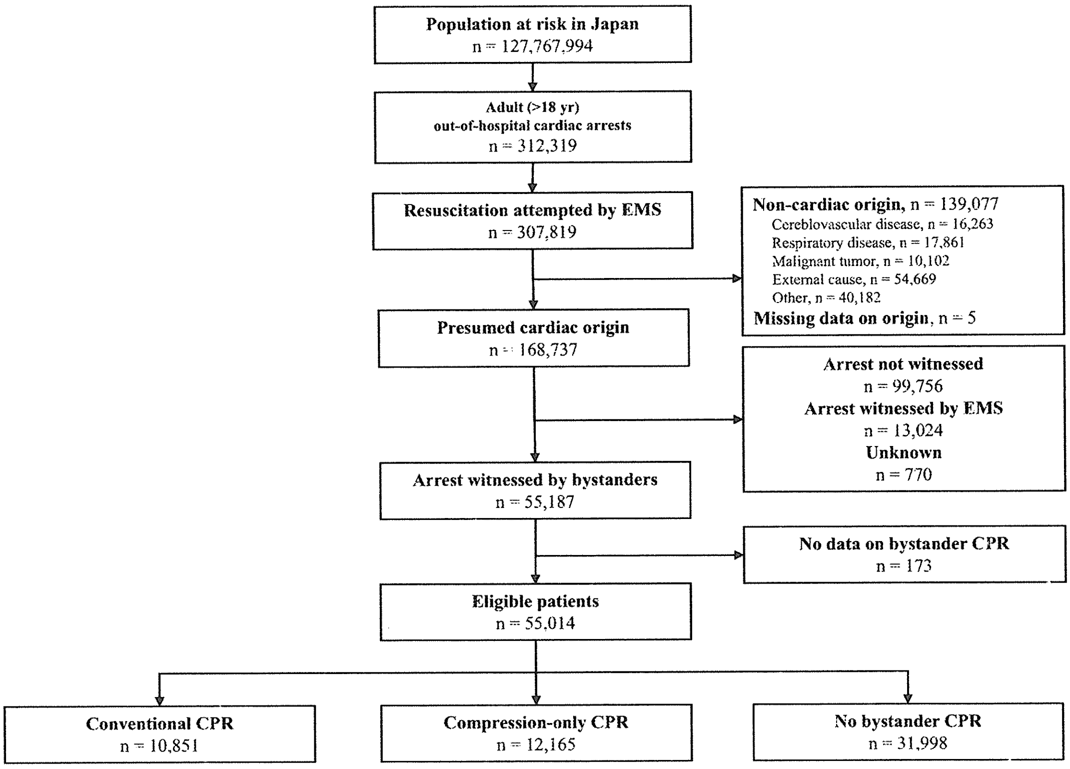


Fig. 1. Flow chart of patients. EMS denotes emergency medical service; CPR, cardiopulmonary resuscitation.

1.6. Statistical analysis

Outcomes after witnessed cardiac arrests of presumed cardiac origin and witnessed ventricular fibrillation (VF) arrests were compared by type of bystander-initiated CPR. Both bystander-initiated conventional CPR and compression-only CPR with rescue breathing were included as bystander CPR, and bystander-initiated rescue breathing without compressions (1.7%) was classified as no bystander CPR. The effect of the type of bystander-initiated CPR was evaluated by 5-min strata of the 'bystander CPR interval', which was defined as the time interval from collapse to the initiation of treatments by EMS. In particular, patients with very-long-duration cardiac arrests ($\geq$15 min) were analysed separately according to our hypothesis that the addition of rescue breathing would benefit these patients because of their many pathophysiological differences.[6,25,26]

Patient characteristics and outcomes by type of bystander-initiated CPR were evaluated using analysis of variance for numerical variables and chi-square test for categorical variables. Trends in categorical values were tested with univariable regression models. The age-adjusted annual incidence of OHCAs was calculated by direct methods using 2005 census data and the 1985 Japanese population model.[20,27] Multivariable analysis was used to assess the contribution of bystander-initiated CPR to 1-month survival with favourable neurological outcome; odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated. Potential

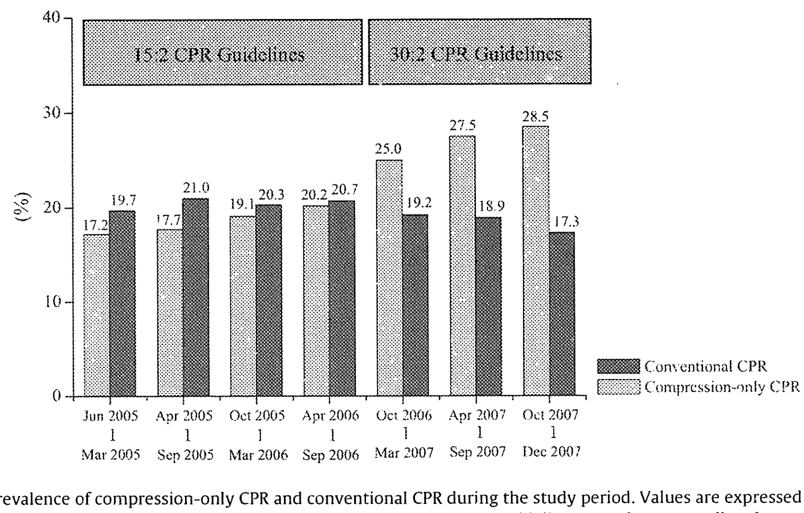


Fig. 2. Temporal trends in the prevalence of compression-only CPR and conventional CPR during the study period. Values are expressed as percentage. The compressions-to-ventilations ratio was changed from 15:2 to 30:2 in October 2006 by the revision of Japan CPR guidelines. CPR denotes cardiopulmonary resuscitation.

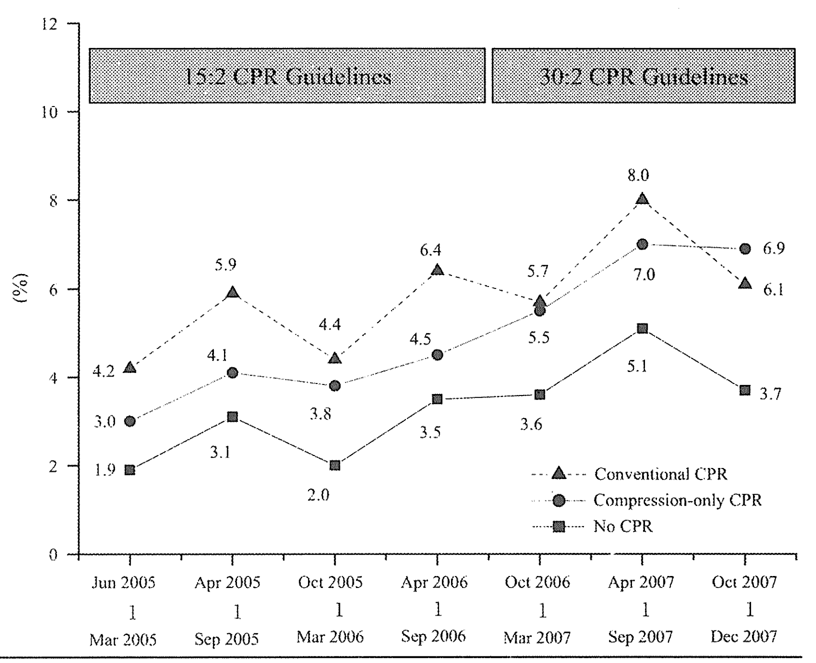
Table 1
Characteristics of bystander-witnessed out-of-hospital cardiac arrest of cardiac origin by bystander CPR.

	No CPR (*n* = 31 998)	Compression-only CPR (*n* = 12 165)	Conventional CPR (*n* = 10 851)	*P*-value*
Age, year, mean (SD)	73.0 (14.4)	73.3 (15.1)	73.3 (14.9)	0.051
Men, *n* (%)	20 676 (64.6)	7720 (63.5)	6297 (58.0)	<0.001
Bystander-witness status, *n* (%)				<0.001
Family member	24 520 (76.6)	7693 (63.2)	5384 (49.6)	
Other	7478 (23.4)	4472 (36.8)	5467 (50.4)	
First documented rhythm (%)				<0.001
VF or pulseless VT	6434 (20.1)	3071 (25.2)	2769 (25.5)	
PEA	11 005 (34.4)	3444 (28.3)	3336 (30.7)	
Asystole	14 559 (45.5)	5650 (46.4)	4746 (43.7)	
Advanced airway management, *n* (%)				<0.001
None	15 265 (47.7)	5842 (48.0)	5387 (49.8)	
Laryngeal mask airway	4579 (14.3)	1599 (13.2)	1408 (13.0)	
Oesophageal obturator airway	10 323 (32.3)	3975 (32.7)	3388 (31.3)	
Endotracheal intubation	1817 (5.7)	743 (6.1)	644 (5.9)	
Intravenous fluid, *n* (%)	6252 (19.5)	2554 (21.0)	2050 (18.9)	<0.001
Epinephrine, *n* (%)	1258 (3.9)	624 (5.1)	430 (4.0)	<0.001
Collapse to CPR by EMS, min, mean (SD)	11.3 (8.0)	12.4 (7.8)	12.8 (7.8)	<0.001
Collapse to shock by EMS, min, mean (SD)†	11.3 (5.9)	12.6 (6.3)	12.7 (6.3)	<0.001
Collapse to hospital arrival, min, mean (SD)	32.1 (10.5)	32.9 (10.2)	33.2 (10.3)	<0.001

CPR denotes cardiopulmonary resuscitation; VF, ventricular fibrillation; VT, ventricular tachycardia; PEA, pulseless electrical activity; and EMS, emergency medical service.
* *P*-values are calculated to test the homogeneity among the three CPR groups.
† Calculated for cases with VF or pulseless VT as first documented rhythm.

confounding factors based on biological plausibility and previous studies were included in the multivariable analysis. These variables included gender, age, bystander-witnessed status, first recorded rhythm, advanced airway management, intravenous fluids, epinephrine, time interval from collapse to the initiation of CPR by EMS and time interval from collapse to hospital arrival. Because outcomes appear to have improved with 2005 Guidelines that included 30:2 compressions-to-ventilations ratios,[28] the period with 15:2 versus 30:2 CPR guidelines was also incorporated in multivariable analyses.

The sample size of victims needed to test our hypothesis was derived from analysis of a previous observational study in Japan.[6] The calculation was based on a twofold improvement in survival with favourable neurological outcome from a baseline of 1.0%, and a 1:1:3 ratio of victims who received conventional CPR versus compression-only CPR versus no CPR. The minimum sample size



	Jun 2005 – Mar 2005	Apr 2005 – Sep 2005	Oct 2005 – Mar 2006	Apr 2006 – Sep 2006	Oct 2006 – Mar 2007	Apr 2007 – Sep 2007	Oct 2007 – Dec 2007
Conventional CPR	2.34 (1.52-3.60)	1.94 (1.43-2.65)	2.29 (1.69-3.01)	1.71 (1.29-2.27)	1.61 (1.23-2.12)	1.56 (1.20-2.03)	1.56 (1.05-2.23)
Compression-only CPR	1.76 (1.08-2.86)	1.38 (1.00-1.97)	1.92 (1.39-2.65)	1.20 (0.90-1.65)	1.55 (1.21-1.98)	1.30 (1.01-1.62)	1.92 (1.34-2.65)
No CPR	Reference	Reference	Reference	Reference	Reference	Reference	Reference

Fig. 3. Temporal trends in neurologically favourable 1-month survival by type of bystander CPR during the study period. Values in figure are expressed as percentage of neurologically favourable 1-month survival by type of bystander-initiated CPR. Values in table indicate adjusted odds ratio (95% confidence interval) of bystander-initiated conventional CPR and compression-only CPR referring to no CPR. Odds ratios and 95% confidential intervals are adjusted for gender, age, bystander-witnessed status, first recorded rhythm, advanced airway management, intravenous fluid, epinephrine, time interval from collapse to the initiation of CPR by EMS and time interval from collapse to hospital arrival. The compressions-to-ventilations ratio was changed from 15:2 to 30:2 in October 2006 by the revision of Japan CPR guidelines. CPR denotes cardiopulmonary resuscitation.

Table 2
Neurologically favourable 1-month survival after witnessed cardiac arrests of presumed cardiac origin and witnessed VF arrests by type of bystander CPR according to the bystander CPR interval.

	No CPR	Compression-only CPR	Conventional CPR
Witnessed cardiac arrests of presumed cardiac origin			
Bystander CPR interval 0–15 min (*n* = 42 332)	967/25 183 (3.8)	589/9171 (6.4)	570/7978 (7.1)
Adjusted OR (95% CI)	Reference	1.55 (1.38–1.74)	1.78 (1.58–2.01)
		Reference	1.16 (0.97–1.33)
Bystander CPR interval >15 min (*n* = 11 704)	45/6151 (0.7)	36/2846 (1.3)	55/2707 (2.0)
Adjusted OR (95% CI)	Reference	1.29 (0.75–1.96)	1.93 (1.27–2.93)
		Reference	1.56 (1.02–2.44)
Witnessed VF cardiac arrests			
Bystander CPR interval 0–15 min (*n* = 10 715)	674/5786 (11.6)	484/2614 (18.5)	443/2315 (19.1)
Adjusted OR (95% CI)	Reference	1.88 (1.65–2.14)	1.94 (1.69–2.22)
		Reference	1.08 (0.92–1.26)
Bystander CPR interval >15 min (*n* = 1425)	22/564 (3.9)	21/439 (4.8)	33/422 (7.8)
Adjusted OR (95% CI)	Reference	1.21 (0.66–2.19)	1.86 (1.06–3.27)
		Reference	1.49 (0.80–2.78)

Bystander CPR interval was defined as the time interval from collapse to the initiation of treatments by EMS. CPR denotes cardiopulmonary resuscitation; VF, ventricular fibrillation; OR, odds ratio; and CI, confidence interval. OR were adjusted for gender, age, type of bystander witness, first recorded rhythm, type of advanced airway management, epinephrine, intravenous fluid, time interval from collapse to CPR by EMS, time interval from collapse to hospital arrival and the period with 15:2 versus 30:2 CPR guidelines.

for comparison of improved outcome was estimated to be 2000 victims for each bystander-initiated CPR group and 6000 no CPR victims based on a two-side α-value of 0.05 and a β-error of 0.10. All statistical analyses were performed using Statistical Package for Social Sciences (SPSS) package ver16.0J (SPSS, Inc., Chicago, IL, USA). All tests were two-tailed, and *P*-values of <0.05 were considered statistically significant.

2. Results

During these 3 years, 312 319 adult OHCAs were documented. The age-adjusted annual incidence of bystander-witnessed OHCA of presumed cardiac origin in Japan during this study period was 9.6/100 000 person-years. The first documented rhythm was VF in 27% (2.6/100 000 person-years).

Fig. 1 shows an overview of the arrests. Out of 307 819 adult OHCA cases with resuscitation attempts, 168 737 were presumed to be of cardiac origin. Of these victims, 55 187 were witnessed by bystanders, 13 024 were witnessed by EMS and 99 756 were not witnessed. Excluding 173 cases without information on bystander-initiated CPR, 55 014 were eligible for our analyses. Among eligible patients, 10 851 (19.7%) received conventional CPR with rescue breathing, 12 165 (22.1%) compression-only CPR and 31 998 (58.2%) no CPR. Neurological status was not obtained for 205 cases (0.4%).

Temporal trends in the proportion of bystander CPR techniques during the study period are shown in Fig. 2. During this time period, the proportion of OHCA patients who received compression-only CPR increased from 17.2% to 28.5% (*P* for trend <0.001). In the 30:2 CPR era (i.e., after compression-only CPR was recommended as 'acceptable'), 6301 (26.6%) received compression-only CPR and 4425 (18.7%) conventional CPR, whereas 5864 (18.7%) received compression-only CPR and 6426 (20.5%) received conventional CPR in the 15:2 CPR era. The proportion of compression-only CPR was higher in the 30:2 CPR era than in the 15:2 CPR era (26.6% vs. 18.6%, OR, 1.58 (95% CI, 1.52–1.64)).

Demographic and resuscitation characteristics of OHCA patients by type of bystander CPR are noted in Table 1. Mean age was similar, but male/female ratio was lower in the conventional CPR group than in the no CPR and the compression-only CPR groups. The conventional CPR group was less likely to be witnessed by family members than the no CPR and compression-only CPR groups. Both bystander CPR groups were more likely to have VF as the initial rhythm. The compression-only CPR group was more likely to receive advanced life-support measures such as epinephrine, tracheal intubation and intravenous fluid than the other groups. Several EMS resuscitation times were longer with either compression-only CPR or conventional CPR than no CPR.

Fig. 3 shows temporal trends in 1-month survival with favourable neurological outcome by the type of bystander CPR. Outcomes gradually improved, irrespective of type of bystander CPR, during the study period. In the 15:2 CPR guidelines era, both compression-only CPR and conventional CPR were associated with higher rates of survival with favourable neurological outcome than no CPR, although ORs were smaller with compression-only CPR. In the 30:2 CPR guideline era, the rate of neurologically favourable survival with conventional CPR and compression-only CPR was 6.6% (292/4425) and 6.4% (401/6301), respectively (adjusted OR, 1.04; 95% CI, 0.87–1.24), and both bystander CPR techniques had similar ORs in comparison to the no CPR control group (Fig. 3).

One-month survival with favourable neurological outcome by type of bystander CPR and 'bystander CPR interval' (time from collapse to the initiation of treatments by EMS) is noted in Table 2 and Fig. 4. When the bystander CPR interval was <15 min, both conventional CPR (7.1% (570/7978)) and compression-only CPR (6.4% (589/9171)) were associated with better outcomes than no CPR (3.8% (967/25183)), and the conventional CPR group had similar outcomes compared with the compression-only CPR group (adjusted OR, 1.16 (95% CI, 0.97–1.33)) (Table 2). When the bystander CPR interval was >15 min, conventional CPR (2.0% (55/2707)) had a significantly higher rate of better outcome than both no CPR (0.7% (45/6151), adjusted OR, 1.93; 95% CI, 1.27–2.93) and compression-only CPR (1.3% (36/2846), adjusted OR, 1.56; 95% CI, 1.02–2.44) (Table 2).

With regard to witnessed VF arrests (Table 2), the outcomes were similarly improved with both conventional CPR and compression-only CPR among OHCAs of 0–15 min duration (19.1% vs. 18.5%; adjusted OR, 1.08 (95% CI, 0.92–1.26)). Only the conventional CPR group had significantly higher rates of favourable neurological outcomes than the no CPR group (7.8% vs. 3.9%; adjusted OR, 1.86 (95% CI, 1.06–3.27)) among OHCAs of >15 min duration, whereas the compression-only CPR group did not (adjusted OR, 1.21 (95% CI, 0.66–2.19)).

3. Discussion

The data from this large nationwide registry of OHCA establish that bystander-initiated conventional CPR with rescue breathing can improve the rate of survival with favourable neurological outcome following OHCA of prolonged duration compared with either no CPR or compression-only CPR. In addition, this investigation