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# Prognosis of Cerebral Function of Cerebrovascular Disease Patients who Caused Out-of-Hospital Cardiac Arrest in Japan

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## Abstract

The prognosis of with out-of-hospital cardiac arrest (OHCA) is poor and the aim of this study was to determine the factors influencing good prognosis of cerebral function in OHCA of cerebrovascular disease patients using the Utstein database of Japan.

**Methods and Material:** Of 925,268 cases in the Utstein database, 41,711 cases of OHCA from cerebrovascular disease were selected.

**Results:** While the rate of good cerebral function at 1 month after OHCA was 2.2% in cerebrovascular disease patients, it improved to 3.9% when restricted to the witnessed OHCAs. Multiple logistic regression analysis revealed that ventricular tachycardia or ventricular fibrillation in the initial electrocardiogram findings and automated external defibrillator usage by the public were beneficial factors, whereas female sex, older age, nighttime onset, and a longer interval from request call for emergency medical services to contact with a patient were deteriorating factors for cerebral function following OHCA.

**Conclusion:** This study indicated a poor prognosis in cerebrovascular disease patients after OHCA in Japan. VT/VF findings in the initial ECG and usage of AED were beneficial factors, whereas older age, request calls during nighttime, and a call-to-patient contact interval of >10 min were factors for poor cerebral function in OHCAs.

***Keywords:*** *Cerebral Function; Out-of-Hospital Cardiac Arrest; Utstein Database; Odds Ratio; Multiple Logistic Model*

## Abbreviations

AED: Automated External Defibrillator; CPR: Cardiopulmonary Resuscitation; EMS: Emergency Medical Service; OHCA: Out-of-Hospital Cardiac Arrest; VF: Ventricular Fibrillation; VT: Ventricular Tachycardia

## Introduction

Successful social rehabilitation without severe neurological or physical impairment after out-of-hospital cardiac arrest (OHCA) is a primary goal of emergency medical services (EMSs). However, it is generally difficult to survive through cardiopulmonary resuscitation (CPR), and only few patients return to society after cardiac failure, multiple organ failure, infections, and hypoxic encephalopathy [1]. Some factors affecting outcome following OHCA such as usage of automated external defibrillation (AED) and methods of CPR has been known, and the prolonged interval of cardiac arrest much deteriorated the cerebral function [2,3]. All OHCA cases reported by emergency medical personnel are available in an Utstein template database (Utstein database), which is a standard for reporting cardiac arrest in-

cidents and is settled at the conference held at the Utstein Abbey in Norway [4]. Using such databases, the efficacy of bystander CPR and EMS can be assessed [5]. In Japan, the Utstein database has been used since January 2005 and has contributed to improved emergency medicine protocols [6-8].

The population of Japan is 127 million, 27.3% of whom are aged >= 65 years, and the number of deaths was 1,310,000 in 2016. Approximately 120,000 patients with OHCA were recorded by EMS, accounting to one tenth of all deaths.

## Aim of the Study

The aim of this study was to determine the factors influencing good prognosis of cerebral function in OHCA of cerebrovascular disease patients using the Utstein database of Japan.

## Methods and Materials

### Study setting

The Utstein database of Japan from 2005 to 2012 was analyzed. In Japan, EMS comprises basic life support ambulances staffed with paramedics. Ambulances are dispatched from municipal fire defense stations. Request calls for an ambulance (phone: 119) are received by a telephone operator or dispatcher. EMS is financed by taxes, and free access to EMS is guaranteed. The data of patients with OHCA are electronically recorded in the Utstein template database at each fire station and sent to the Fire Defense and Disaster Agency.

### Study design

Among 925,268 OHCA cases recorded in the Utstein database from 2005 to 2012, 41,711 cases caused by cerebrovascular diseases were selected for farther analysis (Figure 1).

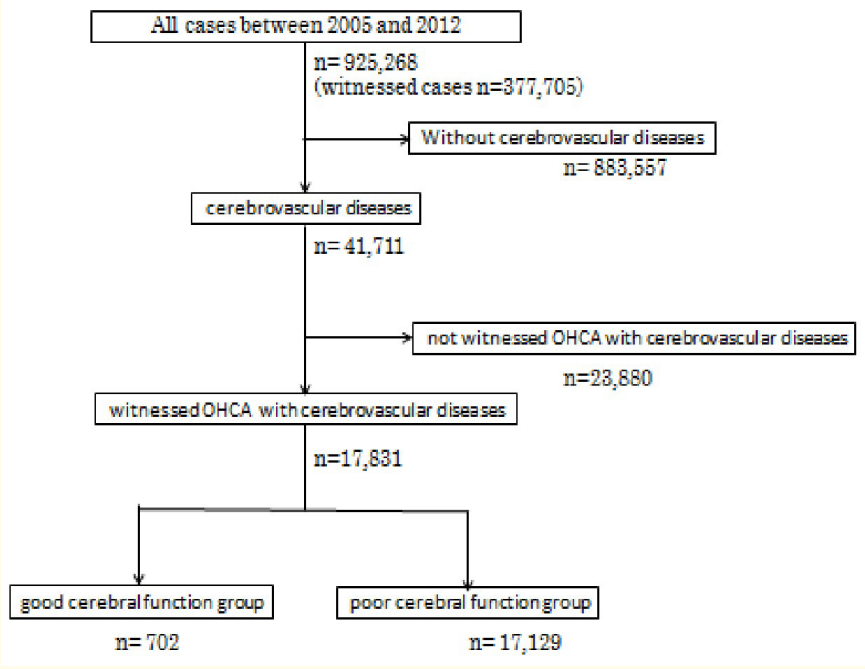


***Figure 1:*** *Flow diagram for data selection from the Utstein database.*

Patients' age and sex, initial electrocardiogram (ECG) findings, presence of a doctor in the ambulance (doctor on an ambulance), oral instructions to the bystander by EMS dispatcher (oral instruction), CPR by the bystander, defibrillation attempts, airway management, intravenous cannulation, adrenaline (epinephrine) administration, onset year and season, time of call request, and cerebral function at 1 month after OHCA were used for analysis.

The initial ECG findings were surveyed and categorized by paremedics according to the presence or absence of ventricular fibrillation or pulseless ventricular tachycardia (VF/VT and non-VF/VT). According to the usage of AEDs, four groups were established, namely defibrillation using an AED by a bystander only (by the public), by EMS staff only (by EMS), by both public and EMS, and by no one. CPR was also divided into four types, namely conventional CPR (chest compressions and artificial ventilation), chest compressions only, artificial ventilation only (ventilation), and none. Periodic changes were compared between 2005 - 2008 and 2009 - 2012. The time of request call was categorized as daytime (from 09:00 to 16:59) or nighttime (from 17:00 to 08:59). Seasons were defined as occurring from March to May (spring), June to August (summer), September to November (autumn), and December to February (winter). The intervals from request call to contact with a patient and to a hospital were calculated after the time series data were cleaned using a previously reported method [8].

### Outcomes

Our outcome was cerebral function, which was defined as the category 1 or 2 in the cerebral performance categories and the category 1 or 2 in the overall categories of the Glasgow Pittsburg Outcome Categories at 1 month after OHCA. Cerebrovascular disease patients with OHCA witnessed by bystanders were divided into two groups, namely a good cerebral function group, with normal or only mild impairment of cerebral performance (categories, 1 and 2) and a poor cerebral function group, with moderate or severe impairment, brain dead, or death (categories, 3 - 5).

### Statistical analysis

We analyzed the proportions of good cerebral function in all patients and witnessed OHCA patients from the Utstein database and those in all patients and witnessed OHCA patients with cerebrovascular diseases. Chi-square test and Bonferroni method were used for the comparison of four groups.

We compared the findings at 1 month after OHCA between the good and poor cerebral function groups, summarized 13 variables examined in two groups, and performed multiple logistic regression analysis to evaluate the relationship between cerebral function and the 13 variables assessed after OHCA to obtain odds ratios (ORs) for the good cerebral function group vs. the poor cerebral function group using the open statistical software R (ver. 3.4.2, The R foundation, Austria).

### Ethics

The Utstein database was analyzed with the permission of the Fire and Disaster Management Agency of the Ministry of Internal Affairs and Communications. This study was approved by the ethical committee of Kokushikan University (No. 27-010).

## Results

### Rate of good cerebral function

The rate of good cerebral function in cerebrovascular disease patients was 2.2%, which was statistically lower than that in all patients from the Utstein database (2.7%). Among the witnessed OHCA patients, the rate of cerebrovascular disease was 3.9%, which was also statistically lower than that in all patients from the Utstein database (5.5%) (Table 1).

| Population | Number | Good Cerebral Function | (%) |
|---|---|---|---|
| All patients in the Utstein database | 925,268 | 25,346 | (2.7) |
| Witnessed OHCA patients in the Utstein database | 377,705 | 20,593 | (5.5) |
| Cerebrovascular disease patients | 41,711 | 918 | (2.2)* |
| Witnessed OHCA patients with cerebrovascular disease | 17,831 | 702 | (3.9)** |

***Table 1:*** *Rates of good cerebral function at 1 month after OHCA.*

**p < 0.0001 cerebrovascular diseases patients against all cases of the Utstein data*

***p < 0.0001 witnessed OHCA patients with cerebrovascular diseases against witnessed OHCA patients in the Utstein database*

| | | Good function group | | Poor function group | | |
|---|---|---|---|---|---|---|
| | | (n = 702) | | (n = 17,129) | | |
| Variable | | n | (%) | n | (%) | Probability |
| Sex | Male | 435 | (62.0) | 8,980 | (52.5) | < 0.0001 |
| | Female | 267 | (38.0) | 8,149 | (47.6) | |
| Age class | 0 - 39 years old | 53 | (7.5) | 684 | (4.0) | < 0.0001 |
| | 40 - 64 years old | 258 | (36.8) | 5,444 | (31.8) | |
| | 65 - 74 years old | 135 | (19.2) | 3,468 | (20.2) | |
| | 75 - 84 years old | 163 | (23.2) | 4,526 | (26.4) | |
| | 85- years old | 93 | (13.2) | 3,005 | (17.5) | |
| Onset year | 2005 - 2008 | 376 | (40.2) | 8,944 | (52.2) | ns |
| | 2009 - 2012 | 326 | (59.8) | 8,185 | (47.8) | |
| Day and night | 09:00 - 16:59 | 333 | (47.4) | 7,699 | (44.9) | ns |
| | 17:00 - 07:59 | 369 | (52.6) | 9,430 | (55.1) | |
| Season | Spring | 172 | (24.5) | 4,307 | (25.1) | ns |
| | Summer | 146 | (20.8) | 3,600 | (21.0) | |
| | Autumn | 173 | (24.6) | 4,183 | (24.4) | |
| | Winter | 211 | (30.1) | 5,038 | (29.4) | |
| Initial ECG | VT/VF | 157 | (22.4) | 1,177 | (6.9) | < 0.0001 |
| Oral instruction | Yes | 214 | (30.6) | 5,574 | (32.5) | ns |
| CPR | Conventional | 139 | (19.8) | 2,134 | (12.5) | < 0.01 |
| | Chest compression | 213 | (29.3) | 3,747 | (21.9) | |
| | Ventilation | 184 | (0.9) | 2,900 | (16.9) | |
| | None | 329 | (52.4) | 11,149 | (65.1) | |
| AED | Public | 184 | (1.9) | 98 | (0.6) | < 0.0001 |
| | EMS | 161 | (22.9) | 1,661 | (9.7) | |
| | Public and EMS | 491 | (69.9) | 26 | (0.2) | |
| | None | 7 | (1.0) | 10,820 | (63.2) | |
| Doctor on an ambulance | Yes | 82 | (11.7) | 1,994 | (11.6) | ns |
| Call-to-contact interval | ≤10 minutes | 130 | (18.5) | 3,790 | (22.1) | ns |
| Call-to-hospital interval | ≤60 minutes | 669 | (95.3) | 16,344 | (95.4) | < 0.0001 |
| IV cannulation | Yes | 71 | (10.1) | 4,490 | (26.2) | < 0.0001 |
| Adrenaline administration | Yes | 17 | (2.4) | 2,082 | (12.2) | < 0.0001 |

***Table 2:*** *Profiles of cerebral function following OHCA in the good and poor cerebral function groups.*

*ns: Not Significant, p ≥ 0.05*

### ORs according to the multiple logistic regression model

ORs for the good cerebral function group vs. the poor cerebral function group obtained through multiple logistic regression analysis are shown in table 3. OR of VT/VF to non-VT/VF in the initial ECG had the highest value of 2.91 (95% confidence interval, 2.04 - 4.19).

| Variable | | Odds Ratio | Lower 95% CI | Upper 95% CI | Probability |
|---|---|---|---|---|---|
| Sex | Male | 1 | | | |
| | Female | 0.74 | 0.63 | 0.88 | < 0.001 |
| Age group (years) | 0 - 39 | 1 | | | |
| | 40 - 64 | 0.65 | 0.48 | 0.9 | < 0.001 |
| | 65 - 74 | 0.55 | 0.39 | 0.78 | < 0.01 |
| | 75 - 84 | 0.52 | 0.37 | 0.79 | < 0.001 |
| | ≥ 85 | 0.45 | 0.31 | 0.64 | < 0.001 |
| Year | 2005 - 2008 | 1 | | | |
| | 2009 - 2012 | 1.53 | 1.3 | 1.81 | < 0.001 |
| Day and night | Daytime | 1 | | | |
| | Nighttime | 0.66 | 0.57 | 0.78 | < 0.01 |
| Season | Spring | 1 | | | |
| | Summer | 1.02 | 0.88 | 1.29 | ns |
| | Autumn | 1.07 | 0.85 | 1.33 | ns |
| | Winter | 1.06 | 0.86 | 1.33 | ns |
| Initial ECG | Non-VT/VF | 1 | | | |
| | VT/VF | 2.91 | 2.04 | 4.19 | < 0.001 |
| CPR | Conventional | 1 | | | |
| | Chest compression | 0.89 | 0.69 | 1.09 | ns |
| | Respiration | 0.71 | 0.34 | 1.31 | ns |
| | None | 0.46 | 0.37 | 0.57 | < 0.001 |
| AED | None | 1 | | | |
| | Public | 2.24 | 2.18 | 3.96 | < 0.01 |
| | EMS | 1.22 | 0.85 | 1.73 | ns |
| | Public and EMS | 2.61 | 0.96 | 6.29 | < 0.05 |
| Doctor on ambulance | No | 1 | | | |
| | Yes | 1.06 | 0.65 | 1.07 | ns |
| Call-to-contact interval | ≤10 minutes | 1 | | | |
| | >10 minutes | 0.72 | 0.58 | 0.87 | < 0.01 |
| Call-to-hospital interval | ≤60 minutes | 1 | | | |
| | >60 minutes | 0.87 | 0.61 | 1.29 | ns |
| IV cannulation | No | 1 | | | |
| | Yes | 0.41 | 0.31 | 0.55 | < 0.001 |
| Adrenaline administration | No | 1 | | | |
| | Yes | 0.31 | 0.17 | 0.53 | < 0.01 |

***Table 3:*** *Results of the multiple regression model.*

The usage of AEDs by the public and EMS and by the public only also had high ORs of 2.61 (2.18 - 3.96) and 2.24 (1.88 - 2.11), respectively. OR for the period of 2009 - 2012 to 2005 - 2008 was 1.53 (1.30 - 1.81). OR decreased with patient age and was 0.45 (0.31 - 0.64) in the age group of > 85 years. OR for nighttime to daytime was 0.66 (0.57 - 0.78). OR for call-to-contact intervals of >10 minutes to <=10 minutes was 0.72 (0.58 - 0.87) compared with an interval of <10 minutes; however, there were no significant differences between call-to-hospital intervals of > 60 minutes to ≤ 60 minutes (0.87 (0.61 - 1.29)).

## Discussion

This study demonstrated that the prognosis of cerebral function among cerebrovascular disease patients with OHCA is poorer than that among all patients with OHCA witnessed by bystanders.

Multiple logistic regression model showed that VT/ VF in the initial ECG and usage of AEDs by the public were beneficial factors for good cerebral function, implying that bystanders witnessed OHCAs and started AED application faster than EMS teams to arrive at the location. EMS should provide a quick response and rapid action. OR for the interval from request call to contact with patients was 0.72 (0.58 - 0.87) and was significantly low in this study, whereas that from request call to a hospital was not significant. Rapid initiation of CPR by a bystander and faster contact with a patient by EMS might improve the outcomes of cerebral function after OHCA in cerebrovascular disease patients. These clinical data are consistent with those of previous animal and clinical investigations [9,10].

The American Heart Association recommends compression-only CPR by bystanders for adult patients with OHCAs [2]. Additionally, the Utstein Osaka project has reported similar outcomes of OHCA in adult patients between conventional and compression-only CPR [11]. Similarly, in this study, OR for chest compression-only CPR had no statistical significance (0.89 (0.69 - 1.09), which was similar to that for conventional CPR in OHCA among cerebrovascular disease patients.

Several reports have stated that the onset time of day affected the outcomes in conditions such as stroke [12], ischemic heart disease [13], and pulmonary embolism [14]; furthermore, the outcomes were poorer in patients affected at nighttime than at daytime [10,15,16]. Similarly in this study, OR of nighttime to daytime was significantly low (0.78 (0.76 - 0.81)).

### Limitations

First, this was just an observational cohort study and samples were not assigned randomizedly. Second, the Utstein template database does not contain the data of diagnoses and disease severity. We could not notice whether patients had subarachnoid hemorrhage, cerebral infarction, or cerebral hemorrhage. And we could not determine the position, size, and cause of the lesions either. Third, we could not assess the social determinants of health such as education, income, treasures, and medical accessibility. Fourth, we did not survey cerebral hypothermia because the data of this parameter were not available in the Utstein database. In a randomized clinical trial, Bernard has reported that treatment with moderate hypothermia improves outcomes in comatose patients after resuscitation from OHCA. Moreover, cerebral hypothermia is widely used for cerebral protection [17-19].

## Conclusion

This study indicated a poor prognosis in cerebrovascular disease patients after OHCA in Japan. VT/VF findings in the initial ECG and usage of AED were beneficial factors, whereas older age, request calls during nighttime, and a call-to-patient contact interval of >10 minutes were factors for poor cerebral function in OHCAs.

## Conflicts of Interest

There were no conflicts of interests through the development of this study.

## Authors' Contributions

I. Kuboyama contributed to the study concept and design. R. Sagisaka contributed to the acquisition of data. And I. Kuboyama contributed to the statistical analysis and interpretation of the data. I. Kuboyama and S. Ito contributed to the drafting of the manuscript. All authors read and approved the final manuscript.

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**Volume 10 Issue 7 July 2018**