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AUTHOR(S):

Yoshimura, Satoshi; Hirayama, Atsushi; Kiguchi, Takeyuki; Irisawa, Taro; Yamada, Tomoki; Yoshiya, Kazuhisa; Park, Changhwi; ... Shimazu, Takeshi; Kitamura, Tetsuhisa; Iwami, Taku

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# Trends in In-Hospital Advanced Management and Survival of Out-of-Hospital Cardiac Arrest Among Adults From 2013 to 2017

## — A Multicenter, Prospective Registry in Osaka, Japan —

Satoshi Yoshimura, MD; Atsushi Hirayama, MD; Takeyuki Kiguchi, MD, PhD; Taro Irisawa, MD, PhD; Tomoki Yamada, MD, PhD; Kazuhisa Yoshiya, MD, PhD; Changhwi Park, MD; Tetsuro Nishimura, MD, PhD; Takuya Ishibe, MD, PhD; Yoshiki Yagi, MD, PhD; Masafumi Kishimoto, MD, PhD; Toshiya Inoue, MD; Yasuyuki Hayashi, MD, PhD; Taku Sogabe, MD, PhD; Takaya Morooka, MD, PhD; Haruko Sakamoto, MD; Keitaro Suzuki, MD; Fumiko Nakamura, MD; Tasuku Matsuyama, MD, PhD; Yohei Okada, MD; Norihiro Nishioka, MD; Daisuke Kobayashi, MD, PhD; Satoshi Matsui, MD; Shunsuke Kimata, MD; Takeshi Shimazu, MD, PhD; Tetsuhisa Kitamura, MD; Taku Iwami, MD, PhD on behalf of the CRITICAL Study Group Investigators

***Background:*** The aim of our study was to investigate in detail the temporal trends in in-hospital characteristics, actual management, and survival, including neurological status, among adult out-of-hospital cardiac arrest (OHCA) patients in recent years.

***Methods and Results:*** From the prospective database of the Comprehensive Registry of Intensive Care for OHCA Survival (CRITICAL) study in Osaka, Japan, we enrolled all OHCA patients aged ≥18 years for whom resuscitation was attempted, and who were transported to participating hospitals between the years 2013 and 2017. The primary outcome measure was 1-month survival with favorable neurological outcome after OHCA. Temporal trends in in-hospital management and favorable neurological outcome among adult OHCA patients were assessed. Of the 11,924 patients in the database, we included a total of 10,228 adult patients from 16 hospitals. As for in-hospital advanced treatments, extracorporeal cardiopulmonary resuscitation (ECPR) use increased from 2.4% in 2013 to 4.3% in 2017 (P for trend <0.001). However, the proportion of adult OHCA patients with favorable neurological outcome did not change during the study period (from 5.7% in 2013 to 4.4% in 2017, adjusted odds ratio (OR) for 1-year increment: 0.98 (95% confidence interval: 0.94–1.23)).

***Conclusions:*** In this target population, in-hospital management such as ECPR increased slightly between 2013 and 2017, but 1-month survival with favorable neurological outcome after adult OHCA did not improve significantly.

**Key Words:** Cardiopulmonary resuscitation; Out-of-hospital cardiac arrest; Patient management; Survival trend

Out-of-hospital cardiac arrest (OHCA) is a leading public health problem in the industrialized world, with approximately 120,000 events occurring in Japan and 360,000 occurring in the USA annually.[1,2] Because of improvements in emergency medical services (EMS) systems, dissemination of public-access automated external defibrillators (AEDs), and bystander cardiopulmonary resuscitation (CPR), survival after OHCA has been improving in many countries, including Japan.[3–5] However, it is still low, even among OHCA patients witnessed by another,[5,6] which is an issue that remains to be solved.[7–10]

The All-Japan Utstein Registry, a nationwide population-based cohort, was launched in Japan in 2005. As per this registry, 1-month survival with favorable neurological outcome improved rapidly until 2009,[5] but its increment has been gradual since 2010.[11] The proportions of survival

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Department of Preventive Services, Kyoto University School of Public Health, Kyoto (S.Y., T. Kiguchi, Y.O., N.N., S.K., T. Iwami); Public Health, Department of Social and Environmental Medicine (A.H.), Department of Traumatology and Acute Critical Medicine (T. Irisawa, T. Shimazu), Division of Environmental Medicine and Population Sciences, Department of Social and Environmental Medicine (S.M., T. Kitamura), Osaka University Graduate School of Medicine, Suita; Critical Care and Trauma Center, Osaka General Medical Center, Osaka (T. Kiguchi); Emergency and Critical Care Medical Center, Osaka Police Hospital,
(Footnote continued the next page.)

to hospital discharge in Canada and survival with favorable neurological outcome in Australia have increased annually since 2000.[12] On the other hand, no temporal changes in survival after OHCA were observed in the USA between 2011 and 2015.[13] Thus, survival trends remain controversial in recent years. Importantly, the trends in favorable neurological outcome among OHCA patients have not been sufficiently evaluated since 2010. In addition, the trends in in-hospital patient care, including advanced care, need further investigation.

To improve survival after OHCA by providing evidence-based therapeutic strategies and medical systems, we launched the Comprehensive Registry of Intensive Care for OHCA Survival (CRITICAL) study, which is a multicenter, prospective observational data registry in Osaka, Japan, designed to accumulate both pre- and in-hospital data on OHCA treatment.[14] Using this database, we evaluated the temporal trends in in-hospital management and favorable neurological outcome among adult OHCA patients between 2013 and 2017.

## Methods

We analyzed the database of the CRITICAL study; a complete description of the study methodology has been described.[14]

### Population and Settings

The target area of the CRITICAL study is the Osaka Prefecture in Japan, which has an area of 1,897 $km^2$ and a residential population of 8,839,469 inhabitants as of 2015; 48.1% of the population are men, 25.8% of whom are ≥65 years old.[15] Osaka had 535 hospitals (108,569 beds) in 2013.[16] A total of 280 hospitals accept emergency patients from ambulances. Of these, 16 hospitals have critical care medical centers (CCMCs) that can accept emergency severely ill patients.[16] In this study, 15 CCMCs and 1 non-CCMC with an emergency care department in Osaka participated. As many as 30% of OHCA patients in Osaka were transported to, and treated at CCMCs.[16] This CRITICAL study, including a retrospective analysis, was approved by the Ethics Committee of Kyoto University (R-1045). The requirement for informed consent for review of outcomes was waived.

### Study Patients

We enrolled all consecutive patients aged ≥18years who experienced an OHCA, for whom resuscitation was attempted, and who were then transported to a participating institution between January 1, 2013 and December 31, 2017. This study excluded OHCA patients who did not receive CPR by physicians after hospital arrival and those with a disagreement about the registry (refusal by patient or patient's family). Additionally, OHCA patients who were transported to participating institutions after receiving any procedures at other hospitals were excluded.

### EMS in Osaka

Details of the EMS system in Osaka have been provided previously.[14] Briefly, the 119 emergency telephone number is accessible anywhere in Japan, including in Osaka, and on receipt of a 119 call, an emergency dispatch center sends the nearest available ambulance to the site. Emergency services are provided 24 h, daily. Each ambulance includes a 3-person unit providing life support. Specially trained emergency life-saving technicians are allowed to carry out tracheal intubation and to administer epinephrine for OHCA patients in Japan. All EMS providers performed CPR as per the Japanese CPR guidelines.[4]

Prehospital resuscitation data were obtained from the All-Japan Utstein Registry of the Fire and Disaster Management Agency (FDMA) of Japan. Details of the registry have been described in detail.[17] Data were collected prospectively using a data form based on the Utstein-style international guideline for reporting OHCA.[18,19] Data on the following were collected: witness status, bystander-initiated CPR, shocks by public-access AED, first documented rhythm, defibrillation by EMS personnel, advanced airway management, adrenaline administration, and resuscitation time course.

### Data Collection and Quality Control

In this registry, we collected detailed information on OHCA patients after hospital arrival. Anonymized data were fed into the Web form by physicians or medical staff in cooperation with the physicians in charge of the patient. Data were logically checked by the system, and were finally confirmed by the CRITICAL study working group. If the data form was incomplete, the working group returned it to the respective institution and the data were revised. In-hospital data were systemically merged with Utstein-style prehospital data gathered from the FDMA by the working group, using 5 data items: prefecture, emergency call time, age, sex, and the cerebral performance category (CPC) score.[18,19]

In-hospital data on OHCA patients after hospital arrival were prospectively collected using an original report form. The cause of arrest was defined as cardiac (acute coronary syndrome, other heart disease, presumed cardiac cause) or non-cardiac (cerebrovascular diseases, respiratory diseases,

Osaka (T.Y.); Department of Emergency and Critical Care Medicine, Kansai Medical University, Takii Hospital, Moriguchi (K.Y.); Department of Emergency Medicine, Tane General Hospital, Osaka (C.P.); Department of Critical Care Medicine, Osaka City University, Osaka (T.N.); Department of Emergency and Critical Care Medicine, Kindai University School of Medicine, Osaka-Sayama (T. Ishibe); Osaka Mishima Emergency Critical Care Center, Takatsuki (Y.Y.); Osaka Prefectural Nakakawachi Medical Center of Acute Medicine, Higashi-Osaka (M.K.); Senshu Trauma and Critical Care Center, Osaka (T. Inoue); Senri Critical Care Medical Center, Saiseikai Senri Hospital, Suita (Y.H.); Traumatology and Critical Care Medical Center, National Hospital Organization Osaka National Hospital, Osaka (T. Sogabe); Emergency and Critical Care Medical Center, Osaka City General Hospital, Osaka (T. Morooka); Department of Pediatrics, Osaka Red Cross Hospital, Osaka (H.S.); Emergency and Critical Care Medical Center, Kishiwada Tokushukai Hospital, Osaka (K.S.); Department of Emergency and Critical Care Medicine, Kansai Medical University, Hirakata (F.N.); Department of Emergency Medicine, Kyoto Prefectural University of Medicine, Kyoto (T. Matsuyama); and Kyoto University Health Services, Kyoto (D.K.), Japan

Mailing address: Professor Taku Iwami, MD, MPH, PhD, Department of Preventive Services, School of Public Health, Kyoto University, Yoshida-Honmachi, Sakyo-ku, Kyoto 606-8501, Japan. E-mail: iwami.taku.8w@kyoto-u.ac.jp


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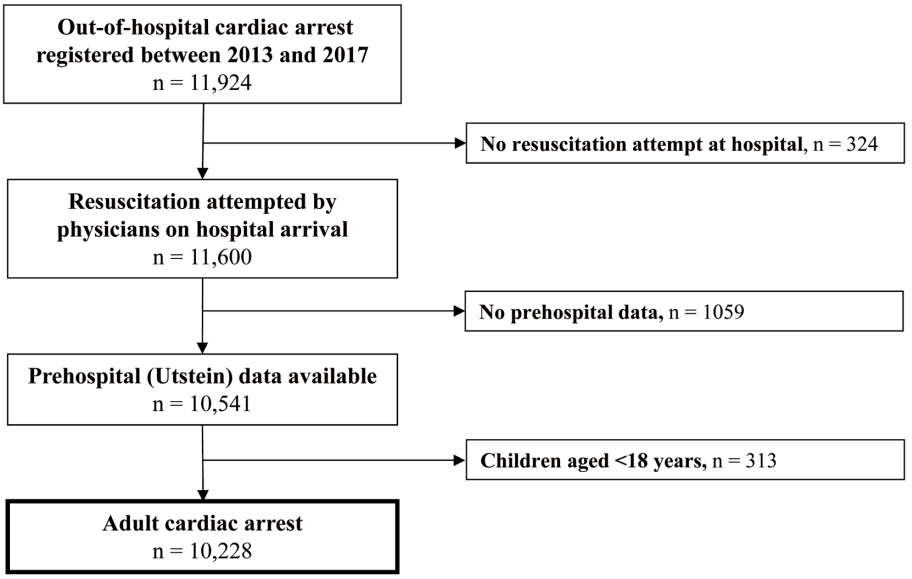


**Figure.** Patient enrollment flowchart.

malignant tumors, external causes including traffic injury, fall, hanging, drowning, asphyxia, drug overdose, or any other external cause).[14] The category of presumed cardiac cause was a diagnosis by exclusion (the diagnosis was made when there was no evidence of a non-cardiac cause). Diagnosis of cardiac or non-cardiac origin was made clinically by the physician in charge. Other baseline information was as follows: return of spontaneous resuscitation (ROSC) after hospital arrival, and first documented rhythm after hospital arrival.

The reporting form also required actual treatment details for OHCA patients (defibrillation, tracheal intubation, extracorporeal life support (ECLS), intra-aortic balloon pumping, coronary angiography, percutaneous coronary intervention, target temperature management (TTM), and drug administration during cardiopulmonary arrest [adrenaline, amiodarone, nifekalant, lidocaine, atropine, magnesium, and vasopressin]).

Outcome data were also prospectively collected and included as follows:[14] 1-month survival and neurological status at 1 month after OHCA using the CPC scale (category 1, normal cerebral performance; category 2, moderate cerebral disability; category 3, severe cerebral disability; category 4, coma or vegetative state; category 5, death/brain death). Survivors underwent a neurologic assessment at 1 month after the event by the physician in charge.

### Outcome Measures

The primary outcome measure was 1-month survival with favorable neurological outcome after OHCA. A favorable neurological outcome was defined as a CPC score of 1 or 2.[19] The secondary outcome measure was 1-month survival and admission to an intensive care unit/ward.

### Statistical Analysis

Data are presented as mean±standard deviation for continuous variables and as percentages for categorical variables. In this study, we assessed the annual trends in the baseline characteristics or in-hospital procedures by using linear trend tests. In the assessment of the annual trend in outcomes, a multivariable logistic regression model was used to adjust potential resuscitation factors associated with 1-month survival with favorable neurological outcome, and the odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. The independent variables considered in this analysis included: age (continuous value), sex (male, female), cause of arrest (cardiac, non-cardiac), witness status (no, yes), bystander CPR (no, yes), first documented rhythm at EMS arrival (ventricular fibrillation [VF], pulseless ventricular tachycardia [pVT], pulseless electrical activity [PEA]/asystole, other), advanced airway management by EMS personnel (no, yes), adrenaline administration by EMS personnel (no, yes), EMS response time (continuous variable), ECLS (no, yes), intra-aortic balloon pump (no, yes), coronary angiography (no, yes), and TTM (no, yes). Moreover, we performed subgroup analyses by first documented rhythm at EMS arrival (VF/pVT, PEA/asystole), cause of arrest (cardiac, non-cardiac), and age group (18–64 years, ≥65 years), using multivariable logistic regression analysis. All P values were two-sided, and those <0.05 were considered to be statistically significant. All statistical analyses were carried out using STATA version 16.0 SE software (Stata Corp.).

## Results

The **Figure** is a flowchart of the enrollment of the study patients. A total of 11,928 OHCA patients were documented between January 2013 and December 2017. After excluding 324 patients who were not resuscitated by physicians after hospital arrival, 1,059 patients without prehospital data, and 313 pediatric patients, a total of 10,228 adult patients were eligible for analysis.

**Table 1** shows the baseline characteristics of the 10,228

**Table 1. Baseline Characteristics by Year of Study**

| | Total (n=10,228) | 2013 (n=1,823) | 2014 (n=2,005) | 2015 (n=1,941) | 2016 (n=2,070) | 2017 (n=2,389) | P for trend |
|---|---|---|---|---|---|---|---|
| **Participating institutions, n** | 16 | 13 | 14 | 14 | 14 | 16 | |
| **Age, years, mean (SD)** | 68.2 (17.4) | 67.5 (17.5) | 68.1 (17.2) | 67.0 (18.1) | 68.2 (17.2) | 69.7 (17.1) | <0.001 |
| **Age group, n (%)** | | | | | | | |
| 18–35 years | 609 (6.0) | 125 (6.9) | 108 (5.4) | 131 (6.8) | 126 (6.1) | 119 (5.0) | 0.080 |
| 36–64 years | 2,856 (27.9) | 539 (29.6) | 583 (29.1) | 582 (30.0) | 540 (26.1) | 612 (25.6) | 0.001 |
| 65–79 years | 3,697 (36.2) | 633 (34.7) | 730 (36.4) | 675 (34.8) | 809 (39.1) | 850 (35.6) | 0.028 |
| 80–89 years | 2,451 (24.0) | 431 (23.6) | 469 (23.4) | 434 (22.4) | 480 (23.2) | 637 (26.7) | 0.039 |
| ≥90 years | 615 (6.0) | 95 (5.2) | 115 (5.7) | 119 (6.1) | 115 (5.6) | 171 (7.2) | 0.028 |
| **Men, n (%)** | 6,470 (63.3) | 1,160 (63.6) | 1,248 (62.2) | 1,229 (63.3) | 1,343 (64.9) | 1,490 (62.4) | 0.995 |
| **Origin, n (%)** | | | | | | | |
| Cardiac | 5,747 (56.2) | 984 (54.0) | 1,110 (55.4) | 1,035 (53.3) | 1,197 (57.8) | 1,421 (59.5) | <0.001 |
| **Departure of ambulance or helicopter with physicians, n (%)** | 1,293 (12.6) | 250 (14) | 228 (11) | 258 (13) | 243 (11.7) | 314 (13.1) | 0.894 |
| **ROSC status, n (%)** | | | | | | | |
| ROSC after hospital arrival | 2,893 (28.3) | 524 (28.7) | 568 (28.3) | 552 (28.4) | 564 (27.2) | 685 (28.7) | 0.779 |
| ROSC before hospital arrival | 939 (9.2) | 156 (8.6) | 161 (8.0) | 219 (11.3) | 195 (9.4) | 208 (8.7) | 0.529 |
| No ROSC | 6,396 (62.5) | 1,143 (62.7) | 1,276 (63.6) | 1,170 (60.3) | 1,311 (63.3) | 1,496 (62.6) | 0.927 |
| **First documented rhythm at hospital arrival, n (%)** | | | | | | | |
| VF/pulseless VT | 509 (5.0) | 92 (5.0) | 88 (4.0) | 92 (4.7) | 115 (5.6) | 122 (5.1) | 0.403 |
| PEA | 2,197 (21.3) | 357 (19.6) | 421 (21.0) | 403 (20.8) | 458 (22.1) | 540 (22.6) | 0.020 |
| Asystole | 6,623 (64.8) | 1,221 (67.0) | 1,341 (66.9) | 1,229 (63.3) | 1,310 (63.3) | 1,522 (63.7) | 0.007 |
| Presence of pulse | 917 (9.0) | 153 (8.4) | 155 (7.7) | 217 (11.2) | 187 (9.0) | 205 (8.6) | 0.501 |

PEA, pulseless electrical activity; ROSC, return of spontaneous circulation; SD, standard deviation; VF, ventricular fibrillation; VT, ventricular tachycardia.

**Table 2. Prehospital Characteristics by Year of Study**

| | Total (n=10,228) | 2013 (n=1,823) | 2014 (n=2,005) | 2015 (n=1,941) | 2016 (n=2,070) | 2017 (n=2,389) | P for trend |
|---|---|---|---|---|---|---|---|
| **Witness status, n (%)** | | | | | | | |
| Witnessed by bystanders | 4,737 (46.2) | 889 (48.8) | 832 (41.4) | 852 (43.9) | 994 (48.0) | 1,170 (49.0) | <0.001 |
| Witnessed by citizens (not EMS personnel) | 3,821 (37.4) | 787 (43.2) | 639 (31.9) | 670 (34.5) | 787 (38.0) | 938 (39.2) | 0.954 |
| Witnessed by EMS personnel | 916 (9.0) | 102 (5.6) | 193 (9.6) | 182 (9.4) | 207 (10.0) | 232 (9.7) | <0.001 |
| Not witnessed | 5,491 (53.7) | 934 (51.2) | 1,173 (58.5) | 1,089 (56.1) | 1,076 (52.0) | 1,219 (51.0) | 0.030 |
| **Bystander-initiated CPR, n (%)** | 3,905 (38.2) | 353 (19.4) | 801 (40.0) | 821 (42.3) | 848 (41.0) | 1,082 (45.3) | <0.001 |
| **Shock by public-access AEDs, n (%)** | 150 (1.5) | 10 (0.5) | 23 (1.1) | 31 (1.6) | 37 (1.8) | 49 (2.1) | <0.001 |
| **First documented rhythm at EMS arrival, n (%)** | | | | | | | |
| VF/pulseless VT | 1,153 (11.3) | 212 (11.6) | 214 (10.7) | 230 (11.8) | 241 (11.6) | 256 (10.7) | 0.689 |
| PEA | 3,408 (33.3) | 782 (42.9) | 666 (33.2) | 632 (32.6) | 641 (31.0) | 687 (28.8) | <0.001 |
| Asystole | 5,307 (51.9) | 772 (42.3) | 1,054 (52.6) | 1,006 (51.8) | 1,127 (54.4) | 1,348 (56.4) | <0.001 |
| Other | 360 (3.5) | 57 (3.1) | 71 (3.5) | 73 (3.8) | 61 (2.9) | 98 (4.1) | 0.297 |
| **Defibrillation by EMS, n (%)** | 1,627 (15.9) | 298 (16.3) | 323 (16.1) | 307 (15.8) | 330 (15.9) | 369 (15.4) | 0.477 |
| **Advanced airway management, n (%)** | 5,634 (55.1) | 1,002 (55.0) | 1,079 (53.8) | 1,071 (55.2) | 1,144 (55.3) | 1,338 (56.0) | 0.304 |
| **Adrenaline administration, n (%)** | 1,854 (18.1) | 315 (17.3) | 331 (16.5) | 329 (17.0) | 371 (17.9) | 508 (21.3) | <0.001 |
| **EMS response time (call to contact with the patient by EMS), min, mean (SD)** | 8.5 (3.8) | 8.3 (3.6) | 8.3 (3.6) | 8.5 (4.0) | 8.4 (3.8) | 8.5 (3.8) | <0.001 |
| **Call to ROSC, min, mean (SD)*** | 19.9 (8.9) | 20.5 (9.3) | 20.1 (8.8) | 18.7 (8.8) | 20 (8.9) | 20.2 (8.5) | 0.789 |

*Calculated only for patients with ROSC. AED, automated external defibrillator; CPR, cardiopulmonary resuscitation; EMS, emergency medical service. Other abbreviations as in Table 1.

**Table 3. In-Hospital Advanced Treatments and Drug Administrations by Year of Study**

| | Total (n=10,228) | 2013 (n=1,823) | 2014 (n=2,005) | 2015 (n=1,941) | 2016 (n=2,070) | 2017 (n=2,389) | P for trend |
|---|---|---|---|---|---|---|---|
| **Defibrillation, n (%)** | 1,069 (10.5) | 203 (11.1) | 194 (9.7) | 200 (10,3) | 231 (11.2) | 241 (10.1) | 0.806 |
| **Tracheal intubation after hospital arrival, n (%)** | 6,245 (61.1) | 1,196 (65.6) | 1,225 (61.1) | 1,185 (61.1) | 1,256 (60.7) | 1,383 (57.9) | <0.001 |
| **Extracorporeal life support, n (%)** | 520 (5.1) | 83 (4.6) | 74 (3.7) | 87 (4.5) | 137 (6.6) | 139 (5.8) | <0.001 |
| Implementation before ROSC, n (%) | 354 (3.5) | 44 (2.4) | 51 (2.5) | 56 (2.9) | 100 (4.8) | 103 (4.3) | <0.001 |
| **Intra-aortic balloon pumping, n (%)** | 418 (4.1) | 83 (4.6) | 71 (3.5) | 75 (3.9) | 87 (4.2) | 102 (4.3) | 0.848 |
| **Coronary angiography, n (%)** | 893 (8.7) | 159 (8.7) | 150 (7.5) | 173 (8.9) | 193 (9.3) | 218 (9.1) | 0.194 |
| **Percutaneous coronary intervention, n (%)** | 417 (4.1) | 79 (4.3) | 67 (3.3) | 77 (4.0) | 87 (4.2) | 107 (4.5) | 0.358 |
| Success of reperfusion, n (%) | 363 (3.5) | 65 (3.6) | 59 (2.9) | 71 (3.7) | 79 (3.8) | 89 (3.7) | 0.142 |
| **Target temperature management, n (%)** | 794 (7.8) | 166 (9.1) | 147 (7.3) | 154 (7.9) | 151 (7.3) | 174 (7.3) | 0.081 |
| 34°C management, n (%) | 536 (5.2) | 126 (6.9) | 100 (5.0) | 105 (5.4) | 97 (4.7) | 108 (4.5) | 0.003 |
| **Drug administration during cardiac arrest (multiple choice)** | | | | | | | |
| Adrenaline, n (%) | 8,338 (81.5) | 1,471 (80.7) | 1,633 (81.5) | 1,562 (80.5) | 1,737 (83.9) | 1,935 (81.0) | 0.344 |
| Amiodarone, n (%) | 409 (4.0) | 72 (3.9) | 73 (3.6) | 67 (3.5) | 86 (4.2) | 111 (4.7) | 0.146 |
| Nifekalant, n (%) | 66 (0.6) | 25 (1.4) | 18 (0.9) | 12 (0.6) | 6 (0.3) | 5 (0.2) | <0.001 |
| Lidocaine, n (%) | 115 (1.1) | 28 (1.5) | 29 (1.4) | 21 (1.1) | 20 (1.0) | 17 (0.7) | 0.008 |
| Atropine, n (%) | 112 (1.1) | 37 (2.0) | 21 (1.0) | 14 (0.7) | 15 (0.7) | 25 (1.0) | 0.009 |
| Magnesium, n (%) | 93 (0.9) | 16 (0.8) | 23 (1.1) | 14 (0.7) | 24 (1.2) | 16 (0.7) | 0.566 |
| Vasopressin, n (%) | 1 (0.0) | 1 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0.750 |

Abbreviations as in Tables 1,2.

**Table 4. Temporal Trends in Outcomes by Year of Study**

| | Total (n=10,228) | 2013 (n=1,823) | 2014 (n=2,005) | 2015 (n=1,941) | 2016 (n=2,070) | 2017 (n=2,389) | P for trend |
|---|---|---|---|---|---|---|---|
| **Admitted to ICU/ward, n (%)** | 3,290 (32) | 519 (28.5) | 582 (29.0) | 618 (32.0) | 654 (32.0) | 917 (38.0) | <0.001 |
| **1-month survival, n (%)** | 961 (9.4) | 182 (10.0) | 175 (8.7) | 201 (10.0) | 187 (9.0) | 216 (9.0) | 0.496 |
| **CPC 1 month after OHCA, n (%)** | | | | | | | |
| CPC 1 or 2 | 527 (5.2) | 103 (5.7) | 81 (4.0) | 120 (6.2) | 119 (5.8) | 104 (4.4) | 0.536 |
| Crude OR (95% CI) | | Ref. | 0.70 (0.52–0.95) | 1.10 (0.83–1.44) | 1.01 (0.78–1.33) | 0.76 (0.57–1.01) | |
| Crude OR for 1-year increment (95% CI) | 0.98 (0.92–1.04) | | | | | | |
| Adjusted OR* (95% CI) | | Ref. | 0.51 (0.24–1.07) | 0.84 (0.43–1.65) | 1.11 (0.61–2.02) | 0.92 (0.50–1.69) | |
| Adjusted OR* for 1-year increment (95% CI) | 1.07 (0.94–1.23) | | | | | | |

ORs adjusted for age, sex, cause of arrest, witness status, bystander cardiopulmonary resuscitation, first documented rhythm at emergency medical service (EMS) arrival, advanced airway management by EMS personnel, adrenaline administration by EMS personnel, EMS response time, extracorporeal life support, intra-aortic balloon pump, coronary angiography, and targeted temperature management. CI, confidence interval; CPC, cerebral performance category; ICU, intensive care unit; OHCA, out-of-hospital cardiac arrest; OR, odds ratio.

patients with OHCA. The mean age was 68.2 years; the mean age for each year increased annually during the study period. The proportion of adults aged 65–79 years, 80–89 years, and ≥90 years was 36.2%, 24.0%, and 6.0%, respectively. Men accounted for 63.3% of the population. The prevalence of OHCA of cardiac origin was 56.2%. The proportion of adult patients with ROSC after hospital arrival was 28.3%, and that of those who had already experienced ROSC before hospital arrival was 9.2%. Of these, 5.0% had VF/pVT as the first documented rhythm after hospital arrival.

Prehospital characteristics based on the Utstein template are given in **Table 2**. Approximately 40% of patients received bystander-initiated CPR, but only 1.5% of these received shocks by public-access AEDs. Of the above, 11.3% had VF/pVT as the first documented rhythm at EMS arrival. As for prehospital treatments by EMS personnel, 15.9% received defibrillation by EMS, 55.1% advanced airway management, and 18.1% had adrenaline administered. The mean time interval from call to CPR started by EMS at the scene was 9.9 min, and that from call to contact with the patient by EMS personnel (EMS response time) was 8.5 min.

In-hospital advanced treatments and drug administrations for the patients with OHCA are noted in **Table 3**. After hospital arrival, 10.5% of the patients underwent defibrillation, 5.1% ECLS, 7.8% TTM, and 81.5% had

**Table 5. Outcomes According to the First Documented Rhythm at EMS Arrival, Cause of Arrest, and Age Group by Year of Study**

| | Total | 2013 | 2014 | 2015 | 2016 | 2017 | OR for 1-year increment (95% CI) |
|---|---|---|---|---|---|---|---|
| **First documented rhythm at EMS arrival** | | | | | | | |
| VF/pulseless VT | | | | | | | |
| CPC 1 or 2, % (n/N) | 27.8 (321/1,153) | 31.6 (67/212) | 21.0 (45/214) | 34.8 (80/230) | 27.0 (65/241) | 25.0 (64/256) | |
| Crude OR (95% CI) | | Ref. | 0.57 (0.37–0.89) | 1.15 (0.78–1.72) | 0.80 (0.53–1.20) | 0.72 (0.48–1.08) | 0.96 (0.87–1.05) |
| Adjusted OR* (95% CI) | | Ref. | 0.41 (0.14–1.19) | 0.92 (0.37–2.31) | 1.04 (0.45–2.38) | 1.57 (0.69–3.57) | 1.20 (0.99–1.46) |
| PEA/asystole | | | | | | | |
| CPC 1 or 2, % (n/N) | 1.5 (130/8,715) | 1.5 (23/1,554) | 1.4 (24/1,720) | 1.3 (21/1,638) | 2.0 (35/1,768) | 1.3 (27/2,035) | |
| Crude OR (95% CI) | | Ref. | 0.94 (0.53–1.68) | 0.86 (0.48–1.57) | 1.34 (0.79–2.29) | 0.90 (0.51–1.57) | 1.02 (0.90–1.15) |
| Adjusted OR* (95% CI) | | Ref. | 1.18 (0.33–4.22) | 0.92 (0.24–3.60) | 1.90 (0.62–5.82) | 0.73 (0.22–2.46) | 0.97 (0.77–1.23) |
| **Cause of arrest** | | | | | | | |
| Cardiac | | | | | | | |
| CPC 1 or 2, % (n/N) | 7.0 (468/6,678) | 7.8 (91/1,164) | 5.7 (71/1,246) | 8.4 (105/1,252) | 7.7 (104/1,343) | 5.8 (97/1,673) | |
| Crude OR (95% CI) | | Ref. | 0.71 (0.52–0.98) | 1.08 (0.81–1.45) | 1.00 (0.74–1.33) | 0.73 (0.54–0.98) | 0.96 (0.90–1.03) |
| Adjusted OR† (95% CI) | | Ref. | 0.53 (0.24–1.23) | 0.85 (0.40–1.83) | 1.07 (0.55–2.10) | 0.96 (0.49–1.88) | 1.07 (0.92–1.24) |
| Non-cardiac | | | | | | | |
| CPC 1 or 2, % (n/N) | 1.7 (59/3,550) | 1.8 (12/659) | 1.3 (10/759) | 2.2 (15/689) | 2.1 (15/727) | 1.0 (7/716) | |
| Crude OR (95% CI) | | Ref. | 0.72 (0.31–1.68) | 1.2 (0.56–2.58) | 1.1 (0.53–2.44) | 0.53 (0.21–1.26) | 0.95 (0.79–1.14) |
| Adjusted OR† (95% CI) | | Ref. | 0.47 (0.07–3.07) | 0.91 (0.18–4.47) | 1.58 (0.36–7.01) | 0.81 (0.16–4.03) | 1.08 (0.76–1.54) |
| **Age group** | | | | | | | |
| 18–64 years | | | | | | | |
| CPC 1 or 2, % (n/N) | 8.1 (280/3,465) | 7.5 (50/664) | 6.2 (43/691) | 10.2 (73/713) | 9.3 (62/666) | 7.1 (52/731) | |
| Crude OR (95% CI) | | Ref. | 0.81 (0.53–1.24) | 1.40 (0.96–2.04) | 1.26 (0.85–1.86) | 0.94 (0.63–1.40) | 1.03 (0.94–1.12) |
| Adjusted OR‡ (95% CI) | | Ref. | 0.83 (0.29–2.35) | 1.15 (0.43–3.11) | 1.43 (0.58–3.57) | 0.87 (0.34–2.20) | 1.02 (0.83–1.24) |
| ≥65 years | | | | | | | |
| CPC 1 or 2, % (n/N) | 3.7 (247/6,763) | 4.6 (53/1,159) | 2.9 (38/1,314) | 3.8 (47/1,228) | 4.1 (57/1,404) | 3.1 (52/1,658) | |
| Crude OR (95% CI) | | Ref. | 0.62 (0.40–0.95) | 0.83 (0.56–1.24) | 0.88 (0.60–1.29) | 0.68 (0.46–1.00) | 0.95 (0.87–1.04) |
| Adjusted OR‡ (95% CI) | | Ref. | 0.25 (0.08–0.82) | 0.63 (0.25–1.62) | 0.93 (0.41–2.10) | 0.92 (0.41–2.07) | 1.11 (0.92–1.34) |

*ORs adjusted for age, sex, cause of arrest, witness status, bystander cardiopulmonary resuscitation, advanced airway management by EMS personnel, adrenaline administration by EMS personnel, EMS response time, extracorporeal life support, intra-aortic balloon pump, coronary angiography, and targeted temperature management. †ORs adjusted for age, sex, witness status, bystander cardiopulmonary resuscitation, first documented rhythm at EMS arrival, advanced airway management by EMS personnel, adrenaline administration by EMS personnel, EMS response time, extracorporeal life support, intra-aortic balloon pump, coronary angiography, and targeted temperature management. ‡ORs adjusted for sex, cause of arrest, witness status, bystander cardiopulmonary resuscitation, first documented rhythm at EMS arrival, advanced airway management by EMS personnel, adrenaline administration by EMS personnel, EMS response time, extracorporeal life support, intra-aortic balloon pump, coronary angiography, and targeted temperature management. Abbreviations as in Tables 1,4.

adrenaline administered. During the study period, the proportion of patients receiving ECLS before ROSC (e.g., extracorporeal CPR) increased from 2.4% in 2013 to 4.3% in 2017. Although the proportion of those receiving TTM did not change in total, the proportion of those receiving 34°C TTM decreased from 6.9% in 2013 to 4.5% in 2017. As for drug administration, the proportion of those receiving nifekalant, lidocaine, and atropine decreased during the study period.

**Table 4** shows the annual trends in outcomes after adult

OHCA occurrence. The proportions of 1-month survival and favorable neurological outcome at 1 month after OHCA occurrence were 9.4% and 5.2%, respectively. The proportion of OHCA patients with favorable neurological outcome did not change during the study period (from 5.7% in 2013 to 4.4% in 2017), and the adjusted OR for a 1-year increment was 0.98 (95% CI: 0.94–1.23). As for secondary outcomes, the trends showed a similar result as above.

**Table 5** shows the annual trends in favorable neurological outcome at 1 month post-OHCA according to the first documented rhythm at EMS arrival, origin of arrest, and age group, among adult patients with OHCA. Among adult patients with VF/pVT, favorable neurological outcome did not change in either the univariable analysis (crude OR for 1-year increment: 0.96, 95% CI: 0.87–1.05) or multivariable analysis after adjusting for potential confounders (adjusted OR for 1-year increment: 1.20, 95% CI: 0.99–1.46). Furthermore, the OR did no change among those with PEA/asystole, those with OHCA of cardiac and non-cardiac origins, in adults aged 18–64 years, or in elderly individuals aged ≥65 years.

## Discussion

Using data from a multicenter, prospective observational data registry in Osaka, Japan, we demonstrated temporal trends in the characteristics, laboratory findings, in-hospital management, and outcomes among adult OHCA patients. The 1-month survival with favorable neurological outcome after OHCA in all patients did not improve significantly during the study period. This is the first to describe detailed in-hospital management procedures and outcomes among adult OHCA patients since 2010 in Japan. Our research provides useful information for further improving neurological outcomes after adult OHCA.

In the present study, the administration of TTM at 34°C for adult OHCA patients decreased gradually during the study period, although the total proportion of OHCA patients with TTM was unchanged. This observation may be explained by the results of a previous randomized controlled trial (RCT) conducted by Nielsen and colleagues in 2013, who reported that neurological outcome at 6 months were similar between OHCA patients with TTM at 33°C and those with TTM at 36°C.[20] After the publication of this report, international CPR guidelines altered the recommended temperature range for TTM from 32–34°C to 32–36°C;[21,22] the number of OHCA patients receiving TTM at 34°C has also decreased in Sweden[23] and Australia.[24] On the other hand, an RCT conducted in 2019 revealed that TTM at 34°C for OHCA patients with non-shockable rhythm increased favorable neurological outcomes compared with TTM at 36°C.[25] Therefore, further studies are needed to find the optimal TTM protocol for OHCA patients as well as to identify patients receiving benefit from TTM.

Our study also underscored the temporal increases in the use of ECLS before ROSC (ECPR) among adult OHCA patients during the study period, although the benefits for OHCA patients of receiving ECPR are controversial. In a systematic review of observational studies, Beyea and colleagues suggested that ECPR for witnessed adult OHCA cases improved patient outcomes.[26] In 2014, an observational study in Japan revealed a positive association between ECPR and favorable neurological outcome among OHCA patients with VF/pVT,[27] which may have led to the increased use of ECPR in Japan. On the other hand, RCTs evaluating the effect of ECPR on OHCA outcomes are lacking, which has been noted as a knowledge gap by the International Consensus Conference on CPR and Emergency Cardiovascular Care Science with Treatment Recommendations (CoSTR). There are several ongoing RCTs comparing outcomes after OHCA with shockable rhythm between ECPR-treated and conventional CPR-treated patients.[28,29] These results will influence the use of ECPR in the near future.

During the study period, vasopressin was used only for one OHCA patient, but adrenaline was used for about 80% patients among the all OHCA patients. Indeed, in the CPR guidelines published in 2015, the use of vasopressin is not recommended as a substitute for adrenaline for OHCA.[20,21,30] On the other hand, the use of lidocaine reduced significantly during the study period. However, in the CPR guidelines updated in 2018, the recommendation level for lidocaine administration was reinforced (Class llb; Level of Evidence B-R), and its use was also added to the advanced cardiac life support algorithm.[31] Thus, the use of lidocaine for OHCA patients may increase in the future.

Furthermore, the use of nifekalant decreased significantly during the 5-year study period. Nifekalant was developed in Japan and has been used for patients with refractory VF. However, in a previous study using the Japanese Diagnosis Procedure Combination Inpatient Database, compared with amiodarone, nifekalant did not significantly reduce in-hospital mortality among OHCA patients with VF on hospital arrival.[32] As of May 2020, there is no evidence for the positive effects of nifekalant on OHCA outcomes, and no related recommendations can be found in international CPR guidelines;[3,21,22,30,31] therefore, the use of this drug for OHCA may be reduced in the future.

In this study, outcomes after adult OHCA did not change (1-month survival: 10.0% in 2013 to 9.0% in 2017; favorable neurological outcome: 5.7% to 4.4%). There were several in-hospital factors that changed during the study period in the CRITICAL study; for example, the proportion of OHCA patients receiving 34°C TTM and drug administration such as nifekalant, lidocaine, and atropine decreased, while the proportion of those receiving ECPR increased. These advanced management procedures were modified according to the latest CPR guidelines and evidence as described above,[21,22] and further continuous monitoring of the trends in these factors is needed in our registry, because these might affect the neurological outcome after hospitalization among OHCA patients in the future. In addition, we also need to obtain detailed information on in-hospital treatments such as the dosages of drugs. On the other hand, even after adjustment for in-hospital factors, we did not observe improved outcomes, and we could not, unfortunately, explain why. However, our results suggest the importance of the detailed assessment of in-hospital procedures as well as the need for new strategies to improve outcomes after OHCA. For example, the citizen responder system using app-dispatch[33] and physiology-guided resuscitation[34] will hopefully improve the outcomes after OHCA, and we should assess their effectiveness as future treatments.

In addition, it typically takes many years to implement new standards in clinical practice. For example, in the "Heart Rescue Project", which is a multistate public health initiative aimed at improving case capture and OHCA care in the community, by EMS, and at the hospital level, over-

all survival to hospital discharge did not improve between 2011 and 2015, in agreement with our results.[13] In the preceding study, the authors pointed out that the study duration was too short to investigate the effect of the "Heart Rescue Project" on study outcomes. Therefore, further follow-up is warranted to assess the effects of revisions of the CPR guidelines and the implementation of new treatments such as TTM on outcomes after OHCA.

In the subgroup analysis, favorable neurological outcome among OHCA patients with VF/pVT tended to improve after adjustment for several factors related to resuscitation. This result suggests there were unmeasured confounding factors that may have been related to improvement in OHCA outcomes. Currently, the importance of CPR quality improvement by team dynamics[35,36] or high-performance CPR[37,38] has been emphasized. These new factors should also be registered to evaluate their effectiveness in improving survival after OHCA.

### Study Limitations

This study has several limitations. First, we were only able to assess neurological status at 1 month after OHCA; longer follow-up (e.g., 1-year survival) data were not available. Second, the category of presumed cardiac arrest was a diagnosis by exclusion (i.e., the diagnosis was made when there was no evidence of a non-cardiac cause), in accordance with the Utstein-style international guidelines for cardiac arrest data reporting. Third, this study focused on adult patients with OHCA transported to CCMCs and a hospital with an emergency department in the Osaka Prefecture; information on patients transported to unregistered CCMCs or non-CCMCs was not available for analysis.

## Conclusions

In the CRITICAL registry, 1-month survival with favorable neurological outcome after adult OHCA did not improve significantly between 2013 and 2017, although there was increased use of advanced in-hospital management such as ECPR. Further monitoring is warranted to assess temporal changes in OHCA outcomes.

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### Data Availability

The deidentified participant data will be shared on a request basis immediately following publication with no end date. The data are applicable only for analyses of our study findings. The data will be shared as csv files with CD-ROM via mail. Please directly contact the corresponding author to request data sharing. The data contain the baseline data follow-up data of patients and the study protocol in Japanese. The data are available immediately. The linear trend test was conducted to temporally investigate trends in various measurements. The logistic regression model was also performed for outcomes. All statistical analyses were performed by STATA version 16 (Stata Corp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC.).

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### IRB Information

The study protocol complies with the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Ethics Committee of Kyoto University (R-1045).

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