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Mid-term (30- to 90-day) neurological changes in out-of-hospital cardiac arrest patients: A nationwide retrospective study (the JAAM-OHCA registry)

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ABSTRACT

Objective: Few studies have focused on mid/long-term neurological changes in out-of- hospital cardiac arrest (OHCA) survivors. Some studies suggest that there is still a slow, small, progressive improvement in cognitive function and quality of life for this population, even in the mid/long term. However, clinical data focused on mid/long-term outcomes for OHCA patients are still lacking. This study aimed to assess mid-term neurological changes in OHCA patients. We summarized patients' improved or worsened neurological changes between 30 and 90 days. Then we identified the relationship between clinical variables and 30- to 90-day neurological improvement.
Methods: A retrospective review of data (Jun 2014 - Dec 2017) from a Japanese nationwide OHCA registry was conducted. Inclusion criteria were OHCA patients ≥18 years old. Exclusion criteria were death within 30 days and missing Cerebral Performance Category (CPC) score at 30 and 90 days. We described the distributions of 30-day and 90-day CPC scores as well as the number and portion of patients whose CPC scores improved and worsened between 30 and 90 days. Additionally, factors affecting improved neurological changes over the time period were examined using multivariable logistic regression.
Results: Of the registry's 34,745 patients, 1868 were analyzed. Favorable neurological outcomes (CPC scores of 1 and 2) were seen in 1020/1868 patients at 90 days. CPC scores at 90 days were: CPC 1: 866 (46%), CPC 2: 154 (8.2%), CPC 3: 224 (12%), and CPC 4: 392 (20%), respectively. A total of 232 patients (CPC 5: 12%) died between 30 and 90 days. In 133 patients (7%), 90-day CPC scores improved compared to their 30-day scores. In 260 patients (14%), 90-day CPC scores worsened compared with their 30-day scores. Application of target temperature management was an independent factor for 30- to 90-day neurological improvement (adjusted odds ratio: 1.69, 95% confidence interval: 1.07–2.68).
Conclusions: In our nationwide registry, 7% of resuscitated patients had improved neurological changes in the 30- to 90-day period; most of the improvements were CPC scores improving from 2 to 1. Target temperature management was an independent factor associated with CPC improvement over the 30- to 90-day period.

1. Introduction

Out-of-hospital cardiac arrest (OHCA) remains a significant public health concern, with favorable neurological outcomes as low as 3–8% [1,2]. The major poor neurological outcomes of cardiac arrest survivors have been attributed to global ischemic brain injury. Brain injury manifested as coma or altered level of consciousness is a severe burden to patients, families, and caregivers. Currently, there is no reliable clinical examination to predict OHCA patient awakening in the short term [3,4] and scarce evidence for prediction in the mid/long term. Due to substantial anticipated poor neurological outcomes in the mid/long term, the majority of deaths after OHCA are associated with withdrawal of life-sustaining treatment [5].

Patients who remain comatose may still wake up, even during or after hospital treatment, and have favorable neurological outcomes [6]. Few studies have focused on the mid/long-term outcomes of

Abbreviations: CI, confidence interval; CPC, Cerebral Performance Category; EMS, emergency medical service; FDMA, Fire and Disaster Management Agency; JAAM, Japanese Association for Acute Medicine; OHCA, out-of-hospital cardiac arrest; OR, odds ratio; TTM, targeted temperature management.

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OHCA survivors; some studies suggest slow, progressive improvement, even after hospital discharge [7,8]. However, clinical data focused on mid/long-term outcomes of OHCA patients are still lacking. Moreover, factors associated with improved neurological changes in the mid/long term are not known.

This study aimed to assess mid-term neurological changes in OHCA patients. We summarized patients with improved and worsened neurological changes at 90 days compared to their condition at 30 days. Then, we identified the relationship between clinical variables and improved neurological changes during the period in resuscitated OHCA patients.

2. Methods

2.1. Study design

This retrospective, observational study used data from the OHCA Registry of the Japanese Association for Acute Medicine (JAAM). The Okayama University Ethics Committee approved the study (K2007–010) and waived the requirement for written informed consent.

2.2. Emergency medical system (EMS) in Japan

The EMS system in Japan has been described in detail previously [9]. Briefly, all emergency calls are handled by local operations centers that dispatch the nearest ambulance to the scene. Each vehicle is staffed by three or four EMS providers, at least one of whom is an advanced EMS provider. Advanced EMS providers can perform airway management, including supraglottic airway placement. In addition, specially trained advanced EMS providers are allowed to perform endotracheal intubation and adrenaline administration under real-time medical direction by physicians. EMS providers are obligated to resuscitate and transport OHCA patients to the hospital unless obvious signs of death are present. OHCA patients are commonly transported to the nearest emergency medical hospital. Data for all OHCA patients are registered to the All-Japan Utstein Registry database run by the Fire and Disaster Management Agency (FDMA). The FDMA prospectively collects data using a form recommended in the Utstein-style international guidelines for reporting OHCA [10].

2.3. Data collection

The JAAM OHCA Registry is a web-based, multicenter, prospective registry of OHCA patients who were transported to critical care medical centers or hospitals with an emergency care department across Japan, including 97 institutions. The JAAM OHCA registry's web-based data collection system has been described in detail previously [2,11]. Briefly, prehospital data for OHCA patients were collected according to the FDMA's All-Japan Utstein registry-style guidelines. Physicians at the participating facilities entered the in-hospital data at each hospital, including patient characteristics, treatments (defibrillation, adrenaline, extracorporeal circulation, targeted temperature management [TTM]), and outcomes (30-day Cerebral Performance Category [CPC] scores, 90-day CPC scores). The 30-day and 90-day CPC scores were determined using hospital medical records or telephone interviews with the patient, surrogate, or transferred hospital physician in charge. Treatment decisions were left to each participating hospital. TTM was applied according to each facility's standards (ranging from 32 to 36 °C). Target temperature was recorded. In this study, the application of TTM was described as a binary variable (yes/no). Finally, JAAM OHCA registry data was integrated with prehospital and in-hospital data using cardiac arrest location (prefecture), gender, age, dispatch time, and CPC score.

2.4. Patient selection and endpoint

All patients with OHCA from cardiac and non-cardiac causes enrolled in the JAAM OHCA registry from June 1, 2014 to December 31, 2017 were eligible for inclusion. Exclusion criteria were death within 30 days and missing CPC data at 30 and 90 days. Primary outcome was 30- to 90-day improved neurological changes. Secondary outcome was 30- to 90-day worsened neurological changes.

2.5. Definitions and measurements

Patient neurological outcomes were defined by CPC score. CPC score was obtained at 30 days and 90 days after cardiac arrest. Improved 30- to 90-day neurological change was defined as improvement in CPC score between the two time points (30 and 90 days). Worsened neurological change was defined as deterioration of CPC score between 30 and 90 days.

2.6. Statistical analysis

We first examined the demographic characteristics of the eligible participants and compared those of patients who survived at 90 days with those who died between 30 and 90 days. Continuous variables were described using median with interquartile ranges. Categorical variables are described using percentages.

We then described distributions of 30-day and 90-day CPC scores and evaluated the consistency between 90-day and 30-day CPC scores. After identifying those with improved, unchanged, or worsened 90-day neurological outcomes, we examined associations between clinical factors and improved neurological changes between 30 and 90 days using multivariable logistic regression. We then estimated odds ratios (ORs) and 95% confidence intervals (CIs). The clinical variables were selected based on our clinical interests and included age, gender, estimated cardiac cause, witness of OHCA, initial cardiac rhythm, use of extracorporeal circulation, and application of TTM. All statistical analysis was performed using Stata version 16 (StataCorp LP, College Station, TX).

3. Results

3.1. Patient characteristics

Fig. 1 shows a patient flow chart. During the study period, data on 34,754 patients were entered into the JAAM OHCA Registry. Patients meeting the exclusion criteria (737 under 18 years old; 30,283 died within 30 days; 829 without 30-day CPC data; 1037 without 90-day CPC data) were excluded. Finally, 1868 patients were included in the analysis, with 232 patients dying throughout the 30 to 90-day period.

Patient characteristics are shown in Table 1. The median age was 67 [54–77], and 1334 patients were male (71%). OHCA was witnessed in 1137 cases (61%); 1088 patients (58%) had an estimated cardiac cause. Shockable rhythms, including pulseless ventricular tachycardia or ventricular fibrillation, and non-shockable rhythms including pulseless electrical activity or asystole were observed in 643/1393 (46%) and 516/1393 patients (37%), respectively. Return of spontaneous circulation was observed in 234/1393 patients (17%) on EMS arrival. Bystander cardiopulmonary resuscitation was performed on 716 patients (51%), EMS used advanced airway for 471 patients (48%), and adrenaline was administered in the prehospital setting in 301 patients (16%). The median total prehospital time was 36 [28–46] minutes. In 1718 cases (92%), receiving hospitals were Nationally Certified Emergency Medical Centers. Extracorporeal circulation was used in 251 cases (13%). Percutaneous coronary intervention was conducted in 431 of the cases (23%). TTM was conducted in 872 of the cases (47%), with a lower target temperature (32–34 °C) applied in 666 cases (36% of all patients; 76% of those receiving TTM). Favorable neurological outcomes

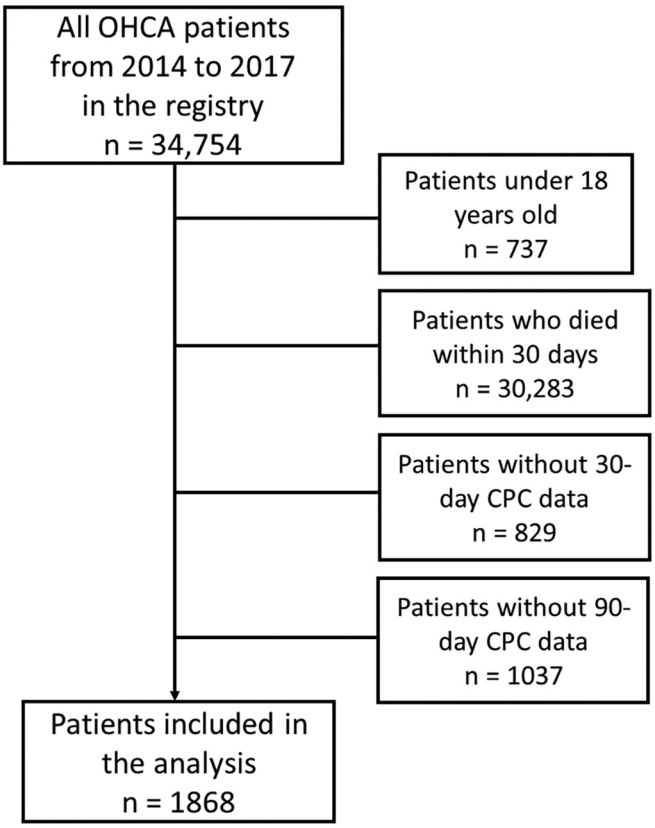

Fig. 1. Flow diagram of patients analyzed. CPC: Cerebral Performance Category, OHCA: out-of-hospital cardiac arrest.

(CPC scores of 1 or 2) were seen in 1000 patients (54%) at 30 days and 1020 patients (55% of all participants; 62% of 90-day survivors) at 90 days.

3.2. Outcomes

The distribution of the 1868 patients' 30-day and 90-day CPC scores is shown in Fig. 2. CPC scores at 30 days were CPC 1: 800 (43%), CPC 2: 200 (11%), CPC 3: 288 (15%), and CPC 4: 580 (31%), respectively. CPC scores at 90 days were CPC 1: 866 (46%), CPC 2: 154 (8.2%), CPC 3: 224 (12%), and CPC 4: 392 (20%), respectively. Of 1868 patients, 232 died (CPC 5: 12%) during the 30- to 90-day time period.

Fig. 3 shows CPC scores at 90 days with corresponding 30-day CPC scores. Of the 200 patients with 30-day CPC 2 scores, 69 improved to CPC 1 at 90 days. Of the 580 patients with 30-day CPC 4 scores, 184 died by 90 days. Detailed numbers of cases are shown in Supplementary data.

The total number and portion of patients with CPC changes over the 30 to 90-day time period is shown in Fig. 4. In 133 of 1868 patients (7%), 90-day CPC scores improved compared to their 30-day scores. In 260 patients (14%), 90-day CPC scores worsened compared with 30-day scores, with 184 patients' 30-day scores deteriorating from CPC 4 to CPC 5 at 90 days. The remaining 76 patients (4%) had worsened changes from 30 days CPC 1/2/3.

3.3. Factors related to favorable changes

Results from multivariable logistic regression analysis for CPC improvement are shown in Table 2. Application of TTM served as an independent factor for 30- to 90-day CPC score improvement (adjusted OR: 1.69, 95% CI: 1.07–2.68).

4. Discussion

Seven percent of resuscitated patients who survived at 30 days in our nationwide registry had improved neurological changes during the 30- to 90-day period. Our study emphasizes that neurological improvement is often observed, even after 30 days, implying the need for continued care. TTM in the acute phase had a potential beneficial effect for further improvement of resuscitated OHCA patients during the 30- to 90-day period. Further study is needed to evaluate the mid/long term improvement of OHCA patients and their outcomes.

Some studies suggest that there is still a slow, small, progressive improvement in cognitive functions and quality of life for these patients, even in the mid/long term [7,8]. Wallin et al. described the time course of OHCA survivors; out of 45 patients who could be followed up over a six-month period, 10 participants were classified as having poor outcomes (CPC scores of 3–4) at discharge from the intensive care unit (ICU). Six participants with CPC scores of 3 at discharge from the ICU had CPC scores that improved to 1, and one participant with a CPC score of 4 improved to CPC 2 at six months [7]. Similarly, Kim et al. showed that two out of 48 patients (4.1%) with poor neurologic outcomes at 30 days showed better neurologic status, with CPC scores improving from 3 to 2 during the first six months [8]. On the contrary, other studies show that most patients experience improvements limited to within the first 45 days after cardiac arrest [12]; more extensive improvements such as increase in CPC score rarely occurred in the long term [13]; however, these studies include only a relatively small number of patients. In our analysis using the large nationwide registry, CPC changes occurred, especially improvement of 30-day CPC 2 scores to CPC 1 at 90 days. Improvement in the detailed neurologic sequelae could not be obtained for our analysis. However, more comprehensive data on cognitive function [7,12,14], activities of daily living [7,15], or quality of life [7,16,17] of post-OHCA patients has been analyzed in other studies and would be increasingly important. Early intervention and rehabilitation, which produce promising results with post-OHCA populations, should be organized [16]. Detecting detailed deficits in post-OHCA patients may help to guide rehabilitation and develop patient-specific interventions.

Our study cohort had 14% of patients with worsened neurological changes in the same period. Most of these deteriorations were attributed to deaths of patients with 30-day CPC 4 scores by 90 days; however, even excluding the 30-day CPC 4 patients' deterioration, there still was a 4% cohort with worsened neurological changes or death during the mid-term. Although we could not verify the cause of deterioration from this registry data, one possible explanation for this decline is recurrent cardiac arrest. Recurrent cardiac arrest after OHCA is reported to occur frequently in survivors [18]. The community's awareness of cardiac arrest symptoms and education in high-risk populations may help to increase the number of early interventions and reduce the incidence of recurrent OHCA and neurological worsening [19].

Although controversies persist [20,21], TTM is only the treatment associated with decreased mortality and improved survival or neurological outcomes [22-24] in the short term. Only a few papers have addressed the relationship between TTM and better mid/long term cognitive functions. TTM lasting 48 h was reported to be associated with reduced memory retrieval deficits and lower relative risk of cognitive impairment compared with 24 h TTM six months after the onset of cardiac arrest [25]. The findings of this study are consistent with those of our study, with TTM the only variable implying mid-term neurological improvement.

A strength of the study is our large sample size and uniform data collection throughout the participating facilities. Patients with both improved and worsened neurological changes were described in our analysis. Furthermore, the effect of TTM on favorable neurological changes was evaluated.

Table 1
Characteristics of participants who survived for 30 days after OHCA.

	All Participants Who Survived for 30 days ($n = 1868$)	Death Between 30 Bays and 90 Days ($n = 232$)	Survived for 90 Days ($n = 1636$)
Baseline and Prehospital Information			
Age (year), median [IQR]	67 [54–77]	74 [64–83]	66 [53–76]
Male, n (%)	1334 (71%)	140 (60%)	1194 (73%)
Witnessed collapse, n (%)	1137 (61%)	114 (49%)	1023 (63%)
Estimated cardiac cause, n (%)	1088 (58%)	86 (37%)	1002 (61%)
Initial cardiac rhythm *			
VF/pulseless VT, n (%)	643 (46%)	36 (16%)	607 (37%)
PEA, n (%)	339 (24%)	51 (22%)	288 (18%)
Asystole, n (%)	177 (13%)	43 (19%)	134 (8.2%)
ROSC at EMS arrival, n (%)	234 (17%)	14 (6.0%)	220 (13%)
Bystander CPR, n (%)	716 (38%)	61 (26%)	655 (40%)
Public AED by bystander, n (%)	193 (10%)	7 (3.0%)	186 (11%)
Advanced airway, n (%)	471 (25%)	67 (29%)	404 (25%)
Adrenaline administration	301 (16%)	55 (24%)	246 (15%)
Total prehospital time (min), median [IQR]	36 [28–46]	36 [28–44]	36 [28–46]
Hospital and treatment information			
Received at Emergency Medical Center, n (%)	1718 (92%)	201 (87%)	1517 (93%)
Number of OHCA cases per year at receiving hospital, n (%)			
1–200	1150 (62%)	163 (70%)	987 (60%)
201–400	622 (33%)	63 (27%)	559 (34%)
≥401	96 (5%)	6 (3%)	90 (6%)
Defibrillation, n (%)	326 (17%)	26 (11%)	300 (18%)
Adrenaline administration, n (%)	646 (35%)	114 (49%)	532 (33%)
Use of extracorporeal circulation, n (%)	251 (13%)	21 (9%)	230 (14%)
Percutaneous coronary intervention, n (%)	431 (23%)	22 (9.4%)	409 (25%)
TTM, n (%)	872 (47%)	85 (37%)	787 (48%)
Target TTM temperature			
32–34 °C, n (%)	666 (36%)	65 (28%)	601 (37%)
35–36 °C, n (%)	206 (11%)	20 (8.6%)	186 (11%)
Outcome			
Favorable outcome defined by CPC score 1, 2, n (%)	1020 (55%)	N/A	1020 (62%)

Abbreviations: AED: automated external defibrillator, CPC: Cerebral Performance Category, CPR: cardiopulmonary resuscitation, EMS: emergency medical service, IQR: interquartile range, N/A: not applicable, OHCA: out-of-hospital cardiac arrest, PEA: pulseless electrical activity, ROSC: return of spontaneous circulation, TTM: targeted temperature management, VF: ventricular fibrillation, VT: ventricular tachycardia.
* Evaluated in 1393 patients.

5. Limitations

The study has some limitations. The study is not free from selection bias, since data was drawn from the JAAM OHCA Registry, with most data coming from Nationally Certified Emergency Centers. There was no unified protocol for obtaining 30-day or 90-day CPC data. There were missing values, especially 90-day CPC scores; this might underestimate the worsened change during the study period. The study sought to examine mid-term changes from 30 to 90 days; a longer period should be studied to elucidate the time course of OHCA patients. We used CPC scores, which could not provide detailed information on cognitive function. We could not obtain information on several factors potentially associated with outcomes such as early cognitive rehabilitation.

6. Conclusions

In our nationwide registry, 7% of resuscitated patients had improved neurological changes over the 30- to 90-day period, with the most improvement being 30-day CPC 2 scores improving to CPC 1 at 90 days. In the same period, 14% of patients experienced worsened neurological changes, with most dying (scores deteriorated from CPC 4 to CPC 5).

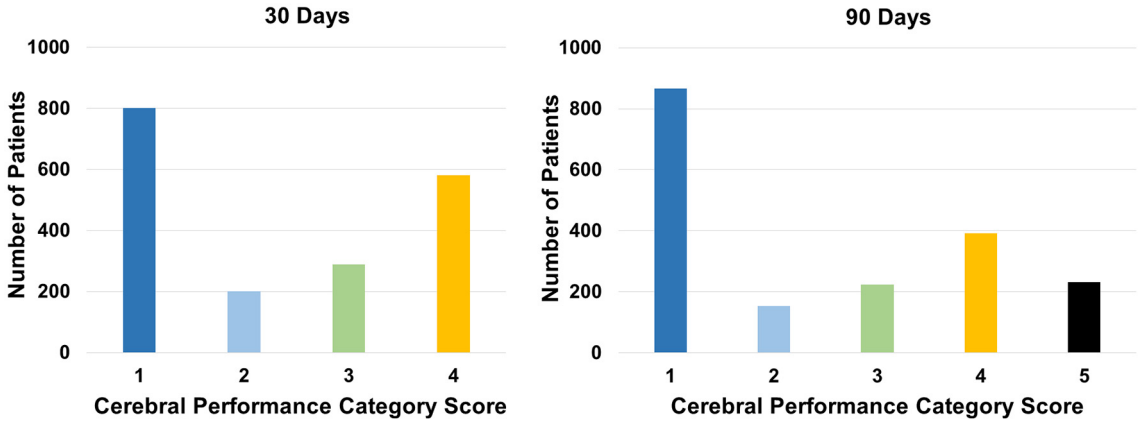

Fig. 2. Distribution of 30-day and 90-day CPC scores for 1868 patients included in the study (patients who survived for 30 days with CPC data for both 30 and 90 days). CPC: Cerebral Performance Category.

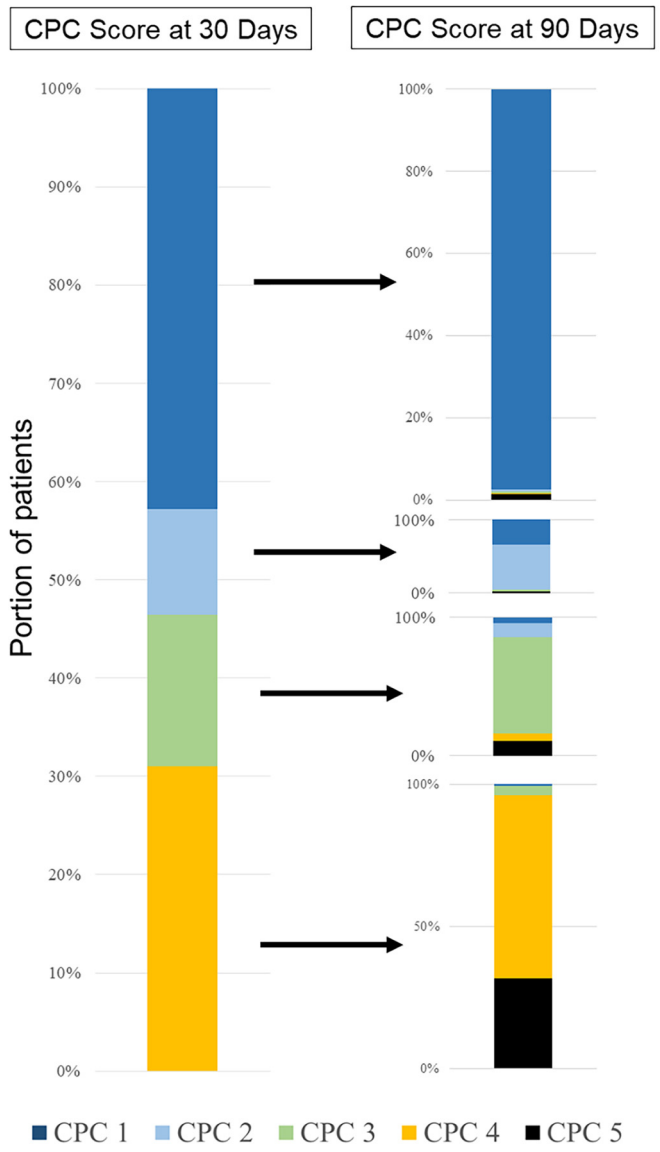

Fig. 3. CPC scores at 90 days with corresponding 30-day CPC scores. The portion of each CPC score at 30 days is described on the left; the portion of CPC scores at 90 days with each corresponding 30-day CPC score is described on the right. CPC: Cerebral Performance Category.

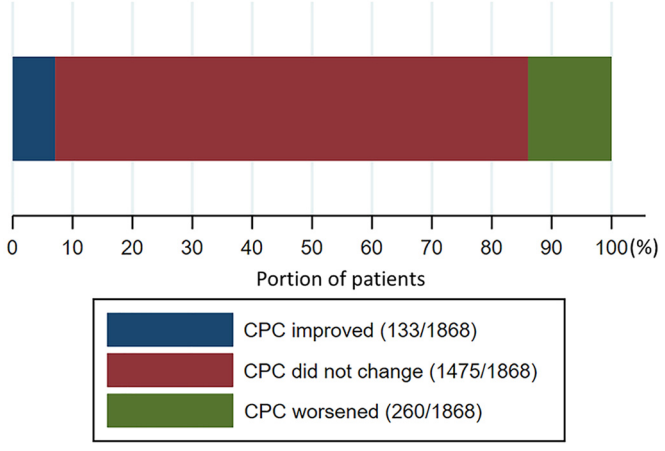

Fig. 4. The total number and portion of patients with CPC changes over the 30- to 90-day time period. CPC: Cerebral Performance Category.

Table 2
Multivariable regression analysis for 30- to 90-day CPC improvement.

Clinical Variables	Adjusted OR	95% CI
Age	1.01	0.996–1.03
Gender (male)	0.93	0.57–1.51
Estimated cardiac cause	0.68	0.37–1.24
Witness of OHCA	1.13	0.65–1.99
Bystander CPR	1.04	0.68–1.60
Initial rhythm		
Non-shockable rhythm	1 (Reference)	
Shockable rhythm	1.35	0.76–2.40
ROSC at hospital arrival	1.18	0.59–2.35
Received at Emergency Medical Center	1.74	0.61–4.93
Number of OHCA cases per year at receiving hospital		
1–200	1(Reference)	
201–400	0.87	0.55–1.37
≥ 401	1.45	0.49–4.27
Percutaneous coronary intervention	1.08	0.64–1.81
TTM application	1.69	1.07–2.68
Extracorporeal circulation use	1.49	0.83–2.67

Multivariable logistic regression was performed to adjust for each variable.
Abbreviations; CI: confidence interval, CPC: Cerebral Performance Category, OHCA: out-of-hospital cardiac arrest, OR: odds ratio, ROSC: return of spontaneous circulation, TTM: targeted temperature management.

TTM was an independent factor associated with neurological improvement over the 30- to 90-day period. Further study is needed to elucidate the mid/long term neurological outcomes of OHCA patients.

Authors' contributions

HN, TN, TY, NF, and AN contributed to the study conception, data acquisition, and analysis and writing of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was performed according to the Helsinki Declaration and institutional review board approval was duly obtained (ID: K2007-010).

Consent for publication

Consent for publication was waived.

Availability of data and materials

The data for the study is obtained from Out-of-Hospital Cardiac Arrest Registry of the Japanese Association for Acute Medicine; the authors do not have permission to share data.

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Conflicts of interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Credit authorship contribution statement

Hiromichi Naito: Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Tsuyoshi Nojima:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Takashi Yorifuji:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Noritomo Fujisaki:**

Writing – review & editing, Methodology, Formal analysis, Data curation, Conceptualization. **Atsunori Nakao:** Writing – review & editing, Supervision, Methodology, Formal analysis, Data curation, Conceptualization.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajem.2022.05.017.

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