Resuscitation 133 (2018) 82–87

Contents lists available at ScienceDirect

Resuscitation

journal homepage: www.elsevier.com/locate/resuscitation

Clinical paper

The effect of different target temperatures in targeted temperature management on neurologically favorable outcome after out-of-hospital cardiac arrest: A nationwide multicenter observational study in Japan (the JAAM-OHCA registry)☆

Taro Irisawa[a,*,1], Tasuku Matsuyama[b,1], Taku Iwami[c], Tomoki Yamada[a,d], Koichi Hayakawa[e], Kazuhisa Yoshiya[c], Kazuo Noguchi[f], Tetsuro Nishimura[g], Toshifumi Uejima[h], Yoshiki Yagi[i], Takeyuki Kiguchi[a,j], Masafumi Kishimoto[k], Makoto Matsuura[l], Yasuyuki Hayashi[m], Taku Sogabe[n], Takaya Morooka[o], Tetsuhisa Kitamura[p], Takeshi Shimazu[a], for the CRITICAL Study investigators

[a] Department of Traumatology and Acute Critical Medicine, Osaka University Graduate School of Medicine, Suita, Japan
[b] Department of Emergency Medicine, Kyoto Prefectural University of Medicine, Kyoto, Japan
[c] Kyoto University Health Services, Kyoto, Japan
[d] Emergency and Critical Care Medical Center, Osaka Police Hospital, Osaka, Japan
[e] Department of Emergency and Critical Care Medicine, Kansai Medical University, Takii Hospital, Moriguchi, Japan
[f] Department of Emergency Medicine, Tane General Hospital, Osaka, Japan
[g] Department of Critical Care Medicine, Osaka City University, Osaka, Japan
[h] Department of Emergency and Critical Care Medicine, Kinki University School of Medicine, Osaka-Sayama, Japan
[i] Osaka Mishima Emergency Critical Care Center, Takatsuki, Japan
[j] Critical Care and Trauma Center, Osaka General Medical Center, Osaka, Japan
[k] Osaka Prefectural Nakakawachi Medical Center of Acute Medicine, Higashi, Osaka, Japan
[l] Senshu Trauma and Critical Care Center, Osaka, Japan
[m] Senri Critical Care Medical Center, Saiseikai Senri Hospital, Suita, Japan
[n] Traumatology and Critical Care Medical Center, National Hospital Organization Osaka National Hospital, Osaka, Japan
[o] Emergency and Critical Care Medical Center, Osaka City General Hospital, Osaka, Japan
[p] Division of Environmental Medicine and Population Sciences, Department of Social and Environmental Medicine, Graduate School of Medicine, Osaka University, Osaka, Japan

ARTICLE INFO

Keywords:
Out-of-hospital cardiac arrest
Targeted temperature management
Post-cardiac arrest syndrome
Neurologically favorable outcome

ABSTRACT

Background: It has been insufficiently investigated whether neurological function after out-of-hospital cardiac arrest (OHCA) would differ by 1 °C change in ordered target temperature of 33–36 °C among patients undergoing targeted temperature management (TTM) in the real-world setting.

Methods: This nationwide hospital-based observational study (The Japanese Association for Acute Medicine-OHCA Registry) conducted between June 2014 and December 2015 in Japan included OHCA patients aged ≥18 years who were treated with TTM. The primary outcome was one-month survival with neurologically favorable outcomes defined by cerebral performance category 1 or 2. To investigate the effect of TTM by 1 °C change in ordered target temperature of 33–36 °C on each outcome, random effects logistic regression analyses were performed.

Results: The final analysis included 738 patients. The proportion of patients with neurologically favorable outcome was 30.4% (7/23), 31.7% (175/552), 28.9% (11/38), and 30.4% (38/125) in the 33 °C, 34 °C, 35 °C, and 36 °C groups, respectively. In the multivariable logistic regression analysis, no group had a higher proportion of neurologically favorable outcome compared with the 34 °C group (vs. 33 °C group, adjusted odds ratio [AOR]

☆ A Spanish translated version of the abstract of this article appears as Appendix in the final online version at doi:https://doi.org/10.1016/j.resuscitation.2018.10.004.

* Corresponding author at: Department of Traumatology and Acute Critical Medicine, Osaka University Graduate School of Medicine, 2-5 Yamada-oka, Suita, Osaka 565-0871, Japan.
E-mail address: taroirisawa@gmail.com (T. Irisawa).
[1] These authors contributed equally to this article.

https://doi.org/10.1016/j.resuscitation.2018.10.004
Received 12 June 2018; Received in revised form 30 September 2018; Accepted 7 October 2018

0.90; 95% confidence interval [CI] 0.25–3.12, vs. 35 °C group, AOR 1.17; 95% CI 0.44–3.13, vs. 36 °C group, AOR 1.26; 95% CI 0.78–2.02).
Conclusions: In this population, we evaluated the difference in outcomes after adult OHCA patients received TTM by 1 °C change in ordered target temperature of 33–36 °C and demonstrated that there was no statistically significant difference in neurologically favorable outcomes after OHCA irrespective of target temperature.

Introduction

Out-of-hospital cardiac arrest (OHCA) is one of the major causes of deaths in industrialized countries [1], and approximately 350,000–700,000 deaths occur due to OHCA annually in the European Union [2], 356,000 in the United States [3], and 120,000 in Japan [4]. In the chain of survival, high-quality intensive care for patients with post-cardiac arrest syndrome (PCAS) after hospital arrival is a key element for improving the outcome after OHCA [1]. Two landmark randomized trials in the early 2000s demonstrated that targeted temperature management (TTM) at 32–34 °C significantly improved neurological function among OHCA patients with return of spontaneous circulation (ROSC) or first documented shockable rhythm compared with conventional therapy [9,10]. Based on these results, TTM has been strongly recommended for OHCA patients with first documented shockable rhythm and has been moderately/mildly recommended for those with first documented non-shockable rhythm in the CPR guidelines [11,12]. On the other hand, a randomized trial in 2013 showed that therapeutic hypothermia at 33 °C did not confer a benefit compared with therapeutic normothermia at 36 °C among OHCA patients with ROSC [13]. Therefore, although updated CPR guidelines recommend TTM with target temperature at 32–36 °C for at least 24 consecutive hours [1,5], optimal target temperature for OHCA patients receiving TTM remains controversial. In addition, it has been insufficiently investigated whether the neurological function after OHCA would differ by target temperature among patients receiving TTM in the real-world setting.

The Japanese Association for Acute Medicine (JAAM)-OHCA Registry, which aims to improve the survival after OHCA by providing an evidence-based therapeutic strategy and emergency medical system, has launched a multicenter, prospective registry that enrolls OHCA patients transported to critical care medical centers or hospitals with an emergency care department in Japan [14] and has enrolled approximately 12,000 OHCA patients between June 2014 and December 2015 from 73 participating institutions. Using this database, we aimed to assess one-month survival with neurologically favorable outcome among adult OHCA patients receiving TTM by 1 °C change in target temperature of 33–36 °C.

Methods

Study design, population, and setting

This study was a retrospective analysis of the JAAM-OHCA Registry [14]. The study period was from June 2014 to December 2015. The inclusion criteria were adult patients with OHCA for whom resuscitation was attempted by emergency medical service (EMS) personnel or bystanders, who were then transported to participating institutions, and were treated with TTM. The exclusion criteria were (1) patients with OHCA who did not receive CPR performed by physicians after hospital arrival and (2) those whose targeted body temperature during TTM was 32 °C or unknown. We excluded patients with 32 °C because the number of them extremely small such as 4. The excluded patients who did not receive CPR by physicians after hospital arrival meant that they did not achieve ROSC on hospital arrival, the clinician judged they had no chance to get ROSC or subsequent survival, and did not perform any CPR.

The JAAM-OHCA Registry

The JAAM-OHCA Registry is a nationwide hospital-based prospective observational data registry. The complete study methodology was previously described [14]. In brief, in Japan, there were 288 critical care medical centers (CCMCs) certified by the Ministry of Health, Labour and Welfare that could provide highly specialized treatments such as extracorporeal cardiopulmonary life support (ECLS), TTM, or percutaneous coronary intervention (PCI), 24 h a day. Both CCMCs and non-CCMCs with an emergency care department can participate in this registry. The registry is ongoing without setting the end date of the registry period. The registry was approved by the Ethics Committee of Kyoto University, and each hospital also approved the JAAM-OHCA Registry protocol as necessary.

The EMS system in Japan

Prehospital resuscitation data were obtained from the All-Japan Utstein Registry of the Fire and Disaster Management Agency (FDMA) of Japan. Details of the EMS system and the registry were previously described [4,14]. Data were prospectively collected using the data form recommended by the Utstein-style international guideline of reporting OHCA [15]. Data on the following aspects were collected: witness status, bystander-initiated CPR, shock applied by public-access AEDs, dispatcher instructions, first documented rhythm, advanced airway management, intravenous fluid, adrenalin administration, and resuscitation time course. A data form was completed by the EMS personnel collaborating with physicians in charge of the patient. The data were uploaded to the registry system of the FDMA database server, logically checked by the computer system, and confirmed by the implementation working group. If a data form was incomplete, the FDMA returned it to the specific fire station and the form was completed.

In-hospital data collection and quality control

The JAAM-OHCA Registry collected substantial information on OHCA patients after hospital arrival (available from: http://www.jaamohca-web.com/download/). Details were provided in a previous study [14]. During the study period, anonymized data were entered into either the web form or the FAX-OCR by the physician or medical staff in cooperation with the physician in charge of the patient, were logically checked by the system; and were finally confirmed by the JAAM-OHCA Registry committee, which consists of specialists in emergency medicine and epidemiology. If there was something incomplete in the data form, a committee member returned it to each institution and the data form was filled out as completely as possible. In-hospital data were systemically combined with prehospital resuscitation data obtained from the All-Japan Utstein Registry of the FDMA, using the five key items in both datasets: prefecture, emergency call time, age, sex, and cerebral performance category (CPC) one month after the OHCA.

In-hospital data of patients with OHCA after hospital arrival were prospectively collected using a uniform data form: age, sex, causes of arrest, ROSC status (ROSC after hospital arrival, ROSC before hospital arrival, no ROSC), first documented rhythm, actual treatments for an OHCA patient (e.g., TTM, PCI, and ECLS), and outcome data. Target (maintenance) body temperature during TTM was also collected (32 °C, 33 °C, 34 °C, 35 °C, 36 °C). The cause of arrest was classified into cardiac

(acute coronary syndrome, other heart disease, presumed cardiac cause) and non-cardiac (cerebrovascular diseases, respiratory diseases, malignant tumors, external causes including traffic injury, fall, hanging, drowning, asphyxia, drug overdose, or any other external cause). The presumed cardiac cause category was determined by exclusion (i.e., the diagnosis was made when there was no evidence of a non-cardiac cause). The diagnosis of cardiac or non-cardiac origin was clinically judged by the physician in charge. Regarding the outcome data, TTM completion, one-month survival, and their neurological status were prospectively collected.

Outcome measurements

The primary outcome of this study was one-month survival with neurologically favorable outcome. Secondary outcomes were TTM completion and one-month survival. The neurological status of the survivors was evaluated by the medical staff at each institution one month after the event. Neurologically favorable outcome was defined as a CPC of 1 or 2 [14,15]. TTM completion" includes those completed all the process of TTM or recovered from coma during TTM, but excluded those died during TTM.

Statistical analysis

Patient characteristics and pre-/in-hospital information were compared among the four groups by Kruskal–Wallis tests for continuous variables and chi-square tests for categorical variables. To investigate the effect of TTM by 1 °C change in ordered target temperature of 33–36 °C on each outcome, both fixed (model 1) and random (model 2) effects logistic regression analyses with hospital treated as a random effect were performed [16], and adjusted odds ratios (AORs) and their 95% confidence intervals (CIs) were calculated. Based on a previous study [17,18], as fixed-effect factors, we adjusted for factors that were biologically essential and considered to be associated with clinical outcomes, including age, sex (men or women), cause of arrest (cardiac or non-cardiac etiology), bystander witness (yes or no), bystander CPR status (yes or no), first documented rhythm (shockable, non-shockable, or presence of pulse), prehospital adrenaline administration (yes or no), and prehospital advanced airway management (yes or no), EMS response time (from call to contact with a patient), PCI (yes or no), and ECLS (yes or no). In the subgroup analysis, the association between TTM by 1 °C change in ordered target temperature of 33–36 °C and favorable neurological outcome according to the first documented rhythm at the scene (shockable or non-shockable) or non-ECLS patients was also assessed using the same fixed and random variables as the main analyses. In addition, as the other subgroup analysis, we performed a 'real-life" repeat of the TTM paper and examine 33–34 versus 35–36. All statistical analyses were performed using the SPSS statistical package version 25.0J (IBM Corp., Armonk, NY, USA). All tests were two-tailed; p values of < 0.05 were considered statistically significant.

Results

During the study period, 13,491 OHCA patients were registered. We combined 89.1% (12,024/13,491) of our data with the prehospital data. After excluding 289 children aged < 18 years, 10,981 patients not having received TTM, 12 with unknown target temperature during TTM, and 4 whose target temperature during TTM was 32 °C, 738 patients were included in our final analyses (Fig. 1). There were 23, 552, 38, and 125 patients who received TTM at the ordered target temperature in the 33, 34, 35, and 36 °C groups, respectively.

Table 1 shows patient characteristics and pre- and in-hospital information of investigated patients. Patients receiving TTM at the ordered target temperature of 33 °C had a higher proportion of younger age, witnessed arrests, first documented shockable rhythm, receiving advanced airway management in the pre-hospital setting, achieving ROSC on arrival at the hospital, and receiving ECLS. In contrast, those receiving TTM at the ordered target temperature of 36 °C were more likely to be older, have non-cardiac etiology of arrests, first documented non-shockable rhythm and less likely to receive ECLS.

Regarding the primary outcome, the proportion of patients with neurologically favorable outcome was 30.4% (7/23), 31.7% (175/552), 28.9% (11/38), and 30.4% (38/125) in the 33 °C, 34 °C, 35 °C, and 36 °C groups, respectively (Table 2). In both the fixed and random effects multivariable logistic regression analysis, no group had a higher proportion of neurologically favorable outcome than the 36 °C group as a reference (vs. 33 °C group, AOR 0.71, 95% CI 0.23–2.21; vs. 34 °C group, AOR 0.80, 95% CI 0.50–1.28; vs. 35 °C group, AOR 0.93, 95% CI 0.31–2.77, in model 2) (Table 3). Regarding secondary outcomes, no significant difference was observed among the four groups with respect to the proportion of TTM completion and 30-day survival (Table 3). In addition, among those who completed TTM, only 7 patients recovered from coma.

The subgroup analyses also demonstrated that no other groups achieved a higher proportion of patients with neurologically favorable outcome than the 36 °C group as a reference both in the first documented rhythm and in non-ECLS patients in any models (Table 4). In the other subgroup analysis, We also found no significant difference in neurologically favorable outcome between the 33–34 °C group and 35–36 °C group (Supplemental Table).

Discussion

Using the Japanese large-scale prospective OHCA registry, we evaluated the difference in outcomes after adult OHCA patients received TTM by 1 °C change in ordered target temperature of 33–36 °C. No statistically significant difference in neurologically favorable outcome after OHCA was observed irrespective of the target temperature. Our nationwide OHCA registry launched by the JAAM is sufficiently large as the real-world database so that we could evaluate neurological outcome among OHCA patients receiving TTM based on detailed target temperatures, and it also provides valuable data for influencing CPR guidelines regarding TTM as intensive care for patients with PCAS.

This study underscored that there was no difference in neurologically favorable outcome after OHCA patients received TTM at the ordered targeted temperature of 33–36 °C. Previous randomized trials and

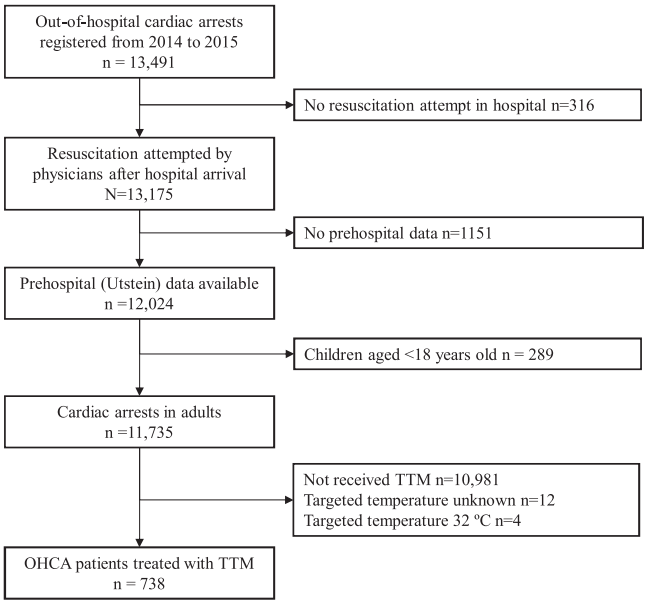

Fig. 1. Patient flow chart of the JAAM-OHCA Registry.
OHCA, out-of-hospital cardiac arrest; TTM, targeted temperature management.

Table 1
Patient characteristics and pre-/in-hospital information among OHCA patients receiving targeted temperature management by 1 °C target temperature stratum at 33–36 °C.

	33 °C (n = 23)	34 °C (n = 552)	35 °C (n = 38)	36 °C (n = 125)	*P* Values[a]
Basic information					
Men	17 (73.9)	423 (76.6)	24 (63.2)	98 (78.4)	0.260
Age, median (IQR) (Years)	51 (42–65)	63 (50–72)	66 (53–73)	68 (53–79)	0.004
Cause of arrest					
Cardiac	17 (73.9)	444 (80.4)	27 (71.1)	84 (67.2)	0.010
Non-cardiac	6 (26.1)	108 (19.6)	11 (28.9)	41 (32.8)	
Prehospital information					
Bystander witness	21 (91.2)	431 (78.1)	28 (73.7)	95 (76.0)	0.381
Bystander CPR	12 (52.2)	277 (50.2)	22 (57.9)	65 (52.0)	0.817
Shock by public-access AEDs	2 (8.7)	52 (9.4)	3 (7.9)	109 (8.0)	0.956
Dispatcher instruction	11 (47.8)	238 (43.1)	19 (50.0)	59 (47.2)	0.716
First documented rhythm at the scene					
Ventricular fibrillation/pulseless ventricular tachyardia	14 (60.9)	305 (55.3)	17 (44.7)	47 (37.6)	0.012
Pulseless electric activity/asystole	8 (34.8)	191 (34.6)	16 (42.1)	65 (52.0)	
Presence of pulse	1 (4.3)	56 (10.1)	5 (13.2)	13 (10.4)	
Epinephrine	7 (30.4)	150 (27.2)	12 (31.6)	28 (22.4)	0.600
Advanced airway management	23 (100.0)	500 (90.6)	37 (97.4)	104 (83.2)	0.010
EMS resuscitation times, median (IQR), (minutes)					
EMS response time (call to contact with a patient)	8 (6–12)	8 (7–9)	8 (6–10)	8 (7–10)	0.853
Hospital arrival time (call to hospital arrival)	34 (25–38)	31 (25–37)	29 (23–39)	31 (25–37)	0.800
In-hospital information					
First documented rhythm after hospital arrival					
Ventricular fibrillation/pulseless ventricular tachyardia	4 (17.4)	119 (21.6)	6 (15.8)	13 (10.4)	0.022
Pulseless electric activity/asystole	6 (26.1)	230 (41.7)	14 (36.8)	50 (40.0)	
Presence of pulse	13 (56.5)	203 (36.8)	18 (47.4)	62 (49.6)	
Percutaneous coronary intervention	5 (21.7)	176 (31.9)	7 (18.4)	30 (24.0)	0.101
Extracorporeal life support	8 (34.8)	169 (30.6)	9 (23.7)	21 (16.8)	0.015

OHCA indicates out-of-hospital cardiac arrests; AED, automated external defibrillator; CPR, cardiopulmonary resuscitation; EMS, emergency medicine personnel, and IQR, interquartile range.

[a] Comparisons between the 4 groups were evaluated with Kruskal–Wallis tests for continuous variables and X^2 test for categorical variables.

Table 2
Outcomes among OHCA patients receiving targeted temperature management by 1 °C target temperature stratum at 33–36 °C.

	33 °C (n = 23)	34 °C (n = 552)	35 °C (n = 38)	36 °C (n = 125)
Targeted Temperature Management completion[a]	16 (69.6)	410 (75.2)	28 (75.7)	102 (82.3)
30-day Survival	16 (69.6)	307 (55.6)	21 (55.3)	79 (63.2)
CPC				
1: good cerebral performance	7 (30.4)	130 (23.6)	9 (23.7)	27 (21.6)
2: moderate cerebral disability	0 (0.0)	45 (8.2)	2 (5.3)	11 (8.8)
3: severe cerebral disability	1 (4.3)	44 (8.0)	1 (2.6)	15 (12.0)
4: coma or vegitative state	8 (34.8)	88 (15.9)	9 (23.7)	26 (20.8)
5: death or brain death	7 (30.4)	245 (44.4)	17 (44.7)	46 (36.8)
30-day Neurologically favorable outcome	7 (30.4)	175 (31.7)	11 (28.9)	38 (30.4)

OHCA indicates out-of-hospital cardiac arrest; CPC, cerebral performance category.

[a] Calculated only 729 patients with outcome data available.

observational studies reported that therapeutic hypothermia improved outcomes among adult OHCA patients with first documented shockable rhythm or ROSC [9,10,19]. In contrast, a landmark trial in 2013 reported that no differences were observed in the outcomes of OHCA patients receiving TTM in the 33 °C and 36 °C groups [13]. After this trial, at an institution where the target temperature was changed from 34 °C to 36 °C, no difference was observed between TTM at 34 °C and 36 °C with respect to mortality nor neurological outcome after OHCA [20]. Thus, these results were consistent with our results. A recent review also demonstrated the importance of avoiding hyperpyrexia and controlling temperature after OHCA rather than lowering temperature excessively [21].

In animal experiments, TTM limited brain injury by decreasing cellular metabolism and the brain's oxygen demand by reducing the production of excitatory neurotransmitters such as glutamate, minimizing the disruption of ion homeostasis, and reducing free radicals that might further injure at-risk neurons [22]. In a clinical study, systemic inflammatory response after cardiac arrest did not differ by TTM at 33 °C or 36 °C [23]; however, the influence of each target temperature on brain metabolism among OHCA patients receiving TTM has not been extensively investigated. Importantly, maintaining target temperature for OHCA patients receiving TTM would be difficult irrespective of the target temperature in clinical settings [24]. Therefore, further studies that consider multilateral factors, such as the brain metabolism and effectiveness/safety of TTM at the target temperature, would be useful for evaluating target temperatures for TTM after OHCA.

If no differences in neurologically favorable outcome after OHCA patients receiving TTM are observed irrespective of the target temperature, it is important to assess the cost-effectiveness of TTM as a next step. Previous reports suggested that TTM after OHCA was a very cost-effective treatment [25], and managing OHCA patients with neurologically favorable outcome in the intensive care unit (ICU) required lower medical cost and shorter length of ICU stay than those with poor outcome [26]. Although there were no clinical studies, including our study, that directly compared the cost of TTM by the ordered target temperature, we need to evaluate the neurological function after OHCA patients receive TTM and its cost-effectiveness and the length of ICU and hospital stay because a target temperature that is medically and economically more useful for both OHCA patients and hospitals may exist.

In this registry, approximately 80% of OHCA patients receiving TTM were managed at the target temperature of ≤34 °C. As with our study area, TTM at ≤34 °C is still being performed for patients with PCAS in

Table 3
Outcomes among OHCA patients receiving targeted temperature management by 1 °C target temperature stratum at 33–36 °C.

	33 °C (n = 23)	34 °C (n = 552)	35 °C (n = 38)	36 °C (n = 125)
Targeted Temperature Management completion[a]	16 (69.6)	410 (75.2)	28 (75.7)	102 (82.3)
Odds Ratio (95% CI)	0.49 (0.18–1.34)	0.66 (0.40–1.08)	0.67 (0.28–1.62)	Reference
Model 1: Adjusted odds ratio (95% CI)[b]	0.46 (0.16–1.34)	0.65 (0.38–1.12)	0.64 (0.25–1.63)	Reference
Model 2: Adjusted odds ratio (95% CI)[c]	0.69 (0.24–1.97)	0.94 (0.39–2.27)	0.84 (0.26–2.73)	Reference
30-day Survival	16 (69.6)	307 (55.6)	21 (55.3)	79 (63.2)
Odds Ratio (95% CI)	1.33 (0.51–3.48)	0.73 (0.49–1.09)	0.72 (0.35–1.50)	Reference
Model 1: Adjusted odds ratio (95% CI)[b]	1.45 (0.49–4.28)	0.62 (0.39–0.98)	0.65 (0.28–1.52)	Reference
Model 2: Adjusted odds ratio (95% CI)[c]	1.88 (0.64–5.44)	0.75 (0.37–1.52)	0.80 (0.26–2.51)	Reference
30-day Neurologically Favorable Outcome	7 (30.4)	175 (31.7)	11 (28.9)	38 (30.4)
Odds Ratio (95% CI)	1.00 (0.38–2.63)	1.06 (0.70–1.62)	0.93 (0.42–2.07)	Reference
Model 1: Adjusted odds ratio (95% CI)[b]	0.68 (0.18–2.61)	0.77 (0.44–1.33)	0.93 (0.34–2.55)	Reference
Model 2: Adjusted odds ratio (95% CI)[c]	0.71 (0.23–2.21)	0.80 (0.50–1.28)	0.93 (0.31–2.77)	Reference

OHCA indicates out-of-hospital cardiac arrest; CI, confidence interval; EMS, emergency medicine personnel.
[a] Caluculated only 729 patients with outcome data available.
[b] Adjusted for age, sex, etiology of arrest, bystander witness, bystander cardiopulmonary resuscitation, first documented rhythm at the scene, prehospital advanced airway management, prehospital adrenaline administration, EMS response time, percutaneous coronary intervention, and extracorporeal life support.
[c] Random-effects logistic regression models. Each hospital was treated as a random effect.

many hospitals worldwide. In the survey by the French Intensive Care Society, even after the TTM trial publication, 56% of respondents continued to implement TTM at 32–34 °C for OHCA patients [27], suggesting the wide variation in the target temperature of TTM in the real-world settings. As real-world evidence, there were few reports regarding characteristics and neurological function among OHCA patients receiving TTM by 1 °C change in target temperature; however, further studies are needed to verify the effect of target temperatures on OHCA patients receiving TTM.

Furthermore, one problem of this study was that there were presumably some reasons that the clinicians chose a specific temperature for a specific patient. This point is borne out by the fact that there were differences in the characteristics of the patient's between those who were maintained at 33 °C versus 36 °C, such as the latter tended to be older, have a lower percentage of cardiac causes of cardiac arrest, a smaller percentage of first documented shockable rhythm, and a lower percentage of ECLS. Although we controlled for these differences in the statistical analyses as much as possible, this study did not demonstrate a difference in outcomes based solely on target temperature. However it could not be denied that clinicians appropriately or inappropriately chose specific temperatures that either improved outcomes in patients who would've done worse, or worsened outcomes in patients who otherwise would have done better. Recently, personalized CPR or new concept such as "Ultra-Mild Hypothermia" have drawn more attention to improve outcomes after OHCA [28,29]. Taken together, in the post-resuscitation care, it may be also important to assess whether each patient has their unique optimal target temperature during TTM for improving outcome.

Limitation

This study has had some inherent limitations. First, this study addressed the impact of "target" temperature rather than actual temperatures achieved. However, 77.2% of the patients in this paper actually achieved target temperature. Furthermore, "intention" is important; clinicians probably decide how to perform TTM such as device, drugs, or duration partially based on the ordered target temperature, which may affect the outcomes. Therefore, we believe that it is valuable to examine the effect of different target temperatures on patient outcomes. Second, the protocol to introduce TTM in each participating institution was unknown, and there could be also other biases between hospitals. To reduce the influence of these confounders, this study used generalized linear mixed models that considered each hospital as a random effect. Third, this hospital-based registry did not enroll all OHCA patients across Japan. However, this study registered all consecutive OHCA patients transported to the participating institutions; thus, the selection bias of this study would be small. Finally, there could be unmeasured confounding factors that could have affected the relationship between TTM and outcomes after OHCA.

Table 4
Neurologically favorable outcome among OHCA patients receiving targeted temperature management by 1 °C target temperature stratum at 33–36 °C according to the first documented rhythm at the scene.

	33 °C	34 °C	35 °C	36 °C
Shockable n/N, (%) (n = 383)	6/14 (42.9)	134/305 (43.9)	7/17 (41.2)	24/47 (51.1)
Odds Ratio (95% CI)	0.72 (0.22–2.39)	0.75 (0.41–1.39)	0.67 (0.22–2.06)	Reference
Model 1: Adjusted odds ratio (95% CI)[a]	0.63 (0.12–3.39)	0.93 (0.43–2.00)	1.14 (0.28–4.74)	Reference
Model 2: Adjusted odds ratio (95% CI)[b]	0.61 (0.13–2.97)	0.97 (0.56–1.68)	1.23 (0.22–7.03)	Reference
Nonshockable n/N, (%) (n = 280)	0/8 (0.0)	16/191 (8.4)	1/16 (6.3)	5/65 (7.7)
Odds Ratio (95% CI)	NA	1.10 (0.39–3.12)	0.80 (0.09–7.37)	Reference
Model 1: Adjusted odds ratio (95% CI)[a]	NA	1.06 (0.33–3.39)	0.59 (0.05–7.21)	Reference
Model 2: Adjusted odds ratio (95% CI)[b]	NA	1.08 (0.47–2.45)	0.99 (0.11–8.72)	Reference
Non-ECLS n/N, (%) (n = 531)	5/15 (33.3)	153/383 (39.9)	9/29 (31.0)	33/104 (31.7)
Odds Ratio (95% CI)	1.08 (0.34–3.40)	1.43 (0.90–2.27)	0.97 (0.40–2.35)	Reference
Model 1: Adjusted odds ratio (95% CI)[a]	0.46 (0.09–2.32)	0.91 (0.50–1.67)	0.78 (0.26–2.39)	Reference
Model 2: Adjusted odds ratio (95% CI)[b]	0.51 (0.10–2.75)	0.92 (0.49–1.71)	0.78 (0.22–2.84)	Reference

OHCA indicates out-of-hospital cardiac arrest; CI, confidence interval; EMS, emergency medicine personnel; ECLS, extracorporeal life support.
[a] Adjusted for age, sex, etiology of arrest, bystander witness, bystander cardiopulmonary resuscitation, prehospital advanced airway management, prehospital adrenaline administration, EMS response time, percutaneous coronary intervention, and extracorporeal life support.
[b] Random-effects logistic regression models. Each hospital was treated as a random effect.

Conclusion

In this study population, we evaluated the difference in outcomes after adult OHCA patients received TTM by 1 ˚C change in ordered target temperature of 33–36 ˚C, and we demonstrated that there was no statistically significant difference in neurologically favorable outcome after OHCA irrespective of the target temperature.

Source of funding

This registry was supportedby a research funding from the JAAM and a scientific research grant from the Ministry of Education, Culture, Sports, Science and Technology of Japan (grant numbers 16K09034, 15H05006, and 17K11572).

Disclosures

None declared.

Conflict of interest statement

The authors declare that they have no conflict of potential.

Acknowledgments

We are deeply indebted to all members and institutions of the JAAM-OHCA Registry for their contribution. The participating institutions of the JAAM-OHCA Registry are listed at the following URL: http://www.jaamohca-web.com/list/. We also thank Ms. Narumi Funayama and Mr. Hiroki Chiba for their support with the JAAM-OHCA Registry; Drs. Yasuo Ohishi, Masashi Kishi, Shota Nakao, and Yoshio Abe for data collection of the CRITICAL Study; and Drs. Junichi Izawa, Tomonari Shimamoto, Toshihiro Hatakeyama, Tomoko Fujii, Takefumi Kishimori, Haruka Shida, and Junya Sado for their cooperation in managing the registry database. This article was supported by the Clinical Investigator's Research Project in Osaka University Graduate School of Medicine.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resuscitation.2018.10.004.

References

[1] Neumar RW, Shuster M, Callaway CW, Gent LM, Atkins DL, Bhanji F, et al. Part 1: executive summary: 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation 2015;132(Suppl. 2):S315–67.

[2] Perkins GD, Handley AJ, Koster RW, Castrén M, Smyth MA, Olasveengen T, et al. European resuscitation council guidelines for resuscitation 2015: section 2. Adult basic life support and automated external defibrillation. Resuscitation 2015;95:81–99.

[3] Benjamin EJ, Virani SS, Callaway CW, Chamberlain AM, Chang AR, Cheng S, et al. Heart disease and stroke statistics-2018 update: a report from the American Heart Association. Circulation 2018;137:e67–492.

[4] Ambulance Service Planning Office of Fire and Disaster Management Agency of Japan. Effect of first aid for cardiopulmonary arrest. http://www.fdma.go.jp/neuter/topics/fieldList9_3.html (Accessed 20 April 2018) (in Japanese).

[5] Monsieurs KG, Nolan JP, Bossaert LL, Greif R, Maconochie IK, Nikolaou NI, et al. European resuscitation council guidelines for resuscitation 2015: section 1. Executive summary. Resuscitation 2015;95:1–80.

[9] Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med 2002;346:549–56.

[10] Bernard SA, Gray TW, Buist MD, Jones BM, Silvester W, Gutteridge G, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med 2002;346:557–63.

[11] Nolan JP, Soar J, Zideman DA, Biarent D, Bossaert LL, Deakin C, et al. European resuscitation council guidelines for resuscitation 2010 section 1. Executive summary. Resuscitation 2010(81):1219–76.

[12] Peberdy MA, Callaway CW, Neumar RW, Geocadin RG, Zimmerman JL, Donnino M, et al. Part 9: post-cardiac arrest care: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation 2010(122):S768–86.

[13] Nielsen N, Wetterslev J, Cronberg T, Erlinge D, Gasche Y, Hassager C, et al. Targeted temperature management at 33 ˚C versus 36 ˚C after cardiac arrest. N Engl J Med 2013;369:2197–206.

[14] Kitamura T, Iwami T, Atsumi T, Endo T, Kanna T, Kuroda Y, et al. The profile of Japanese Association for Acute Medicine - out-of-hospital cardiac arrest registry in 2014-2015. Acute Med Surg 2018;5:249–58.

[15] Perkins GD, Jacobs IG, Nadkarni VM, Berg RA, Bhanji F, Biarent D, et al. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update of the utstein resuscitation registry templates for Out-of-Hospital cardiac arrest: a statement for healthcare professionals from a task force of the International Liaison Committee on Resuscitation (American Heart Association, European Resuscitation Council, Australian and New Zealand Council on Resuscitation, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Southern Africa, Resuscitation Council of Asia); and the American Heart Association Emergency Cardiovascular Care Committee and the Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation. Circulation 2015;132:1286–300.

[16] Matsuyama T, Kiyohara K, Kitamura T, Nishiyama C, Nishiuchi T, Hayashi Y, et al. Hospital characteristics and favorable neurological outcome among patients with out-of-hospital cardiac arrest in Osaka, Japan. Resuscitation 2017;110:146–53.

[17] Matsuyama T, Iwami T, Yamada T, Hayakawa K, Yoshiya K, Irisawa T, et al. Effect of serum albumin concentration on favorable neurological outcome after out-of-hospital cardiac arrest (from the CRITICAL study in Osaka, Japan). Am J Cardiol 2018;121:156–61.

[18] Matsuyama T, Iwami T, Yamada T, Hayakawa K, Yoshiya K, Irisawa T, et al. Prognostic impact of serum albumin concentration for neurologically favorable outcome in patients treated with targeted temperature management after out-of-hospital cardiac arrest: a multicenter prospective study. Ther Hypother Temp Manage 2018;8:165–72.

[19] Bro-Jeppesen J, Kjaergaard J, Horsted TI, Wanscher MC, Nielsen SL, Rasmussen LS, et al. The impact of therapeutic hypothermia on neurological function and quality of life after cardiac arrest. Resuscitation 2009;80:171–6.

[20] Arvidsson L, Lindgren S, Martinell L, Lundin S, Rylander C. Target temperature 34 vs. 36˚C after out-of-hospital cardiac arrest—a retrospective observational study. Acta Anaesthesiol Scand 2017;61:1176–83.

[21] Vargas M, Sutherasan Y, Servillo G, Pelosi P. What is the proper target temperature for out-of-hospital cardiac arrest? Best Pract Res Clin Anaesthesiol 2015;29:425–34.

[22] Hunter BR, Ellender TJ. Targeted temperature management in emergency medicine: current perspectives. Open Access Emerg Med 2015;7:69–77.

[23] Bro-Jeppesen J, Kjaergaard J, Wanscher M, Nielsen N, Friberg H, Bjerre M, et al. The inflammatory response after out-of-hospital cardiac arrest is not modified by targeted temperature management at 33 ˚C or 36 ˚C. Resuscitation 2014;85:1480–7.

[24] Bray JE, Stub D, Bloom JE, Segan L, Mitra B, Smith K, et al. Changing target temperature from 33 ˚C to 36 ˚C in the ICU management of out-of-hospital cardiac arrest: a before and after study. Resuscitation 2017;113:39–43.

[25] Behringer W. Targeted temperature management: a health economic perspective. BMC Emerg Med 2015;15(Suppl. 1):A5.

[26] Petrie J, Easton S, Naik V, Lockie C, Brett SJ, Stümpfle R. Hospital costs of out-of-hospital cardiac arrest patients treated in intensive care; a single centre evaluation using the national tariff-based system. BMJ Open 2015;5:e005797.

[27] Deye N, Vincent F, Michel P, Ehrmann S, da Silva D, Piagnerelli M, et al. Changes in cardiac arrest patients' temperature management after the 2013 "TTM" trial: results from an international survey. Ann Intensive Care 2016;6:4.

[28] Friess SH, Sutton RM, Bhalala U, Maltese MR, Naim MY, Bratinov G, et al. Hemodynamic directed cardiopulmonary resuscitation improves short-term survival from ventricular fibrillation cardiac arrest. Crit Care Med 2013;41:2698–704.

[29] Kochanek PM, Jackson TC. The brain and hypothermia-from aristotle to targeted temperature management. Crit Care Med 2017;45:305–10.