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Clinical paper

# Non-linear association between the time required to reaching temperature targets and the neurological outcome in patients undergoing targeted temperature management after out-of-hospital cardiac arrest: Observational multicentre cohort study

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## Abstract

**Purpose**: We evaluated associations between outcomes and time to achieving temperature targets during targeted temperature management of out-of-hospital cardiac arrest.

**Methods**: Using Comprehensive Registry of Intensive Care for out-of-hospital cardiac arrest Survival (CRITICAL) study, we enrolled all patients transported to participating hospitals from 1 July 2012 through 31 December 2017 aged ≥18 years with out-of-hospital cardiac arrest of cardiac aetiology and who received targeted temperature management in Osaka, Japan. Primary outcome was Cerebral Performance Category scale of 1 or 2 one month after cardiac arrest, designated as "one-month favourable neurological outcome". Non-linear multivariable logistic regression analyses

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assessed the primary outcome based on time to reaching temperature targets. In patients subdivided into quintiles based on time to achieving temperature targets, multivariable logistic regression calculated adjusted odds ratios and 95% confidence intervals.
**Results**: We analysed 473 patients. In non-linear multivariable logistic regression analysis, *p* value for non-linearity was <0.01. In the first quintile (≤26.7 minutes), second quintile (26.8–89.9 minutes), third quintile (90.0–175.1 minutes), fourth quintile (175.2–352.1 minutes), and fifth quintile (≥352.2 minutes), one-month favourable neurological outcome was 32.6% (31/95), 40.0% (36/90), 53.5% (53/99), 57.4% (54/94), and 37.9% (36/95), respectively. Adjusted odds ratios with 95% confidence intervals for one-month favourable neurological outcome in the first, second, third, and fifth quintiles compared with the fourth quintile were 0.38 (0.20 to 0.72), 0.43 (0.23 to 0.81), 0.77 (0.41 to 1.44), and 0.46 (0.25 to 0.87), respectively.
**Conclusion**: Non-linear multivariable logistic regression analysis could clearly describe the association between neurological outcome in patients with out-of-hospital cardiac arrest and the time from the introduction of targeted temperature management to reaching the temperature targets.
**Keywords**: Cardiac arrest, Cardiopulmonary resuscitation, Emergency medical services, Emergency medicine, Resuscitation, Targeted temperature management

## Introduction

Targeted temperature management (TTM) is a key treatment to improve neurological outcome after cardiac arrest. [1–4] Pre-hospital cooling can be used safely to increase application of in-hospital TTM.[5] The latest guidelines recommended providing TTM for out-of-hospital cardiac arrest (OHCA) with coma. [6,7]

It is uncertain whether a shorter time between the implementation of TTM and reaching temperature targets could improve survival after an OHCA. Animal studies of TTM suggested that early interventions can improve survival and neurological outcomes. [8] In addition, some human studies reported that faster cooling during TTM may be beneficial for patients with cardiac arrest. [9–12] However, other reports indicated that faster cooling may not be beneficial for patients who received TTM although those reports did not clearly indicate whether linear regression models were appropriate to address this issue. [13–17] One reason may have been that it was not evaluated whether a linear multivariable logistic regression analysis would be a reasonable choice.

We designed the current study to test the hypothesis that a non-linear multivariable logistic regression analysis can clearly describe how the time from the introduction of TTM to reaching the temperature targets is associated with neurological outcome after an OHCA of cardiac aetiology such as acute coronary syndrome, other heart diseases, or presumed cardiac cause.

## Methods

### *Ethical considerations*

This was a retrospective analysis of the database of the Comprehensive Registry of Intensive Care for OHCA Survival (CRITICAL) study. [18] The procedures described in this registry were performed in routine clinical practice, and inclusion in the registry presented no additional risks to patients. Therefore, the requirement to provide individual informed consent was waived by the Act on the Protection of Personal Information and the Ethical Guidelines for Medical and Biological Research Involving Human Subjects of Japan. The registry that was used in the current study was approved by the Ethical Committee of Osaka Metropolitan University Graduate School of Medicine (4238), the Ethics Committee of Kyoto University Graduate School of Medicine (R1045), and each participating institution.

### *Study setting*

The CRITICAL study in Osaka Prefecture, Japan, is a hospital-based multicentre prospective observational study aimed to acquire information to improve neurological outcome after OHCAs. This study was previously described. [18] Using the CRITICAL study registry, we collected information on experiences of OHCA patients including those on in-hospital care. In Osaka Prefecture, Japan, 15 critical care medical centres and 1 non-critical care medical centre with an emergency care department have taken part in this registry upon request.[18] The registry started on 1 July 2012 and remains open, with no end date assigned for registration. Critical care medical centres in Japan are certified by the Ministry of Health, Labor and Welfare to provide highly specialised treatments such as percutaneous coronary interventions and TTM 24 hours a day. The medical professionals in these centres can utilise expert treatments to rescue severely ill patients including those with OHCAs. [19]

### *Study population*

We analysed data on patients who experienced an OHCA who were at least 18 years of age, whose collapse was of cardiac aetiology, and who were provided in-hospital TTM after resuscitation by medical professionals from 1 July 2012 through 31 December 2017. The study period was decided upon to avoid the impact of further changes in TTM practices resulting from findings of preceding studies. [1,20] Patients with missing data on care were excluded from the analyses. The meaning of cardiac aetiology in the current study includes acute coronary syndrome, other heart diseases, or presumed cardiac cause.

### *Pre-hospital data collection*

We obtained pre-hospital resuscitation data on patients who had experienced an OHCA from the All-Japan Utstein Registry, which is managed by the Fire and Disaster Management Agency (FDMA) of Japan. The Japanese Emergency Medical Services (EMS) and registry profile were previously described in detail. [19,21–24] Data were uniformly collected according to the Utstein-style international guidelines for reporting OHCAs. The following information was collected: prefecture where the cardiac arrest occurred, EMS performance-related time, witness status, bystander-initiated CPR, first documented cardiac rhythm, and outcomes. EMS performance-related time data, such as emergency call time, arrival at the scene, contact with the patient, and arrival at the hospital were recorded at the emergency dispatch centre. A data form was completed by each

EMS personnel in cooperation with the attending physicians in charge of the patient. Data were uploaded to the registry system of the FDMA database server, checked for freedom from logical contradictions by a computer system, and confirmed as correct by the implementation working group of the FDMA. Incomplete data sheets were returned by the FDMA to the appropriate fire department for completion.

### *CRITICAL study registry*

The CRITICAL study registry has collected substantial data on OHCA patients after their arrival at the hospital, details of which were previously published. [18,22,23] For this registry, anonymised data were entered into the web sheet either by the physician or medical staff collaborating with the attending physician in charge of the patient. Then data were checked for freedom from logical contradictions. Finally, data were confirmed by the CRITICAL study registry committee, which consists of experts in emergency medicine and clinical epidemiology. Incomplete data sheets were returned by a committee member to the participating institution where they were made as complete as possible. Using five key items in both datasets, which were the prefecture of the occurrence of the OHCA, emergency call time, patient's age, patient's sex, and Cerebral Performance Category (CPC) scale one month after the OHCA event, in-hospital data were systemically combined with pre-hospital resuscitation data based on the All-Japan Utstein Registry from the FDMA. As mentioned above, pre-hospital information and in-hospital information from each source were checked separately before their combination.

### *In-hospital data collection*

The following information after arrival at the hospital was prospectively collected using a uniform data sheet: prefecture of the cardiac arrest, emergency call time, patient's age, patient's sex, cause of cardiac arrest, in-hospital treatments such as percutaneous coronary intervention, TTM, neurological status, and outcome. The cause of cardiac arrest was classified as either cardiac (acute coronary syndrome, other heart diseases, presumed cardiac cause) or non-cardiac (cerebrovascular diseases, respiratory diseases, malignant tumors, external causes including traffic injury, fall, hanging, drowning, asphyxia, drug overdose, or any other external cause). Each cause of cardiac arrest was determined by the physician in charge at the hospital. Specifically, entry into the presumed cardiac cause category was determined by exclusion of other possible causes.

### *Definition of "cardiac arrest"*

Cardiac arrest was defined as the cessation of cardiac mechanical activity confirmed through the absence of signs of circulation. [24] The signs of circulation were confirmed by emergency medical professionals by checking movements, breathing, pulsation of the carotid artery, and electrocardiogram. [24] These diagnoses were clinically made by the physicians in charge of the patient in collaboration with EMS personnel.

### *Definition of "first documented cardiac rhythm"*

When encountering a patient with sudden cardiac arrest, EMS personnel records cardiac rhythm by determining whether the carotid artery is pulsating and by a 3-lead electrocardiogram monitor. [25] In this study, we called this the first documented cardiac rhythm, which was subdivided into the first documented non-shockable cardiac rhythm and first documented shockable cardiac rhythm. [25]

### *Primary and secondary outcomes*

Primary outcome was favourable neurological outcome, which was designated according to a CPC scale of 1 or 2 one month after the cardiac arrest. The primary outcome was designated as "one-month favourable neurological outcome". Specifically, CPC 1 denotes good cerebral performance; CPC 2, moderate cerebral disability; CPC 3, severe cerebral disability; CPC 4, coma or vegetative state; and CPC 5, death. [26] The neurological status of survivors was evaluated by medical staff at each institution visited by the patient one month after the event. Secondary outcome was survival one month after the occurrence of cardiac arrest and was designated as "one-month survival" in this study.

### *Statistical analyses*

Non-linear univariable and multivariable logistic regression analyses and linear univariable and multivariable logistic regression analyses were performed to assess the time from the introduction of TTM to achieving the temperature target and the probability of primary and secondary outcomes. Variable factors that were biologically essential and thought to be associated with clinical outcomes were considered as important factors in the non-linear multivariable logistic regression model. [19,21–23,25,27] Those were patient's age (one-year increments), patient's sex (men, women), witness status (witnessed, none), bystander CPR (yes, no), first documented cardiac rhythm (shockable, non-shockable), temperature targets of TTM (≦33 °C, 34 °C, 35 °C, 36 °C), and temperature at the introduction of TTM (one-degree increments). To avoid overfitting and to confirm the robustness of our analyses, a score was calculated via principal component analysis based on the following: patient's age, patient's sex, witness status, bystander CPR, first documented cardiac rhythm, temperature at the implementation of TTM, coronary angiography, extracorporeal membrane oxygenation, and intra-aortic balloon pumping. Then this score was used to adjust for covariates in the logistic regression analyses**.** Moreover, we subdivided patients into groups of quintiles according to the time from the introduction of TTM to reaching the temperature targets to describe the association between patients' outcome and the time from implementation of targeted temperature management to reaching temperature targets in as much detail as possible. Based on these groups, patients' characteristics were summarised using median and interquartile ranges for continuous variables and numbers and proportions for categorical variables. To compare the probability of neurological outcome in each quintile**,** a multivariable logistic regression analysis was used to calculate the adjusted odds ratios (AORs) and 95% confidence intervals (CIs). To be used easily by most clinicians, the highest quintile of a one-month favourable neurological survival was regarded as a reference when calculating the AORs and 95%CIs. To explore the differences in outcomes between normothermia and hypothermia, patients were also divided into two groups according to temperature targets of ≦34 °C and ≧35 °C. Similarly, to explore the differences in outcomes based on the performance of percutaneous coronary intervention, patients were divided into two groups according to the presence and absence of the application of percutaneous coronary intervention. All statistical analyses were performed using R, version

4.0.1 (The R Foundation for Statistical Computing, Vienna, Austria). All tests were two-tailed, and a *p* value of <0.05 was considered statistically significant.

## Results

### *Flow of patients from multicentre cohort registry*

A total of 12,594 patients who had an OHCA during the study period were documented. After excluding patients who met the inclusion criteria but with missing data, 473 patients were eligible for analyses (Fig. 1).

### *Outcomes of non-linear multivariable logistic regression analysis*

Fig. 2a, Fig. 2b, Fig. 2c shows the probability of a one-month favourable neurological outcome after an OHCA according to the time from the implementation of TTM to achievement of the temperature targets. All associations between the initiation of TTM to achievement of the temperature targets and favourable neurological outcome at one month were significantly non-linear (*p* value for non-linearity <0.01). Similarly, Supplementary Figure-a, -b, -c shows the probability of one-month survival after an OHCA according to the time from the introduction of TTM to achievement of temperature targets.

### *Patients' baseline characteristics*

We subdivided patients into quintiles according to the time from the introduction of TTM to achieving the temperature targets. Characteristics of OHCA patients are shown in Table 1.

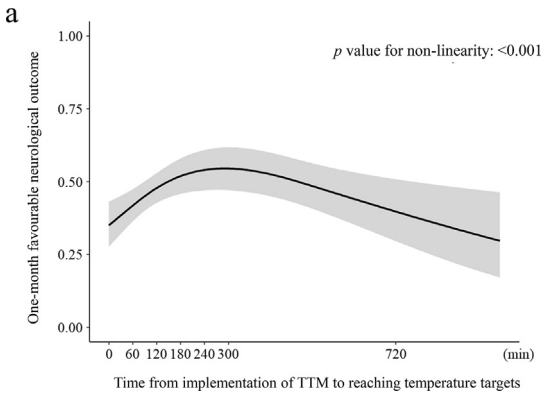


**Fig. 2a – Probabilities of one-month favourable neurological outcome after OHCA are shown based on the time from the implementation of TTM to reaching the temperature targets without adjustments.**

### *One-month favourable neurological outcome*

One-month favourable neurological outcome was highest in patients in the fourth quintile at 57.4% (54/94), followed by the third quintile at 53.5% (53/99) (Table 2). After adjusting for age, sex, witness status, bystander CPR, first documented cardiac rhythm, temperature targets of TTM, and temperature at the implementation of TTM, AORs with 95% CIs for one-month favourable neurological outcome in the first, second, third, and fifth quintiles compared with the fourth quintile as the reference were 0.38 (95%CI: 0.20 to 0.72), 0.43 (95%CI: 0.23 to 0.81), 0.77 (95%CI: 0.41 to 1.44), and 0.46 (95%CI: 0.25 to 0.87), respectively.

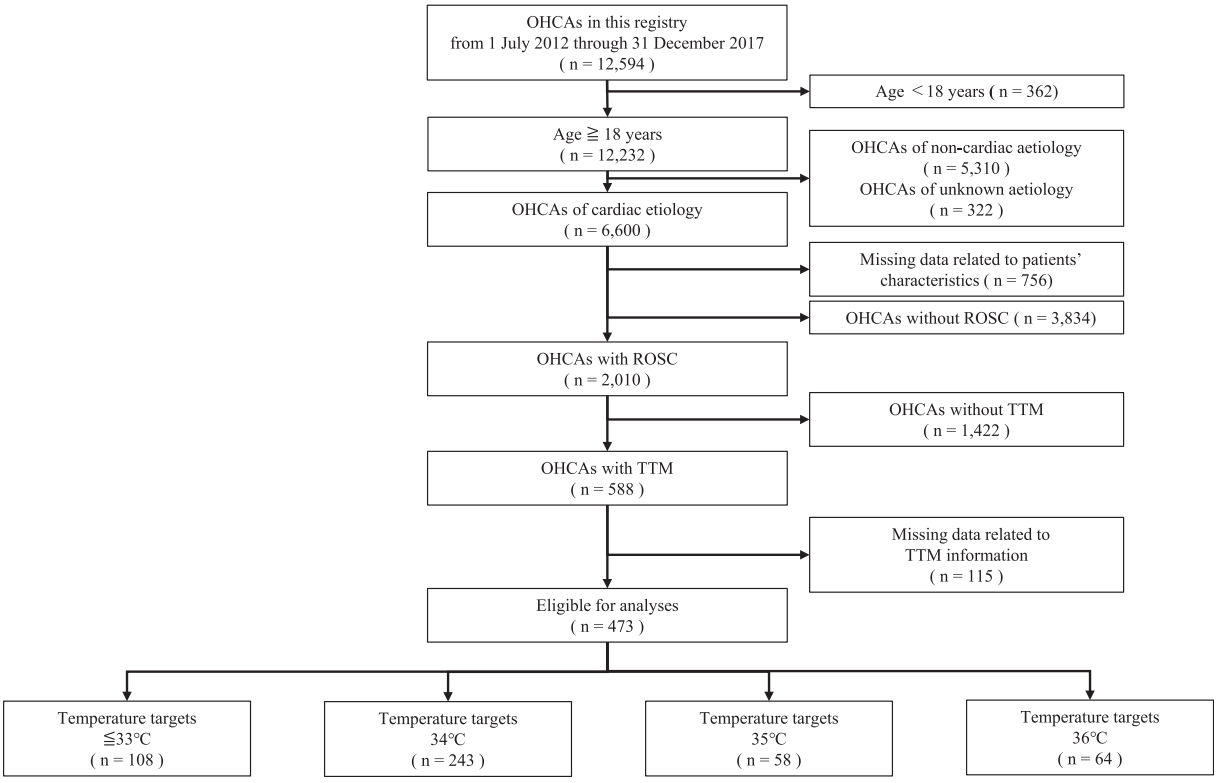


**Fig. 1 – Flow of patients from a hospital-based multicentre prospective observational registry. OHCA: out-of-hospital cardiac arrest; ROSC: return of spontaneous circulation; TTM: targeted temperature management.**

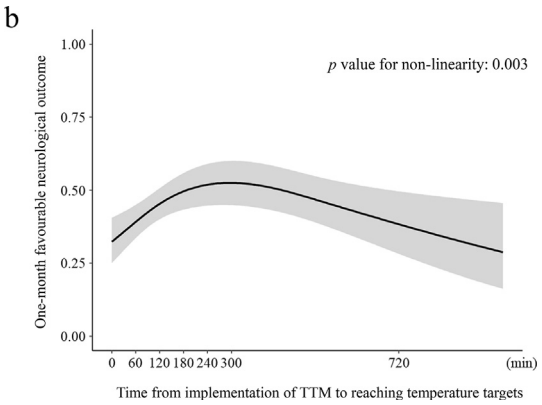


**Fig. 2b – Probabilities of one-month favourable neurological outcome after OHCA are shown based on the time from the implementation of TTM to reaching the temperature targets after adjustments for patient's age, patient's sex, witness status, cardiopulmonary resuscitation by bystanders, first documented cardiac rhythm, temperature targets for TTM, and temperature at the introduction of TTM.**

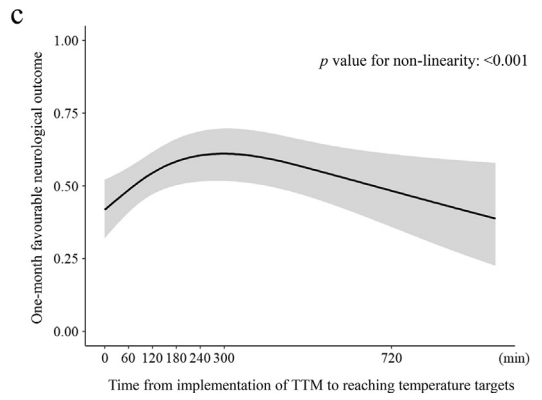


**Fig. 2c – Probabilities of one-month favourable neurological outcome after OHCA are shown based on the time from the implementation of TTM to reaching the temperature targets after adjusting calculated score by principal component analysis based on patient's age, patient's sex, witness status, bystander cardiopulmonary resuscitation, first documented cardiac rhythm, temperature at the implementation of TTM, coronary angiography, extracorporeal membrane oxygenation, and intra-aortic balloon pumping. These figures show *p* value for non-linearity to be <0.01 in the non-linear multivariable logistic regression analysis. Favourable neurological outcome was designated according to a cerebral performance category scale of 1 or 2. TTM: targeted temperature management; OHCA: out-of-hospital cardiac arrest; min: minutes.**

### *One-month survival*

One-month survival was highest in the fourth quintile at 76.6% (72/94), followed by that in the third quintile at 70.7% (70/99) (Table 2). The AORs with 95% CIs for one-month survival in the first, second, third, and fifth quintiles compared with the fourth quintile as the reference were 0.43 (95%CI: 0.22 to 0.82), 0.79 (95%CI: 0.40 to 1.55), 0.71 (95%CI: 0.37 to 1.37), and 0.57 (95%CI: 0.30 to 1.09), respectively.

### *Outcome in patients divided by two temperature targets: ≦34 °C or ≧35 °C*

For the probability of a one-month favourable neurological outcome in patients divided according to temperature targets, the *p* value for interaction of each temperature target was 0.253 and *p* value for non-linearity were 0.025 for ≦ 34 °C and 0.03 for ≥ 35 °C (Supplementary Figure-d).

### *Outcome in patients divided according to the performance of percutaneous coronary intervention*

For the probability of a one-month favourable neurological outcome in patients divided according to the presence or absence of percutaneous coronary intervention, the *p* value for interaction of each group was 0.479. Also, those for non-linearity were 0.01 for the presence of percutaneous coronary intervention and 0.122 for the absence of percutaneous coronary intervention (Supplementary Figure-e).

### *Outcomes of linear multivariable logistic regression analysis*

Supplementary Table 1 shows the probabilities of a one-month favourable neurological outcome and one-month survival after an OHCA according to the time from the implementation of TTM to achievement of the temperature targets using linear logistic regression.

## Discussion

Based on the time from the introduction of TTM to reaching the temperature targets, patients in the first (≤26.7 minutes), second, (26.8–89.9 minutes) and fifth quintiles (≥352.2 minutes) compared with the fourth quintile (175.2–352.1 minutes) had significantly poorer probabilities of a one-month favourable neurological outcome. Our results indicate that the body temperature of patients with a poor outcome would drop quickly because homeostasis was not maintained. In other words, the results of the current study may indicate that patients who reached the target temperature very early had lost the ability to regulate their body temperature. Various methods of stratification considering severity after return of spontaneous circulation have been used. [28,29] However, appropriate stratification of patients who recovered spontaneous circulation after an OHCA has not been established. The time from the introduction of TTM to reaching temperature targets may reflect biological reactions after cardiac arrest.

Previous studies indicated the benefit of low temperature targets for patients with cardiac arrest. [30,31] On the other hand, several meta-analyses focussing on randomised controlled trials showed that hypothermia improves neither survival nor neurological outcome after cardiac arrest and increases the risk of arrhythmias. [32–34] In fact, the latest clinical randomised controlled trial conducted by Dankiewicz et al. [4], i.e., the TTM2 trial, did not find differences among temperature targets, including avoidance of fever. Therefore, further exploration of this issue is required, including consideration of the time from the implementation of TTM to reaching temperature targets. Because the *p* value for interaction of each temperature target

**Table 1 – Baseline characteristics of patients experiencing out-of-hospital cardiac arrest.**

| Time from implementation of TTM to reaching temperature targets | All n = 473 | First quintile (–26.7 min) n = 95 | Second quintile (26.8–89.9 min) n = 90 | Third quintile (90.0–175.1 min) n = 99 | Fourth quintile (175.2–352.1 min) n = 94 | Fifth quintile (352.2– min) n = 95 |
|---|---|---|---|---|---|---|
| **Patinents' characteristics** | | | | | | |
| Age, year, median (IQR) | 64.0 (51.0, 72.0) | 65.0 (54.0, 73.0) | 65.0 (50.0, 73.0) | 60.0 (46.0, 73.0) | 63.0 (53.0, 71.0) | 65.0 (55.0, 72.0) |
| Men, n (%) | 379 (80.1) | 74 (77.9) | 73 (81.1) | 75 (75.8) | 74 (78.7) | 83 (87.4) |
| Witnessed by bystanders, n (%) | 365 (77.2) | 70 (73.7) | 73 (81.1) | 83 (83.8) | 68 (72.3) | 71 (74.7) |
| CPR performed by bystanders, n (%) | 372 (78.6) | 74 (77.9) | 74 (82.2) | 84 (84.8) | 69 (73.4) | 71 (74.7) |
| First documented shockable cardiac rhythm, n (%) | 343 (72.5) | 65 (68.4) | 65 (72.2) | 75 (75.8) | 70 (74.5) | 68 (71.6) |
| Temperature at the introduction of TTM, median (IQR) | 35.6 (34.7, 36.1) | 35.5 (34.2, 36.0) | 35.7 (35.1, 36.1) | 35.4 (34.4, 36.2) | 35.5 (34.9, 36.3) | 35.5 (34.6, 36.0) |
| **Information related to treatments** | | | | | | |
| Temperature targets, n (%) | | | | | | |
| ≦33 | 108 (22.8) | 18 (18.9) | 69 (76.7) | 84 (84.8) | 21 (22.3) | 70 (73.7) |
| 34 | 243 (51.4) | 33 (34.7) | 8 (8.9) | 7 (7.1) | 56 (59.6) | 12 (12.6) |
| 35 | 58 (12.3) | 20 (21.1) | 13 (14.4) | 8 (8.1) | 11 (11.7) | 13 (13.7) |
| 36 | 64 (13.5) | 24 (25.3) | 0 (0.0) | 0 (0.0) | 6 (6.4) | 0 (0.0) |
| Coronary angiography, n (%) | 372 (78.6) | 73 (76.8) | 66 (73.3) | 74 (74.7) | 77 (81.9) | 82 (86.3) |
| Percutaneous coronary intervention, n (%) | 182 (38.5) | 37 (38.9) | 31 (34.4) | 34 (34.3) | 36 (38.3) | 44 (46.3) |
| Intra-aortic balloon pumping, n (%) | 163 (34.5) | 38 (40.0) | 28 (31.1) | 26 (26.3) | 33 (35.1) | 38 (40.0) |
| Extracorporeal membrane oxygenation, n (%) | 194 (41.0) | 47 (49.5) | 36 (40.0) | 33 (33.3) | 37 (39.4) | 41 (43.2) |
| **Etiology of cardiac arrest** | | | | | | |
| Acute coronary syndrome, n (%) | 228 (48.2) | 50 (52.6) | 40 (44.4) | 45 (45.5) | 48 (51.1) | 45 (47.4) |
| Other heart diseases, n (%) | 152 (32.1) | 24 (25.3) | 29 (32.2) | 32 (32.3) | 34 (36.2) | 33 (34.7) |
| Presumed cardiac cause, n (%) | 93 (19.7) | 21 (22.1) | 21 (23.3) | 22 (22.2) | 12 (12.8) | 17 (17.9) |

IQR: interquartile range; CPR: cardiopulmonary resuscitation; TTM: targeted temperature management; min: minutes.

**Table 2 – One-month favourable neurological outcome and one-month survival after out-of-hospital cardiac arrest based on the time to reaching temperature targets.**

| Time from implementation of TTM to reaching temperature targets | First quintile (–26.7 min) n = 95 | Second quintile (26.8–89.9 min) n = 90 | Third quintile (90.0–175.1 min) n = 99 | Fourth quintile (175.2–352.1 min) n = 94 | Fifth quintile (352.2– min) n = 95 |
|---|---|---|---|---|---|
| One-month favourable neurological outcome, n (%) | 31 (32.6) | 36 (40.0) | 53 (53.5) | 54 (57.4) | 36 (37.9) |
| Crude odds ratio (95% confidence intervals) | 0.36 (0.20 to 0.65) | 0.49 (0.27 to 0.89) | 0.85 (0.48 to 1.51) | Reference | 0.45 (0.25 to 0.81) |
| Adjusted odds ratio (95% confidence intervals)* | 0.36 (0.20 to 0.66) | 0.46 (0.25 to 0.84) | 0.78 (0.44 to 1.41) | Reference | 0.45 (0.25 to 0.82) |
| Adjusted odds ratio (95% confidence intervals)† | 0.38 (0.20 to 0.72) | 0.43 (0.23 to 0.81) | 0.77 (0.41 to 1.44) | Reference | 0.46 (0.25 to 0.87) |
| One-month survival, n (%) | 53 (55.8) | 65 (72.2) | 70 (70.7) | 72 (76.6) | 60 (63.2) |
| Crude odds ratio (95% confidence intervals) | 0.39 (0.21 to 0.72) | 0.79 (0.41 to 1.54) | 0.74 (0.39 to 1.41) | Reference | 0.52 (0.28 to 0.99) |
| Adjusted odds ratio (95% confidence intervals)* | 0.39 (0.21 to 0.73) | 0.79 (0.41 to 1.53) | 0.73 (0.38 to 1.39) | Reference | 0.52 (0.28 to 0.99) |
| Adjusted odds ratio (95% confidence intervals)† | 0.43 (0.22 to 0.82) | 0.79 (0.40 to 1.55) | 0.71 (0.37 to 1.37) | Reference | 0.57 (0.30 to 1.09) |

TTM: targeted temperature management; min: minutes.

Favourable neurological outcome is defined as Cerebral Performance Category score 1 or 2.

* Adjusted odds ratios and 95% confidence intervals were adjusted for patients' age and sex.

† Adjusted odds ratios and 95% confidence intervals were adjusted for patients' age and sex, witness status, bystander cardiopulmonary resuscitation, first documented cardiac rhythm, temperature targets, and temperature at the implementation of TTM.

was more than 0.05 (Supplementary Figure-d), the current study did not find completely different biological effects among temperature targets. However, further research is required because the number of analysed patients in the current study was not large. An additional observational study with an expanded study population is needed. Findings from interventional studies also are required to improve the TTM protocol on the association between neurological outcome of patients with OHCA and the time from the introduction of TTM to reaching the temperature targets. Especially, a large randomised controlled trial is desired in which patients experiencing OHCA will be randomised according to the time from the implementation of TTM to achieving temperature targets before the implementation of TTM.

Results did not show a significant difference between the presence and absence of a percutaneous coronary intervention because the *p* value for the interaction of each group was >0.05 (Supplementary Figure-e). This result reinforced the robustness of the current findings. On the other hand, although the *p* value for non-linearity for the presence of a percutaneous coronary intervention was <0.05, the *p* value for non-linearity for the absence of a percutaneous coronary intervention was >0.05. This difference may indicate that the percutaneous coronary intervention would extend the time to reaching temperature targets. However, as the registry data were limited, it is impossible to further investigate the difference related to the performance of percutaneous coronary interventions. More extensive research is required to obtain additional knowledge in this field.

Our study has several strengths. Firstly, this multicentre cohort study using pre-hospital data and in-hospital data of all consecutive patients provided robust data and scant missing information. Secondly, we used a non-linear multivariable logistic regression analysis to identify the association between patient outcomes and the time from the introduction of TTM to achieving temperature targets. These findings showed that non-linear multivariable logistic regression analysis could be applied in the evaluation of the association between neurological outcome after an OHCA and the time from the introduction of TTM to reaching temperature targets.

This study also has several limitations. First, we must address critical selection bias. Future guidelines could incorporate an approach to avoid fever (>37.5 °C) according to the findings from the landmark clinical trial by Dankiewicz et al. [4] However, before that study's publication, the present study used registry data collected from 1 July 2012 through 31 December 2017. Therefore, we could not evaluate the association between patients' outcomes and the time from the introduction of TTM to achieving temperature targets that included an approach to avoid fever (>37.5 °C). In addition, quintiles of each temperature target did not include an equal number of patients. However, after adjusting for several factors including temperature targets in TTM, we confirmed that findings were similar compared with the results without adjustment which led to the belief that selection bias was limited. Furthermore, the current registry did not include all hospitals in Osaka, Japan although we enrolled all OHCA patients transported to the participating institutions. Second, we must address information bias in this study. Persons in charge of evaluation of patients' outcomes in this study were not blinded. However, they evaluated the outcomes based on a CPC scale derived from hospital medical records which would limit information bias regarding this issue. Third, as in previous observational studies, unmeasured factors may have influenced the association between the time from the implementation of TTM to achievement of the temperature targets and patients' outcome. The registry used in the current study did not provide data on brain damage after cardiac arrest and the exact time from collapse to initiation of resuscitation. Additionally, we were unable to assess several important factors such as quality of CPR performed by bystanders; quality of CPR performed by medical professionals; bystanders' characteristics, including age, sex, weight, and experience with basic life support; bystanders' occupations (medical professional or not); strategy of each participating institution for providing specialised treatments after cardiac arrest; and the detailed TTM protocols at each participating hospital and non-participating hospital in Japan, including how to choose the cooling device and the general criteria for TTM. These major unmeasured factors may have caused a critical bias in our findings. Finally, we should note that the registry used for this study is not an international collaborative registry, but a local registry limited to Japan. Therefore, our findings may not be fully applicable in other regions due to differences in legislation and in systems of emergency medicine worldwide.

## Conclusions

The findings of the current study showed that non-linear multivariable logistic regression analysis could clearly describe the association between neurological outcome after the occurrence of OHCA and the time from the introduction of TTM to reaching the temperature targets. To obtain additional knowledge for appropriate TTM practice, a large randomised controlled trial is desired in which patients experiencing OHCA would be randomised according to the time from the implementation of TTM to achieving temperature targets before the implementation of TTM. Further findings from such a randomised controlled trial would aid in updating guideline for clinical practice of TTM for patients with cardiac arrest.

## CRediT authorship contribution statement

**Tetsuro Nishimura:** Writing – review & editing, Visualization, Software, Resources, Investigation, Conceptualization. **Toshihiro Hatakeyama:** Writing – review & editing, Writing – original draft, Visualization, Validation, Project administration, Methodology, Investigation, Conceptualization. **Hisako Yoshida:** Writing – review & editing, Visualization, Software, Methodology, Investigation, Formal analysis, Conceptualization. **Satoshi Yoshimura:** Writing – review & editing, Data curation. **Takeyuki Kiguchi:** Writing – review & editing, Data curation. **Taro Irisawa:** Writing – review & editing, Data curation. **Tomoki Yamada:** Writing – review & editing, Data curation. **Kazuhisa Yoshiya:** Writing – review & editing, Data curation. **Changhwi Park:** Writing – review & editing, Data curation. **Takuya Ishibe:** Writing – review & editing, Data curation. **Yoshiki Yagi:** Writing – review & editing, Data curation. **Masafumi Kishimoto:** Writing – review & editing, Data curation. **Sung-Ho Kim:** Writing – review & editing, Data curation. **Yasuyuki Hayashi:** Writing – review & editing, Data curation. **Yusuke Ito:** Writing – review & editing, Data curation. **Taku Sogabe:** Writing – review & editing, Data curation. **Takaya Morooka:** Writing – review & editing, Data curation. **Haruko Sakamoto:** Writing – review & editing, Data curation. **Keitaro**

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## Declaration of competing interest

Osaka Metropolitan University and Dokkyo Medical University are attempting to file a patent application in Japan on the current findings. Tetsuro Nishimura from Osaka Metropolitan University and Toshihiro Hatakeyama from Dokkyo Medical University will be listed as inventors on the patent application related to this study. Toshihiro Hatakeyama also received an overseas scholarship from Dokkyo Medical University. Yohei Okada received a research grant from the ZOLL Foundation, an overseas scholarship from the FUKUDA Foundation for medical technology and a research grant from the International Medical Research Foundation. These organizations have no role in conducting this research. The other authors have no financial and personal relationships to declare.

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## Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resplu.2024.100607.

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