

# Lower target temperature management in patients with post-cardiac arrest syndrome could not show advantage, with or without resuscitation interval $\leq 30$ minutes. Retrospective analysis of nationwide multi-center observational study in Japan

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## Abstract

**Introduction:** Target temperature management (TTM) is one of the effective therapies for patients with post-cardiac arrest syndrome (PCAS). A low target temperature is traditionally believed to be more effective, but this has not been confirmed in recent studies, even in any patient subgroup. Our previous study suggested the possible effectiveness of low TTM for patients with PCAS when the period from collapse to the return of spontaneous circulation (ROSC) is  $\leq 30$  minutes. Therefore, we tested this hypothesis in a nationwide Japanese registry.

**Methods:** This was a retrospective subanalysis based on a registry of patients who experienced out-of-hospital cardiac arrest (OHCA), which was established by the Japanese Association for Acute Medicine. Witnessed cases of adult OHCA were selected. Univariate and multivariate analyses were used to compare the neurolog-

ical outcomes of patients treated with low (32-33 °C) or mild (34-36 °C) TTM or no temperature management. The analysis was performed in both the total patients and in patients in whom the interval from collapse to ROSC was  $\leq 30$  minutes.

**Results:** We analyzed 1763 cases of PCAS. There was no significant difference in the neurological outcomes of patients treated with low or mild TTM, with or without an interval from collapse to ROSC of  $\leq 30$  minutes. However, neurological outcomes of patients treated with low or mild TTM differed significantly from no temperature management, with or without an interval from collapse to ROSC of  $\leq 30$  minutes.

**Conclusions:** Even in the subgroup in which the interval from collapse to ROSC was  $\leq 30$  minutes, neurological outcomes in the low TTM group did not differ significantly from those in the mild TTM group.

**Key words:** Therapeutic hypothermia, neurological outcome, cerebral performance category.

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## Introduction

In Japan, a population-based observational study suggested that the neurological outcomes of patients with out-of-hospital cardiac arrest (OHCA) has improved nationwide. (1) This improvement is related to increased public access to automated external defibrillation, bystander-initiated chest compression, and the earlier responses of emergency medical services. This nationwide epidemiological analysis suggested that the apparent improvement in neurological outcomes was related solely to prehospital factors.

Conventionally, therapeutic hypothermia (TH) for patients with post-cardiac arrest syndrome (PCAS) arising from OHCA is one of the therapies expect-

ed to improve the neurological outcome in these patients. The efficacy of TH was reported in two conventional randomized controlled trials (RCTs) in 2002. (2,3) Both RCTs showed that TH of 32-34 °C for 12-24 h improved the neurological outcome; however, a more recent report (Nielsen, et al, 2013) suggested that the effectiveness of target temperature management (TTM) is determined by the target temperature, but that the target temperature does not affect the neurological outcome (even 33 °C or 36 °C). (4) Therefore, the current theory holds that only anti-fever treatment is useful for patients with PCAS.

Traditionally, TH was expected to exert a neuroprotective effect on post brain ischemia, and the effect of TH was demonstrated with behavioral and histological assessments in an experimental model. (5) We hypothesized that the subgroup, which is similar setting of experimental model, could be treatable by TH, which is replaced as lower TTM. We also consider that the ischemic interval is the most important factor in PCAS. In our previous study, we suggested that a lower TTM better improves the neurological outcome than a higher TTM in patients with PCAS when the interval from collapse to the return of spontaneous circulation (ROSC) is  $\leq 30$  minutes. (6) Here, we tested whether another analysis with the same cut-off value would confirm the effectiveness of low TTM in a different database of patients with OHCA.

In Japan, the Japanese Association for Acute Medicine (JAAM) established a registry of OHCA in 2014. This registry categorizes patients as receiving TTM, with target temperatures of 32-36 °C, or as not receiving temperature treatment. We performed a secondary analysis of the JAAM-OHCA Registry to investigate the relationship between TTM and neurological outcome in patients with PCAS. The neurological outcomes were compared in all witnessed cases of OHCA treated with low or mild TTM or no temperature management. We also compared the results of patients in whom the interval between collapse and ROSC was  $\leq 30$  minutes. Our hypothesis was that lower TTM better improves the neurological outcomes of PCAS patients than mild TTM, when the interval between collapse and ROSC is  $\leq 30$  minutes.

## Methods

### *Study design*

In this study, we used the JAAM-OHCA Registry, a prospective cohort database of PCAS patients at 288 Japanese critical-care medical centers. The registry was approved by the Ethics Committee of Kyoto University, the corresponding institution,

and each hospital also approved the JAAM-OHCA Registry protocol. In this study, the database entries from June 2014 to December 2015 were accessed, and this subanalysis was performed as a retrospective cohort study.

### *Patients*

From June 2014 to December 2015, the JAAM-OHCA Registry recorded 13,491 cases of OHCA in Japan. Patients satisfying the following criteria were eligible for registration: (1) collapse with OHCA was witnessed; (2) no extracorporeal cardiopulmonary resuscitation; (3) ROSC and hospitalization; and (4) older than 18 years. The selection and enrolment of patients is shown in **Figure 1**. Ultimately, 1763 patients with OHCA were deemed eligible for the study.

### *Study outcomes and statistical analysis*

Each patient's neurological outcome was assessed with the Glasgow-Pittsburgh Cerebral Performance Category (CPC), which includes five categories: CPC 1 (good recovery), CPC 2 (moderate disability), CPC 3 (severe disability), CPC 4 (vegetative state), and CPC 5 (death). (7) In the present study, a favorable neurological outcome was defined as CPC 1-2 at 1 month after collapse.

In the JAAM-OHCA Registry, the target temperature was categorized as 32 °C, 33 °C, 34 °C, 35 °C, or 36 °C, or as no temperature management. In the present study, TTM was divided into three categories: low TTM (32-34 °C), mild TTM (35-36 °C), and no TTM. A target temperature of 35-36 °C was defined as mild because the recommended TTM before 2015 was 32-34 °C, which we treated as the low TTM.

The patients were divided into two groups: the favorable (CPC 1-2) and unfavorable (CPC 3-5) neurological outcome groups. They were then compared using univariate and multivariate analyses. The univariate analysis was performed with the Mann-Whitney U test or Fisher's exact test, as appropriate. The multivariate analysis was performed with a logistic regression analysis, in which the objective variable was a favorable neurological outcome (CPC 1-2). The variables tested were age, sex (male), bystander cardiopulmonary resuscitation (BCPR), ventricular fibrillation/ventricular tachycardia as the initial rhythm (VF/VT), cardiogenic cardiac arrest, total Glasgow Coma Scale (GCS) at ROSC, interval from collapse to ROSC, and category of the TTM. The variables (described above) were analyzed in all eligible patients, according to whether the interval from collapse to ROSC was  $\leq 30$  minutes.

All statistical analyses were performed with SPSS version 16.0 (IBM, Armonk, NY, USA).

## Results

The registry included 13,491 patients, and 1763 patients met the inclusion criteria (witnessed OHCA, no extracorporeal CPR, hospitalization, and older than 18 years) and were therefore eligible for the study (**Figure 1**). A total of 408 patients received TTM, 25 patients (6%) were treated by intravascular cooling, and the others (94%) were treated by surface cooling only.

**Table 1** compares the patient groups with favorable (CPC 1-2) and unfavorable (CPC 3-5) neurological outcomes, including all the patients analyzed. A multivariate analysis detected significant differences between the groups in age, BCPR, VF/VT, cardiogenic cardiac arrest, total GCS at ROSC, and target temperature. However, the percentage with a favorable outcome among patients treated with mild TTM (35-36 °C) group differed significantly from that for patients treated no TTM group ( $p=0.003$ ), as was also the case for patients treated with low TTM (32-34 °C) group ( $p<0.001$ ). The patients treated with low TTM (32-34 °C) did not differ from those treated with mild TTM (35-36 °C) in terms of the percentage with a favorable (CPC 1-2) neurological outcome (odds ratio 1.140 [0.627-2.071],  $p=0.668$ ; these data are not listed in Table 1).

**Table 2** compares the favorable (CPC 1-2) neurological outcome among the three groups for which the interval between collapse and ROSC was  $\leq 30$  minutes. The multivariate analysis showed that the outcome groups differed significantly in age, BCPR, VF/VT, cardiogenic cardiac arrest, total GCS at ROSC, the interval from collapse to ROSC, and the target temperature. However, the target temperature only differed significantly between the no TTM and mild TTM (35-36 °C) groups ( $p=0.022$ ), and between the no TTM and low TTM (32-34 °C) groups ( $p=0.002$ ). The patients treated with low TTM (32-34 °C) did not differ from those treated with mild TTM (35-36 °C) in terms of the percentage with a favorable (CPC 1-2) neurological outcome (odds ratio 0.934 [0.438-1.992],  $p=0.860$ ; these data are not listed in Table 2).

**Figure 2** compares the favorable (CPC 1-2) neurological outcome among the three groups in all cases, collapse to ROSC was  $\leq 30$  minutes, and  $>30$  minutes. Favorable (CPC 1-2) neurological outcome in the low TTM (32-34 °C) group did not differ significantly from that in the mild TTM (35-36 °C) group. However, favorable (CPC 1-2) neu-

rological outcome of the low TTM (32-34 °C) or the mild TTM (35-36 °C), differ from no TTM (mild TTM vs no TTM:  $p<0.01$ , low TTM vs no TTM:  $p<0.001$ ).

## Discussion

In this study, the low TTM regimen did not improve the neurological outcome better than the mild TTM, even among patients in whom the interval from collapse to ROSC was  $\leq 30$  minutes. However, both the low and mild TTM groups showed significant improvement in their neurological outcomes compared with the no TTM group. Unexpectedly, the efficacy of TTM was demonstrated. The improvement in neurological outcome afforded by TTM was also observed in the patients in whom the interval from collapse to ROSC was  $\leq 30$  minutes.

We used the interval from collapse to ROSC to indicate the severity of PCAS, but could not demonstrate that the low TTM regimen improved the neurological outcome better than mild TTM. Based on a similar assumption that PCAS severity is determined by the resuscitation interval, another study suggested that low TTM improves the outcome, especially in PCAS patients with a 'no flow time' of  $>8$  minutes. (8) However, the post hoc analysis in Nielsen's RCT showed no advantage of lower TTM, (9) so that the no flow time is not a factor that can be used to identify PCAS patients who might benefit from TTM. In this study, the no flow time could not be calculated from the registry data, so the 'no flow time' hypothesis was not tested.

Although our hypothesis and the main theme of this study was not that optimal TTM would improve the outcomes of patients with PCAS, our data suggest that controlled (target) temperature management confers an advantage over no temperature management in patients with PCAS. The earliest RCTs also demonstrated this advantage, and those studies showed the greater effectiveness of low TTM than no TTM. (2,3) Recent studies have also shown that there was no optimal target temperature in the range of 32-36 °C, (4,10) even in terms of cognitive function. (11) In addition, the neurological outcomes for each target temperature were compared using a nationwide database, revealing no significant differences. (12) Although our data was a significant difference in the outcomes of the no TTM group and both TTM groups, there also showed no significant difference in the neurological outcomes of patients treated with low and mild TTM. These differences were observed in both settings, with or without an interval from col-

lapse to ROSC of  $\leq 30$  minutes.

We only compared mild (35-36 °C), low (32-34 °C), and no TTM, whereas in our previous study we compared mild (34-35 °C) and low (32-33.5 °C) target temperatures. (6) In this study, only 15 patients were treated with a target temperature of 32 or 33 °C, whereas most were treated with TTM of 34-36 °C. Favorable neurological outcomes occurred in 33% (5/15 cases) of those 15 patients (32 or 33 °C), and in 57% (4/7 cases) of those in whom the interval from collapse to ROSC was  $\leq 30$  minutes, which was a superior outcome. However, the sample size was too small to ensure a valid analysis. The use of low TTM has decreased in Japan since the study of Nielsen, et al. (4)

In the present study, the nationwide cohort data did not include the body temperature during TTM. Therefore, the division of patients into groups was based solely on treatment policy, and it remains possible that the groups analyzed in this study did not reflect the actual body temperatures of the patients. In addition, in the clinical setting the physician tends to use TTM for patients who are expected to have a good neurological outcome. The use of multivariate analysis might reduce this selection bias; however, this effect still has the possibility of affecting our results.

This study has several limitations. First, although it included a nationwide cohort, the study was performed retrospectively, so there will have been some bias. Second, the neurological outcomes were assessed with CPC at 1 month after resuscitation, and it is possible that this assessment might have changed after 6 months or 1 year. Third, most patients were not treated with TTM, so the treated population was small.

## Conclusions

In a nationwide Japanese cohort study, there was no significant difference in the neurological outcomes of PCAS patients treated with low or mild TTM, regardless of whether the interval between collapse to ROSC was more or less than 30 minutes. However, TTM might improve the neurological outcomes of these patients compared with those not treated with TTM.

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## Authors' contributions

All the authors conceived and designed the study, wrote the study protocol, and contributed to the acquisition of clinical data. KO and TK contributed equally to the study, and performed the statistical analyses and wrote the first draft of the manuscript. All the authors revised and commented on the manuscript, and approved the final version.

**Table 1.** Total patients

Variable	CPC 1-2 (n=355)	CPC 3-5 (n=1408)	Univariate p value	Multivariate p value	Odds ratio (95% CI)
Age (years)	61 (50-73)	76 (65-84)	<0.001	<0.001	0.966 (0.956-0.976)
Male	262 (74%)	834 (59%)	<0.001	0.573	0.898 (0.619-1.303)
BCPR	204 (57%)	561 (40%)	<0.001	0.031	1.451 (1.036-2.034)
VF/VT	195 (55%)	146 (10%)	<0.001	<0.001	4.497 (3.053-6.623)
Cardiogenic	318 (90%)	732 (52%)	<0.001	<0.001	3.035 (1.934-4.763)
GCS at ROSC	3 (3-9)	3 (3-3)	<0.001	<0.001	1.629 (1.489-1.782)
Interval from collapse to ROSC (min)	13 (8-18)	35 (24-47)	<0.001	0.832	1.000 (0.997-1.002)
Target temperature			<0.001	<0.001	
- None	183 (52%)	1163 (83%)	Reference	Reference	1.000
- 35-36 °C	33 (9%)	64 (5%)	<0.001	0.003	2.443 (1.355-4.406)
- 32-34 °C	136 (39%)	175 (12%)	<0.001	<0.001	2.784 (1.866-4.154)

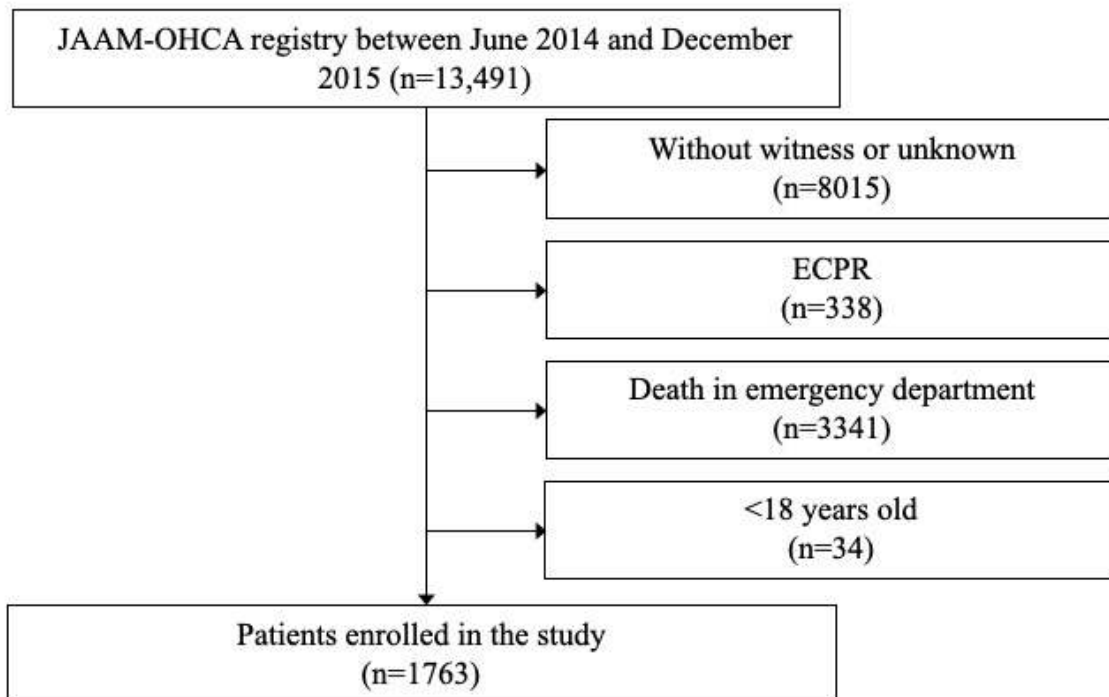
Legend: Data are median values (interquartile range). BCPR=bystander cardiopulmonary resuscitation; VF=ventricular fibrillation; VT=ventricular tachycardia; GCS=Glasgow coma scale; ROSC=return of spontaneous circulation; CPC=Glasgow-Pittsburgh Cerebral Performance Category; CI=confidence intervals.

**Table 2.** Patients in whom the interval from collapse to ROSC was ≤30 minutes

Variable	CPC 1-2 (n=318)	CPC 3-5 (n=511)	Univariate p value	Multivariate p value	Odds ratio (95% CI)
Age (years)	62 (50-73)	76 (66-83)	<0.001	<0.001	0.953 (0.939-0.967)
Male	237 (75%)	307 (60%)	<0.001	0.226	0.745 (0.462-1.200)
BCPR	185 (58%)	177 (35%)	<0.001	<0.001	2.446 (1.556-3.846)
VF/VT	175 (55%)	64 (13%)	<0.001	<0.001	3.911 (2.337-6.545)
Cardiogenic	285 (90%)	258 (50%)	<0.001	<0.001	4.046 (2.343-6.988)
GCS at ROSC	3.5 (3-10)	3 (3-3)	<0.001	<0.001	1.254 (1.145-1.373)
Interval from collapse to ROSC (min)	12 (7-17)	21 (15-26)	<0.001	<0.001	0.859 (0.830-0.888)
Target temperature			<0.001	0.004	
- None	164 (52%)	385 (76%)	Reference	Reference	1.000
- 35-36 °C	30 (10%)	35 (7%)	0.008	0.022	2.388 (1.133-5.034)
- 32-34 °C	121 (38%)	87 (17%)	<0.001	0.002	2.230 (1.327-3.747)

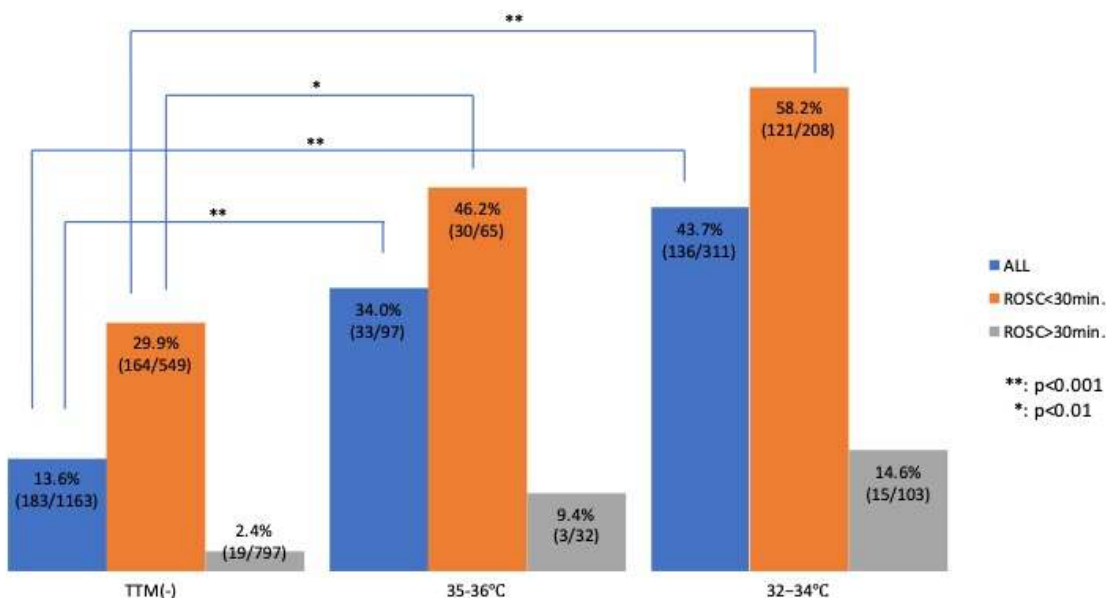
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**Figure 1.** Selection and inclusion of patient data



Legend: JAAM-OHCA=Japanese Association of Acute Medicine-out-of-hospital cardiac arrest; ECPR=extracorporeal cardiopulmonary resuscitation. A total of 1763 patients were considered eligible after the inclusion criteria were applied (witnessed, no extracorporeal cardiopulmonary resuscitation, survival in the Emergency Department, and older than 18 years).

**Figure 2.** Comparison of neurological outcomes among all cases, the group of ROSC  $\leq$ 30 minutes, and ROSC >30 minutes



Legend: ROSC=return of spontaneous circulation; TTM=target temperature management.

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