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ORIGINAL RESEARCH

Effect of different combinations of initial body temperature and target temperature on neurological outcomes in out-of-hospital cardiac arrest patients treated with targeted temperature management

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Abstract

We hypothesized that different combinations of initial and target temperatures during targeted temperature management (TTM) may be associated with neurological outcomes in out-of-hospital cardiac arrest (OHCA) survivors. Adult patients with OHCA who underwent TTM were enrolled. The study participants were divided into four groups: lower initial body temperature and lower target temperature (Low-Low group), lower initial body temperature and higher target temperature (Low-High group), higher initial body temperature and lower target temperature (High-Low group), and higher initial body temperature and higher target temperature (High-High group). Initial body temperature was dichotomized based on the median value (35.6 °C) as a cutoff, and the target temperature was dichotomized with a target temperature of 34 °C as a cutoff. The primary outcome was defined as a favorable 28-day neurological outcome. In total, 231 patients were included in the analysis, and 74 (32.0%), 43 (18.6%), 82 (35.5%), and 32 (13.9%) patients were classified into the Low-Low, Low-High, High-Low, and High-High groups, respectively. The proportion of patients with favorable 28-day neurological outcomes differed among the study groups (Low-Low, 14 (18.9%); Low-High, 7 (16.3%); High-Low, 37 (45.1%); High-High, 11 (34.4%); $p = 0.001$). In the multivariable analysis, the Low-High group was independently associated with a less favorable 28-day neurological outcome compared to the High-Low group (adjusted odds ratio, 0.22; 95% confidence interval, 0.06–0.91; $p = 0.036$). In conclusion, higher initial body temperature and lower target temperature during TTM were independently associated with a more favorable 28-day neurological outcome compared to the lower initial body temperature and higher target temperature in patients resuscitated from OHCA of medical etiology.

Keywords

Cardiac arrest; Targeted temperature management; Hyperthermia; Hypothermia

1. Introduction

Out-of-hospital cardiac arrest (OHCA) is an important health and economic problem. The incidence of OHCA ranges from 52.5 to 112.9 per 100,000 person-years worldwide, and most patients do not often achieve neurologically favorable recovery after OHCA [1–3], causing a substantial economic burden [4, 5].

Current international guidelines recommend TTM in comatose survivors of cardiac arrest to improve neurological outcomes [6, 7]. Guidelines recommend that body temperature should be maintained between 32 °C and 36 °C during TTM. However, a specific target temperature for an individual patient was not provided, and the target temperature range did not consider the initial temperature.

Hyperthermia after cardiac arrest and return of spontaneous circulation (ROSC) have been associated with unfavorable neurological outcomes in cardiac arrest survivors before the wide implementation of targeted temperature management (TTM) [8–10]. The mechanisms underlying brain injury after ischemia-reperfusion are yet to be fully understood; however, some are exaggerated in a dose-dependent manner as the temperature rises [11–13]. Thus, the same maintenance temperature during TTM can lead to more severe neurological injury in patients with a lower initial temperature after ROSC because the temperature gap is larger in these patients.

The association between hyperthermia and unfavorable neurological outcomes is well-known in cardiac arrest survivors treated with TTM [14–17]. If a cardiac arrest victim's initial temperature is very low and they are treated with a higher target temperature (*e.g.*, 36 °C), the patient may be exposed to relatively higher temperatures during TTM, which may affect neurological outcomes. However, we do not know whether different initial body temperatures and different target temperatures during TTM simultaneously affect neurological outcomes in cardiac arrest survivors treated with TTM. To be more specific, a target temperature that is relatively higher than the initial body temperature during TTM may be less neuroprotective or even harmful, whereas a relatively lower target temperature may be more neuroprotective. We hypothesized that different combinations of initial and target temperatures during TTM may be associated with neurological outcomes in OHCA survivors.

2. Methods

2.1 Study design and setting

We performed a retrospective analysis of prospectively collected registry data from three academic hospitals (A, B, and C) in the Republic of Korea from December 01, 2013, to December 31, 2018. OHCA patients admitted to the emergency departments of these study hospitals who achieved ROSC were included.

The registry consists of prehospital-level variables, including age, sex, baseline cerebral performance category (CPC) score, height, weight, past medical history, current medication, witnessed cardiac arrest, bystander cardiopulmonary resuscitation (CPR), initial electrocardiography rhythm, total no-flow time, total low-flow time, and hospital-level variables. Total no-flow time was defined as the interval between recognition of cardiac arrest and initiation of bystander or emergency medical service-provided CPR, and total low-flow time was defined as the interval between initiation of CPR and achievement of sustained ROSC.

2.2 Study population

Patients who fulfilled the following criteria were eligible for inclusion: (1) age $\geq$18 years, (2) OHCA due to medical causes, and (3) treatment with TTM. Patients were excluded if (1) initial body temperature data were missing, (2) target temperature data during TTM were missing, (3) primary outcome data were missing, (4) the patients had received extracorporeal membrane oxygenation, and (5) the baseline CPC score was equal to or higher than 3.

2.3 Post-resuscitation care

Patients who achieved ROSC were provided post-resuscitation care, including TTM, in compliance with the latest international guidelines for CPR and post-resuscitation care [18, 19]. The target temperature was set according to clinical decisions made by the physicians on duty at the time of TTM initiation, and the target temperature was maintained for at least 24 h. In hospitals A and B, a randomized controlled trial was conducted from August 2016 to December 2019, in which post-cardiac arrest patients treated with TTM were enrolled [20]. The target temperature during TTM in the patients who were enrolled in the trial was randomly set at 33 °C or 36 °C, according to the allocated groups, and only 32 patients in hospital A were included in both the randomized trial and this study. TTM was provided using external cooling devices in all participating hospitals. Neuroprognostication was performed according to independent protocols for each institution, which consisted of electroencephalography, serial serum neuron-specific enolase measurements, and more prognostic measures.

2.4 Patient groups and outcome measures

To evaluate the effect of initial body temperature and target temperature during TTM on neurological outcomes, we divided the study participants into four groups according to the initial body temperature and target temperature during TTM: lower initial body temperature and lower target temperature group (Low-Low group), lower initial body temperature and higher target temperature group (Low-High group), higher initial body temperature and lower target temperature group (High-Low group), and higher initial body temperature and higher target temperature group (High-High group). Initial body temperature was dichotomized based on the median value of the initial body temperature, and the target temperature was dichotomized with a target temperature of 34 °C, which is in the middle of the recommended TTM target range according to the current guidelines [7]. The primary outcome was defined as the neurological outcome on Day 28. We defined a favorable neurological outcome as a CPC score of 1 or 2, and an unfavorable neurological outcome as a CPC score of 3, 4, or 5. The secondary outcome was 28-day survival.

2.5 Data analysis

Continuous variables are presented as the mean $\pm$ standard deviation, whereas categorical variables are presented as n (%). Student's *t*-test or Wilcoxon rank sum test was used to compare continuous variables, while the chi-square test or Fisher's exact test was used to compare categorical variables, as appropriate. We performed a post-hoc chi-square test or Fisher's exact test with Bonferroni correction to compare the primary and secondary outcomes among the study groups. Linear mixed effect models were used to analyze differences in body temperature during TTM according to study group and the presence of group-time interactions.

Univariable logistic regression analyses were performed using predictor variables for the primary outcome. Continuous variables, including age, total no-flow time, total low-flow time, blood urea nitrogen, serum creatinine, total bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, prothrombin time, serum troponin I, arterial pH, serum lactate, and Acute Physiology and Chronic Health Evaluation (APACHE) II score were dichotomized according to their median values, while mean arterial pressure and heart rate were dichotomized according to their own cut-off values for normal ranges (65 mmHg and 90 mmHg for mean arterial pressure and 50 beats per min and 100 beats per min for heart rate). Multivariable logistic regression analysis was performed

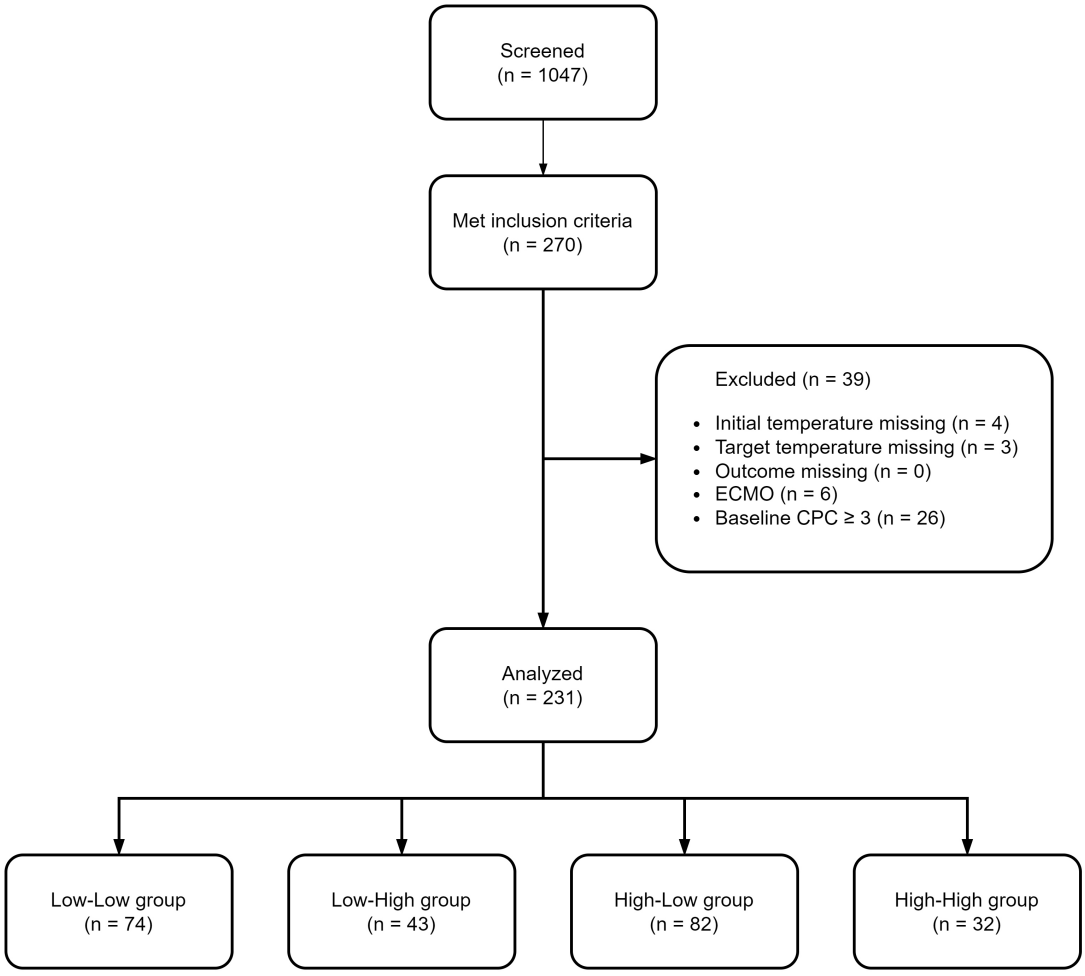

FIGURE 1. Study flow. This figure describes the full study flow from screening, including and excluding the study participants. ECMO, extracorporeal membrane oxygenation; CPC, cerebral performance category.

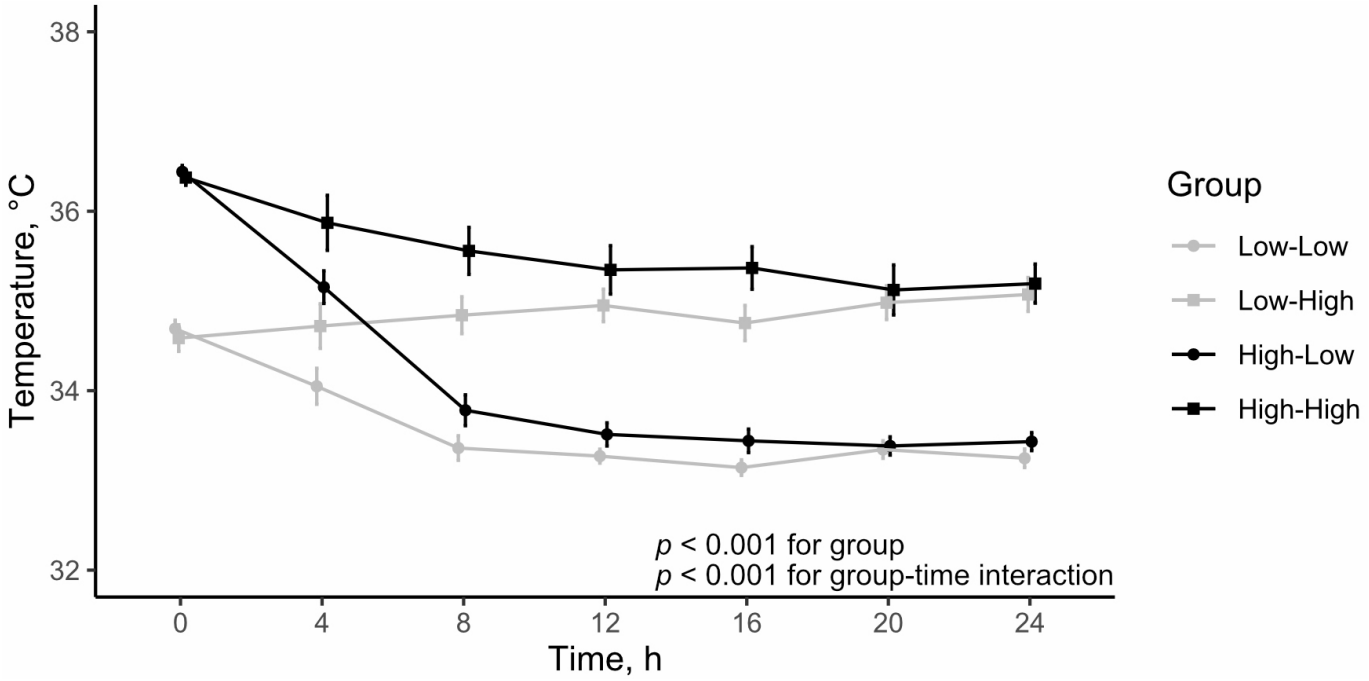

FIGURE 2. Body temperature change during targeted temperature management according to study groups. There was significant difference in body temperature among the study groups. A significant interaction was found between the study group and time for body temperature.

to evaluate the association between patient group and primary outcome. As the study population was small, we included variables with p values < 0.01 in univariable analyses to optimize the number of predictor variables in the multivariable analysis. The APACHE II score consists of multiple variables including age, pH, and creatinine, and it was significantly associated with the primary outcome. We excluded variables that showed significance in the univariable analyses but were included in the APACHE II score in the multivariable analysis.

Statistical significance was set at two-sided $p < 0.05$, and all statistical analyses were performed using R 4.1.2 (R Foundation, Vienna, Austria).

3. Results

A total of 1047 patients were screened for study inclusion, and 270 met the inclusion criteria. After excluding 39 patients, 231 patients were finally included in the analysis, and 74 (32.0%), 43 (18.6%), 82 (35.5%), and 32 (13.9%) were classified into the Low-Low, Low-High, High-Low, and High-High groups, respectively (Figs. 1,2). The median initial body temperature was 35.6 °C and temperature trends during the first 24 h of TTM according to the study group are presented in Fig. 2. Body temperature was significantly different among the study groups ($p < 0.001$), and there was a significant interaction between study group and time for body temperature ($p < 0.001$).

The clinical characteristics of patients are presented in Table 1. Patient ages differed among the study groups, while no significant difference was noted in terms of sex and comorbidities. Among prehospital variables, the proportion of initial shockable rhythm and total low-flow time showed significant differences among the groups. The mean arterial pressure, heart rate, initial APACHE II score, and initial temperature differed among the study groups.

The proportion of patients with favorable 28-day neurological outcomes was different among the study groups ($p = 0.001$, Table 2). In the post hoc tests, the proportion of favorable 28-day neurological outcomes was higher in the High-Low group (45.1%) than in the Low-Low (18.9%, adjusted $p = 0.006$, Fig. 3A) and Low-High groups (16.3%, adjusted $p = 0.016$, Fig. 3A). Survival on day 28 showed differences among the study groups ($p = 0.011$, Table 2); however, the post hoc test failed to show a significant difference between the groups (Fig. 3B).

Variables including diabetes mellitus, bystander CPR, prehospital shockable rhythm, total low-flow time, cardiac etiology, blood urea nitrogen, prothrombin time, initial APACHE II score, and study group were finally included in the multivariable model. There was a statistically significant association between the study group and the 28-day neurological outcomes only when comparing the Low-Low group with the High-Low group, and when comparing the Low-High group with the High-Low group in the univariable analyses, we set the High-Low group as reference in the multivariable analysis. In the multivariable logistic regression analysis, the total low-flow time ($p = 0.001$), cardiac etiology ($p = 0.013$), and Low-High group compared with the High-Low group ($p = 0.036$) showed independent associations with 28-day neurological outcomes (Table 3).

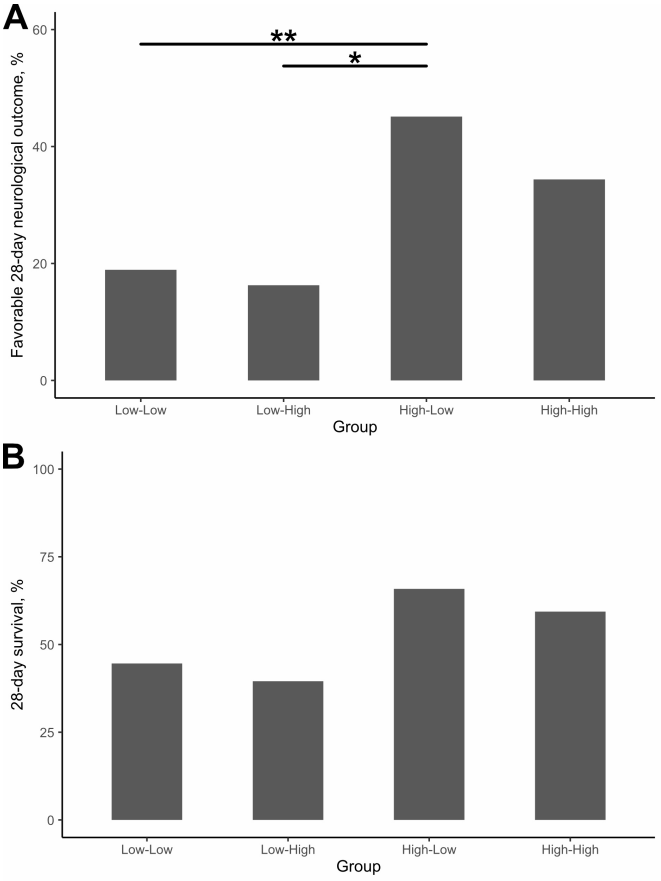

FIGURE 3. Neurological outcomes and survival rate at day 28 according to study groups. Comparison of (A) proportion of favorable 28-day neurological outcomes and (B) proportion 28-day survival according to study groups. There was statistically significant difference in the proportion of favorable 28-day neurological outcomes between the Low-Low and High-Low groups and between the Low-High and the High-Low groups. *p-value < 0.05; **p-value < 0.01.

4. Discussion

In the present study, the proportion of favorable 28-day neurological outcomes was highest in the High-Low group and was significantly higher than in both the Low-Low and Low-High groups. Furthermore, higher initial body temperature and lower target temperature during TTM (High-Low group) were independently associated with favorable 28-day neurological outcomes compared with lower initial body temperature and higher target temperature (Low-High group) in patients resuscitated from OHCA.

Hyperthermia has been associated with unfavorable outcomes in cardiac arrest survivors in previous studies [8–10]. Nolan *et al.* [9] reported that hospital mortality increased as body temperature increased in survivors of cardiac arrest. This dose-dependent association between hyperthermia and survival was consistent with the findings of Suffoletto *et al.* [10], and also in another study specifically in cardiac arrest survivors [21]. These findings were consistent with those of the present study. In the Low-High group, in which the

TABLE 1. Baseline characteristics according to study groups.

	Low-Low (n = 74)	Low-High (n = 43)	High-Low (n = 82)	High-High (n = 32)	*p* value
Age, years	63.7 ± 17.0	66.0 ± 12.7	58.4 ± 15.1	59.6 ± 14.8	0.030
Male sex, n (%)	53 (71.6%)	30 (69.8%)	65 (79.3%)	25 (78.1%)	0.565
Comorbidities					
Diabetes mellitus, n (%)	23 (31.1%)	13 (30.2%)	26 (31.7%)	12 (37.5%)	0.910
Hypertension, n (%)	34 (45.9%)	23 (53.5%)	37 (45.1%)	19 (59.4%)	0.476
Dyslipidemia, n (%)	5 (6.8%)	4 (9.3%)	5 (6.1%)	2 (6.2%)	0.921
Prehospital variables					
Witnessed cardiac arrest, n (%)	53 (71.6%)	35 (81.4%)	61 (74.4%)	29 (90.6%)	0.147
Bystander CPR, n (%)	36 (48.6%)	18 (41.9%)	32 (39.0%)	18 (56.2%)	0.336
Prehospital initial rhythm, n (%)					0.001
Shockable	21 (28.4%)	17 (39.5%)	47 (57.3%)	12 (37.5%)	
Non-shockable	49 (66.2%)	21 (48.8%)	35 (42.7%)	19 (59.4%)	
Unknown	4 (5.4%)	5 (11.6%)	0 (0.0%)	1 (3.1%)	
Total no-flow time, min	5.6 ± 7.3	6.0 ± 9.9	4.6 ± 4.9	4.4 ± 5.2	0.626
Total low-flow time, min	28.5 ± 17.9	27.5 ± 17.0	19.4 ± 11.6	21.8 ± 14.3	0.002
Cardiac etiology	42 (56.8%)	23 (53.5%)	56 (68.3%)	15 (46.9%)	0.135
Hospital variables†					
Mean arterial pressure, mmHg	100.4 ± 31.3	94.2 ± 30.3	100.5 ± 31.3	115.5 ± 38.7	0.045
Heart rate, beats per min	100.6 ± 28.4	97.9 ± 31.0	98.7 ± 23.9	114.6 ± 30.2	0.037
Blood urea nitrogen, mg/dL	27.6 ± 17.2	31.9 ± 29.1	27.2 ± 19.6	22.0 ± 12.0	0.240
Serum creatinine, mg/dL	1.9 ± 1.9	2.2 ± 2.1	2.3 ± 2.5	1.5 ± 0.8	0.264
Total bilirubin, mg/dL	0.7 ± 0.5	0.9 ± 0.8	0.8 ± 0.6	1.0 ± 0.6	0.276
Aspartate aminotransferase, U/L	372.9 ± 671.8	418.7 ± 860.6	327.7 ± 442.7	477.1 ± 1090.0	0.780
Alanine aminotransferase, U/L	242.7 ± 463.1	213.6 ± 389.3	194.4 ± 218.1	313.6 ± 719.2	0.619
Alkaline phosphatase, U/L	94.8 ± 39.1	102.0 ± 50.7	101.1 ± 44.0	134.6 ± 139.6	0.055
Prothrombin time INR	1.6 ± 1.1	1.7 ± 1.3	1.3 ± 0.3	1.5 ± 0.7	0.056
Troponin I, ng/mL	1.3 ± 3.3	5.9 ± 15.9	9.8 ± 33.1	1.0 ± 1.8	0.066
pH	7.0 ± 0.2	7.0 ± 0.2	7.0 ± 0.2	6.9 ± 0.2	0.795
Lactate, mmol/L	13.5 ± 6.9	11.6 ± 3.5	12.0 ± 3.6	11.6 ± 5.4	0.365
Initial APACHE II score	29.6 ± 7.5	28.3 ± 6.3	25.9 ± 8.5	28.7 ± 9.2	0.040
Initial body temperature, °C	34.7 ± 0.8	34.6 ± 1.0	36.4 ± 0.6	36.4 ± 0.5	< 0.001
Target temperature, °C	33.0 ± 0.2	35.0 ± 1.0	33.0 ± 0.1	35.1 ± 1.0	< 0.001
Temperature measurement site					0.919
Esophagus	48 (64.9%)	30 (69.8%)	54 (65.9%)	22 (68.8%)	
Bladder	5 (6.8%)	1 (2.3%)	8 (9.8%)	1 (3.1%)	
Rectum	16 (21.6%)	9 (20.9%)	14 (17.1%)	6 (18.8%)	
Unknown	5 (6.8%)	3 (7.0%)	6 (7.3%)	3 (9.4%)	

†All the hospital variables were measure within 6 h after return of spontaneous circulation.
APACHE II, acute physiologic and chronic health evaluation II; CPR, cardiopulmonary resuscitation; INR, international normalized ratio; TTM, targeted temperature management.

TABLE 2. Outcome measures according to study groups.

	Low-Low (n = 74)	Low-High (n = 43)	High-Low (n = 82)	High-High (n = 32)	*p* value
28-day neurological outcome, n (%)					0.001
Favorable	14 (18.9%)	7 (16.3%)	37 (45.1%)	11 (34.4%)	
Unfavorable	60 (81.1%)	36 (83.7%)	45 (54.9%)	21 (65.6%)	
28-day survival, n (%)					0.011
Survived	33 (44.6%)	17 (39.5%)	54 (65.9%)	19 (59.4%)	
Deceased	41 (55.4%)	26 (60.5%)	28 (34.1%)	13 (40.6%)	

TABLE 3. Multivariable logistic regression analysis for favorable 28-day neurological outcomes.

	Adjusted odds ratio	95% confidence interval	*p* value
Diabetes mellitus	0.48	0.16–1.43	0.187
Bystander CPR	1.57	0.63–3.88	0.331
Shockable initial rhythm	2.65	0.91–7.71	0.074
Total low flow time >23 min	0.20	0.07–0.51	0.001
Cardiac etiology	4.47	1.38–14.42	0.013
Blood urea nitrogen >20.5 mg/dL	0.62	0.25–1.53	0.295
Prothrombin time INR >1.22	0.72	0.28–1.84	0.488
APACHE II score >28	0.46	0.18–1.19	0.107
Study group			
High-Low	Reference		
Low-Low	0.58	0.20–1.67	0.313
Low-High	0.22	0.06–0.91	0.036
High-High	0.84	0.24–3.00	0.792

APACHE II, acute physiology and chronic health evaluation II; CPR, cardiopulmonary resuscitation; INR, international normalized ratio.

target temperature tended to be relatively higher than the initial body temperature, patients might have been warmed to some degree during the TTM period. The relative elevation in body temperature during TTM may affect neurological outcomes in a disadvantageous manner with a dose-dependent manner.

Prevention of hyperthermia and maintenance of hypothermia set several neuroprotective mechanisms into motion, including decreased cerebral metabolism, decreased lactate accumulation, improved glucose usage, decreased apoptosis, and decreased inflammatory cytokine release [22]. In animal experiments, the lower the body temperature, the more prominent the effect of hypothermia. For instance, radical oxygen species production, neuronal apoptosis, inflammatory cellular infiltration, and endothelial activation are suppressed as the temperature decreases in a dose-dependent manner [11–13]. Our study results, in which the 28-day neurological outcome was better in the High-Low group than in the Low-High group, suggest that the relative body temperature drop compared to the initial body temperature, as well as lower body temperature per se, might be associated with the neuroprotective effect of hypothermia.

Recent guidelines have recommended the application of TTM for comatose cardiac arrest survivors based on clinical trials that have reported the efficacy of TTM in neurological outcomes [6, 7]. The results of these studies suggested that prevention of hyperthermia might improve neurological outcomes after cardiac arrest; however, they could not determine the temperature at which cardiac arrest survivors should be maintained during TTM [23–25].

The most important strength of our study is that we compared the different associations of target temperature during TTM according to the initial body temperature with neurological outcomes in OHCA survivors. Little is known about whether the difference between target temperature during TTM and initial body temperature is associated with neurological outcomes. Our study results may raise further questions about the benefit of determining a specific lower target temperature during TTM when the initial presenting temperature is low.

Our study had several limitations. First, because of the retrospective nature of the study, it is unclear whether there is a causal relationship between the study groups according to initial body temperature, target temperature, and neurological outcome in OHCA survivors. Moreover, the target temperature was mostly determined by individual physicians making clinical decisions as well as being affected by other randomized controlled trials in some patients; uncontrolled confounding factors might be related to the target temperature determination. Second, the study might have been underpowered, owing to the small number of participants. Approximately three-quarters of the screened patients were not included in the study, mostly due to a non-medical etiology or not being treated with TTM. The large proportion of non-inclusion may have resulted in some degree of selection bias. Nevertheless, the Low-High group was independently associated with unfavorable neurological outcomes compared with the High-Low group, supporting our hypothesis. Finally, since this study was a clinical investigation, the pathophysiological basis of the possibly different neuroprotective effects of relatively higher or lower target temperatures compared with the initial body temperature during TTM could not be evaluated.

5. Conclusions

In conclusion, higher initial body temperature and lower target temperature during TTM were independently associated with favorable 28-day neurological outcomes compared to lower initial body temperature and higher target temperature in patients resuscitated from OHCA of medical etiology.

AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

HK—conceptualization, methodology, software, validation, formal analysis, investigation, writing—original draft, writing—review & editing; TK—conceptualization, methodology, software, validation, formal analysis,

investigation, resources, data curation, writing—original draft, writing—review & editing, visualization, supervision, project administration; JS—investigation, resources, writing—review & editing, supervision, project administration; WYK—conceptualization, methodology, writing—review & editing, supervision, project administration; HC—conceptualization, methodology, validation, investigation, writing—review & editing; JHL—conceptualization, methodology, validation, investigation, writing—review & editing; GJS—conceptualization, methodology, writing—review & editing, supervision, project administration; YSJ—conceptualization, methodology, resources, writing—review & editing; HJL—conceptualization, methodology, resources, writing—review & editing; KMY—conceptualization, methodology, resources, writing—review & editing; SMP—conceptualization, methodology, resources, writing—review & editing; YTO—conceptualization, methodology, resources, writing—review & editing, all authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The institutional review boards (IRBs) of the participating hospitals (hospital A, IRB no. 1408-012-599; hospital B, IRB no. 16-2013-157; hospital C, IRB no. B-1401/234-402) approved the study protocols for collecting data for the registry and the IRB of the hospital A (IRB no. 2008-161-1151) for the main analyses. Informed consent was waivered by the same IRBs for collecting and analyzing data from study participants.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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