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Optimal temperature in targeted temperature management without automated devices using a feedback system: A multicenter study

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ABSTRACT

Purpose: Targeted temperature management (TTM) at 32 °C–36 °C improves patient outcomes following out-of-hospital cardiac arrest (OHCA). TTM using automated temperature management devices with feedback systems (TFDs) is recommended, but the equipment is often unavailable. This study aimed to investigate therapeutic relations between targeted temperatures and TFDs on the outcomes of OHCA patients with TTM.
Methods: This multicenter study analyzed nontraumatic OHCA registry data between October 2015 and June 2020 from 29 institutions. Patients were classified into four groups based on targeted temperatures and TFD implementation: TTM at 33 °C with TFD (33TFD), TTM at 36 °C with TFD (36TFD), TTM at 33 °C without TFD (33NTFD), and TTM at 36 °C without TFD (36NTFD). Clinical outcomes were survival till hospital discharge and neurological status at discharge.
Results: A total of 938 patients were included in the analysis. There was an independent association between the 33NTFD patients with the least survival and the worst neurological outcomes among the four groups after adjustment for covariates. However, no significant differences were observed in survival and neurological outcomes among the 33TFD, 36TFD, and 36NTFD groups after adjusting for covariates. Compared to 33NTFD, 36NTFD patients exhibited significantly higher adjusted ORs for survival and favorable neurological status at hospital discharge.
Conclusion: In OHCA patients receiving TTM without TFDs, the adjusted predicted probability of survival and good neurological outcomes at hospital discharge was greater for TTM at 36 °C than that at 33 °C. This suggests that a TTM of 36 °C rather than 33 °C is associated with more favorable clinical outcomes if TFDs are unavailable.

1. Introduction

Despite recent advances in emergency medicine and resuscitation care, post-cardiac arrest brain injury remains a major cause of mortality and disability [1,2]. Targeted temperature management (TTM) is employed to reduce neurological damage of patients resuscitated from cardiac arrest [3,4]. Following landmark clinical trials in 2002 demonstrating that TTM at 32–34 °C for 12–24 h improved neurological outcomes after out-of-hospital cardiac arrest (OHCA), widespread use of therapeutic hypothermia protocols targeting 33 °C was implemented [5,6]. High-quality trials reported that TTM at 33 °C did not confer clinical benefits in post-cardiac arrest patients compared with 36 °C [7]. Current international guidelines recommend TTM of unconscious patients who have been resuscitated from cardiac arrest at 32–36 °C for at least 24 h [8].

TTM methods can be classified into two major categories according to the temperature feedback systems [9]. Temperature management devices with feedback systems (TFDs) have a controlled feedback loop that continuously measures the patients' core temperature and adjusts the temperature of the cooling element accordingly [10]. However, TTM can also be performed without the use of sophisticated controlled feedback systems by using ice and/or cold packs, fans and cold blankets, and manual temperature management which requires frequent assessment by staff [10,11]. TTM with feedback devices provides more accurate maintenance of targeted temperatures and prevents overcooling and rebound of hyperthermia compared to TTM without feedback devices [10]. However, TTM without temperature feedback devices (NTFD) is still employed in situations for which equipment is unavailable for various reasons [9]. A survey of TTM in post-cardiac arrest survivors reported that only 76% of intensive care units harnessed TFDs

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[12]. Although several studies have compared TTM at 33 °C and 36 °C with regards to the accuracy of temperature control and post-cardiac arrest outcomes [13,14], evidence for the relationship between targeted temperatures and TFDs remains scarce. We hypothesized that the therapeutic effect of using TFDs may be different according to the targeted temperature. In this study, we investigated therapeutic relationships between targeted temperatures and TFDs on the clinical outcomes of OHCA patients with TTM. Moreover, we aimed to find the optimal temperature for OHCA patients receiving TTM without TFDs.

2. Methods

2.1. Study design and population

This multicenter observational study used data from the Korean Cardiac Arrest Research Consortium (KoCARC) registry, which is a web-based prospective database that collects data on patients with OHCA from 62 academic emergency departments (EDs) in the South Korea [15]. The KoCARC is a collaborative research network developed to support studies in the field of OHCA and to foster collaborations among research groups. The registry enrolled OHCA patients who were transported to participating EDs by emergency medical services (EMSs) with resuscitation attempts and with cardiac arrests of presumed cardiac origin as determined by emergency physicians. Exclusion criteria of the KoCARC registry are OHCA due to definite non-cardiac etiologies, such as trauma, drowning, burning, hanging, poisoning, and asphyxia. Patients under hospice care, patients with a terminal illness documented by medical records, patients with pre-documented "Do Not Attempt Resuscitation" records, and pregnant women were also excluded. Researchers at each hospital were trained in data extraction from hospital medical records to ensure correct data entry into the standardized web-based electronic case report form. The case report form consisted of more than 200 variables, including demographics, cardiac arrest characteristics, past medical history, laboratory tests, EMS care, therapeutic interventions, and patient outcomes. Outliers or incorrect values were filtered using a predefined data-entry system. The KoCARC quality management committee, comprising physicians, local research coordinators, and investigators from each participating institution, regularly monitored and reviewed data quality. The KoCARC registry collecting protocol was reviewed and approved by the institutional review board of each participating hospital. This study was purely observational, and therefore, the institutional review board waived the need for informed consent. The KoCARC registry was registered at clinicaltrials.gov as protocol NCT03222999 [16].

Patients in the KoCARC registry who received TTM from October 2015 to June 2020 were included in this study. Patients younger than 18 years of age, patients with the provision of extracorporeal cardiopulmonary resuscitation (CPR), patients with incomplete information about TTM and prognosis, and patients who died in the ED prior to ICU admission were excluded. Patients transferred from other hospitals were excluded if they had spent > 24 h in other hospitals. TTM was defined as the control of core body temperature to the targeted temperature regardless of the cooling technique, device, or cooling interval. TTM without TFDs was defined as the use of a water jet pan, underarm ice pack, or cooling blanket that was not connected to an automated thermostat controlling system. TTM with TFDs was defined as the use of specific commercial devices, such as Arctic Sun® (Medivance Corp, Louisville, KY, USA), GAYMAR (Gaymar Industries, Orchard Park, NY, USA), Blanketrol III (Cincinnati Sub-Zero Products, Cincinnati, OH, USA), and EMCOOLS Flex.Pad™ (EMCOOLS, Vienna, Austria) or intravascular devices, such as CoolGard 3000 Thermal Regulation System (Alsius Corporation, Irvine, CA). These devices were connected to an automated feedback thermostat that controlled the temperature of the circulating saline based on the patients' rectal or esophageal temperature.

The study population was divided into four groups according to the targeted temperatures and implementation of TFD: 33 °C TTM with TFD (33TFD), 36 °C TTM with TFD (36TFD), 33 °C TTM without TFD (33NTFD), and 36 °C TTM without TFD (36NTFD) (Fig. 1). Information on individual factors, including age, sex, underlying disease, laboratory data, initial vital signs, Utstein factors, such as primary electrocardiogram (ECG) (shockable rhythm versus non-shockable rhythm), location, witnessed arrest, and bystander CPR was collected. Data on total arrest time, defined as the time from onset of the arrest until return of spontaneous circulation, and hospital factors, such as the provision of coronary interventions and TTM induction time, were collected.

2.2. Outcome measures

The primary outcomes were survival and neurological status at hospital discharge. We defined a favorable neurological status as a cerebral performance category (CPC) score of 1 or 2.

2.3. Statistical analyses

As all eligible study participants during the designated study period were included, sample size estimation using power analysis was not performed; instead, a retrospective power analysis was implemented. Continuous variables are presented as means ± standard deviation and categorical variables are presented as absolute or relative frequencies. Group comparisons were performed using analysis of variance for continuous variables and the chi-squared test for categorical variables. The Bonferroni post hoc test was used to perform pairwise comparisons of groups. Multivariable logistic regression analyses with adjustment for the influence of confounders were performed to determine the association between survival discharge and neurological outcome and TFDs or targeted temperatures. To assess whether associations between TFDs use and clinical outcome differed by targeted temperatures (33 °C or 36 °C), the interactions between TFDs and targeted temperatures were tested in a multivariable logistic regression model. The *P* value for statistical significance was set at <0.05 for an interaction term.

Additional multivariable logistic regression analyses were performed to estimate the independent association between survival discharge and favorable neurological outcome among the four groups, which were divided according to the combination of TFDs and targeted temperatures, with the 33NTFD group as the reference group. Pairwise comparisons of the adjusted odds ratio were subsequently evaluated to further investigate any differences between the individual groups in more detail. All multivariable logistic regression models were adjusted for age, sex, type of treating hospital, witness, bystander CPR, primary ECG rhythm, total arrest time, and provision of coronary intervention. Variables were selected from univariable analysis and amended by variables derived from clinical considerations. Moreover, Kaplan–Meier survival curves were created using 30-day mortality data, and between-group differences were assessed with the log-rank test. *P*-values <0.05 were considered to be statistically significant at the 95% confidence level. The *P* value of the Bonferroni correction for multiple comparisons was set at 0.0083 (0.05/6).

All statistical analyses were conducted using SAS software (version 9.2; SAS Institute Inc., Cary, NC, USA) and R software for Windows (version 3.2.5; the R foundation for statistical computing, Vienna, Austria [http://www.R-project.org/]).

3. Results

Enrolment and clinical outcome data for the OHCA patients registered in the KoCARC registry from October 2015 to June 2020 are presented in Fig. 1. Of the patients who received TTM, 91 were excluded due to age < 18 years, provision of extracorporeal CPR, and missing data on body temperature and devices, resulting in 938 patients from 29 institutions in the final analysis. Of these, 471 (50.2%) patients survived at hospital discharge and 302 (32.2%) patients were discharged with favorable neurological outcomes, i.e., CPC score of 1 or 2.

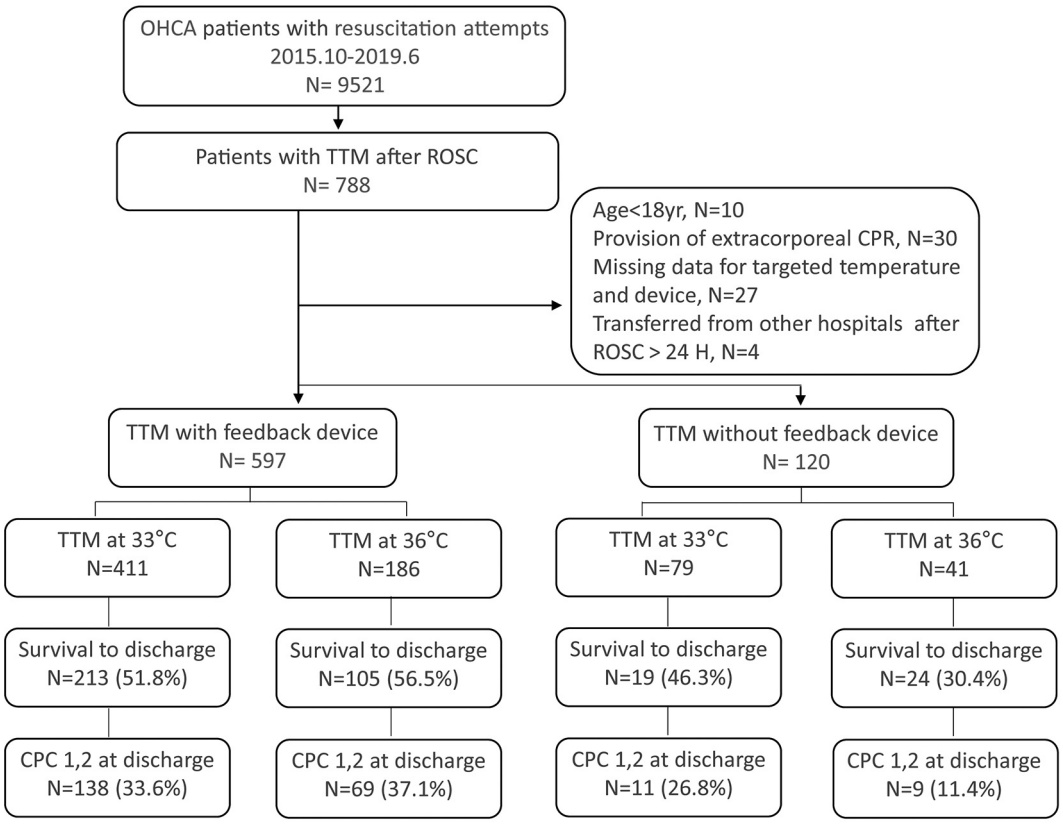

Fig. 1. Flow diagram of the study population.
Abbreviations: TTM, targeted temperature management; CPC, cerebral performance category; OHCA, out-of-hospital cardiac arrest.

Clinical characteristics of the participants divided into the four groups according to TFD use and targeted temperatures are shown in Table 1. The 33NTFD group exhibited the least survival rate and favorable neurological outcome compared to the other groups. There were no significant differences at baseline for the demographic and clinical characteristics of the study participants with the exception of the provision of coronary intervention. The provision of coronary intervention was performed more frequently in patients in the 36TFD group than in patients in the 33TFD or 33NTFD groups (46.8% vs. 29.7%; $P < 0.001$, 46.8% vs. 31.1%; $P = 0.007$, respectively). We also investigated the level of ED where patients were treated. Patients in the 33NTFD group had higher rate of treatment at regional emergency center compare with 36 NTFD group (Table 1 and Supplementary Table S1). No significant differences were noted in the clinical characteristics between the TFD and NTFD groups. Further, the proportion of favorable neurological outcomes was higher in the TFD groups (35.1% vs 18.8%, $P < 0.01$) (Table 1). The TFD groups were independently associated with better survival rate (odds ratio [OR]: 1.66, 95% CI: 1.11–2.50, $P = 0.015$) and more favorable neurological outcomes (odds ratio [OR]: 2.39, 95% CI: 1.40–4.09, $P = 0.001$) than the NTFD groups. TFDs use and targeted temperatures had significant association with the survival ($P = 0.013$) and neurological outcomes ($P = 0.036$) of OHCA patients with TTM via the interaction term between the two factors, after adjusting for age, sex, type of treating hospital, witness, bystander CPR, primary ECG rhythm, total arrest time, and provision of coronary intervention (Table 2).

Among the four groups, patients with 33NTFD were independently associated with the least survival and favorable neurological outcomes after adjusting for confounders including age, sex, type of treating hospital, witness, bystander CPR, primary ECG rhythm, total arrest time, and provision of coronary interventions (Table 3 and Supplementary Fig. S1). Patients with 36NTFD exhibited a significantly higher OR for survival (OR: 2.65, 95% CI: 1.21–5.78) and favorable neurological outcome (OR: 4.11, 95% CI: 1.44–11.74) compared with 33NTFD patients after adjusting for covariates (Table 3A). Moreover, the 36NTFD group showed no significant differences in the survival and neurological outcomes at hospital discharge compared with 36TFD or 33TFD groups after adjusting for covariates (Table 3B). Kaplan–Meier curves showed that the survival rate was most unfavorable for patients who received 33NTFD compared with other groups. (Fig.2 and Supplementary Table S2). Finally, in a power analysis based on the results from the present study, we had a power of 96.5% to detect a difference of neurological outcome among the four groups.

4. Discussion

The primary purpose of this study was to investigate the optimal target temperature in TTM without TFDs in terms of survival and neurological outcomes in post cardiac arrest patients. The main finding of this study was that TTM with 33NTFD was significantly associated with higher mortality and poorer neurological outcome than TTM with TFDs and even 36NTFD. Despite differences in cost, medical resource use, and invasiveness, there were no significant differences in patient outcomes among the 36TFD, 33TFD, and 36NTFD groups in our cohort. Our findings suggest that a targeted temperature of 36 °C rather than 33 °C is associated with more favorable clinical outcomes when TFDs is unavailable. Moreover, our results implied that 36NTFD could provide a therapeutic effectiveness non-inferior to TFDs in OHCA patients treated with TTM. To the best of our knowledge, this study is the first to identify the optimal targeted temperature in TTM without TFDs with regards to survival and neurological outcomes in OHCA patients.

Consistent with the findings of previous research, no significant differences were observed in the clinical outcomes between the targeted temperatures of 33 °C and 36 °C regardless of the use of TTM devices.

Table 1
Clinical characteristics of study patients stratified according to targeted temperature and temperature control device.

Variables	Total	TTM at 36 °C		TTM at 33 °C		overall	Post-hoc analysis p-value					
		(1) NTFD	(2) TFD	(3) NTFD	(4) TFD	*P*	1 vs 2	1 vs 3	1 vs 4	2 vs 3	2 vs 4	3 vs 4
	N = 938	*N* = 61	*N* = 237	*N* = 104	*N* = 536							
Age (years)	59.1 ± 17.1	60.5 ± 16.8	61.1 ± 15.8	60.3 ± 19.4	57.9 ± 17.2	0.077	0.807	0.959	0.260	0.712	0.016	0.179
Male sex [n (%)]	688(73.4)	41(67.2)	175(73.8)	76(73.1)	396(73.9)	0.733	0.301	0.423	0.265	0.883	0.991	0.865
Vital sign after ROSC												
SBP (mmHg)	130 ± 76	124 ± 32	140 ± 125	129 ± 50	126 ± 46	0.272	0.231	0.725	0.850	0.360	0.058	0.774
DBP (mmHg)	76 ± 27	75.553 ± 23	78 ± 27	79 ± 33	75 ± 26	0.667	0.687	0.578	0.896	0.778	0.326	0.336
Heart rate (bpm)	100 ± 34	106 ± 33	100 ± 32	92 ± 39	101 ± 33	0.231	0.304	0.063	0.450	0.183	0.559	0.073
Medical history, [n (%)]												
Hypertension	203(21.66)	8(13.11)	55(23.21)	21(20.19)	119(22.24)	0.362	0.085	0.249	0.099	0.538	0.768	0.644
Diabetes mellitus	151(16.12)	9(14.75)	37(15.61)	22(21.15)	83(15.51)	0.527	0.869	0.310	0.876	0.213	0.972	0.156
Chronic pulmonary disease	28(2.99)	3(4.92)	11(4.64)	2(1.92)	12(2.24)	0.189	>0.999	0.360	0.191	0.358	0.071	>0.999
Cardiovascular disease	156(16.65)	11(18.03)	46(19.41)	15(14.42)	84(15.70)	0.551	0.807	0.539	0.637	0.269	0.204	0.742
Cerebral vascular disease	41(4.38)	3(4.92)	12(5.06)	6(5.77)	20(3.74)	0.617	>0.999	>0.9999	0.721	0.788	0.394	0.412
Chronic kidney disease	51(5.44)	1(1.64)	14(5.91)	6(5.77)	30(5.61)	0.601	0.321	0.262	0.354	0.960	0.868	0.948
Malignancy	44(4.70)	4(6.56)	14(5.91)	4(3.85)	22(4.11)	0.551	0.770	0.469	0.327	0.433	0.275	>0.999
Cardiac arrest characteristics												
Witnessed collapse, [n (%)]	706(75.3)	49(81.67)	173(73.0)	76(73.79)	408(76.55)	0.201	0.158	0.251	0.371	0.219	0.475	0.547
Bystander CPR, [n (%)]	490(54.14)	33(58.93)	116(49.15)	46(49.46)	295(56.73)	0.164	0.188	0.262	0.752	0.960	0.053	0.194
First monitored rhythm, [n (%)]						0.416	0.738	0.484	0.608	0.179	0.783	0.098
Non-shockable	517(56.32)	35(58.33)	132(55.93)	62(63.92)	288(54.86)							
Shockable	401(43.68)	25(41.67)	104(44.07)	35(36.08)	237(45.14)							
Arrest in public location [n (%)]	424(45.20)	26(42.62)	107(45.15)	37(35.58)	254(47.39)	0.235	0.872	0.666	0.649	0.237	0.197	0.056
No-flow time (min)	6.8 ± 6.7	6.2 ± 7.0	6.5 ± 6.4	6.7 ± 8.1	7.0 ± 6.6	0.713	0.802	0.696	0.415	0.819	0.342	0.659
Low-flow time (min)	25.6 ± 19.3	24.4 ± 18.6	26.6 ± 19.9	26.4 ± 21.0	25.1 ± 18.8	0.710	0.447	0.532	0.813	0.945	0.323	0.520
Arrest to ROSC time (min)	32.3 ± 20.3	30.7 ± 20.5	33.0 ± 20.5	33.1 ± 21.8	32.0 ± 20.0	0.819	0.421	0.469	0.621	0.992	0.532	0.641
Coronary reperfusion intervention, [n (%)]	322(34.48)	23(37.70)	111(46.84)	32(31.07)	156(29.27)	<0.001*	0.201	0.384	0.174	0.007**	<0.001**	0.714
Induction time of TTM (hour)	4.19 ± 3.7	3.8 ± 2.2	4.5 ± 5.3	4.0 ± 2.7	4.1 ± 2.5	0.784	0.422	0.832	0.686	0.530	0.429	0.870
Rewarming rate [n (%)]						0.922	0.669	0.627	0.705	>0.999	0.727	0.752
0.25 °C/h	912(97.23)	59(96.72)	231(97.47)	102(98.08)	520(97.01)							
0.5 °C/h	26(2.77)	2(3.28)	6(2.53)	2(1.92)	16(2.99)							
Type of hospital [n (%)]						<0.001*	0.325	0.002**	0.006**	0.002**	0.003**	0.185
Regional emergency center	480(51.17)	22(36.07)	102(43.04)	64(61.54)	292(54.48)							
Local emergency center	458(48.83)	39(63.93)	135(56.96)	40(38.46)	244(45.52)							
Laboratory data after ROSC												
Hemoglobin (mg/dL)	12.7 ± 2.7	12.9 ± 2.4	12.5 ± 2.9	13.2 ± 2.4	12.8 ± 2.6	0.189	0.240	0.609	0.611	0.038	0.216	0.174
Platelets (10^3/uL)	205 ± 83	220 ± 114	204 ± 77	203 ± 74	205 ± 83	0.602	0.193	0.241	0.208	0.972	0.843	0.857
PT(INR)	1.45 ± 1.69	1.46 ± 1.55	1.45 ± 1.20	1.34 ± 0.38	1.47 ± 2.02	0.956	0.984	0.714	0.958	0.649	0.901	0.572
Sodium (mEq/L)	139.5 ± 24.7	138.0 ± 5.3	139.5 ± 6.2	139.2 ± 5.7	139.8 ± 33.0	0.963	0.678	0.766	0.603	0.928	0.892	0.845

(continued on next page)

Table 1 (*continued*)

Variables	Total	TTM at 36 °C		TTM at 33 °C		overall	Post-hoc analysis p-value				
		(1) NTFD	(2) TFD	(3) NTFD	(4) TFD	*P*	1 vs 2	1 vs 3	1 vs 4	2 vs 3	2 vs 4	3 vs 4
	N = 938	*N* = 61	*N* = 237	*N* = 104	*N* = 536							
Potassium (mEq/L)	5.4 ± 12.8	4.3 ± 1.0	4.9 ± 3.2	8.3 ± 32.4	5.3 ± 8.7	0.154	0.775	0.069	0.598	0.036	0.707	0.045
Chloride (mEq/L)	101.9 ± 11.1	101.5 ± 6.3	103.0 ± 13.2	102.4 ± 7.3	101.3 ± 11.1	0.294	0.379	0.659	0.854	0.656	0.062	0.389
Base excess	10.0 ± 12.8	5.9 ± 14.6	9.9 ± 10.1	11.6 ± 11.0	10.0 ± 13.8	0.367	0.196	0.076	0.147	0.427	0.922	0.396
PH	7.07 ± 0.22	7.09 ± 0.21	7.08 ± 0.20	7.03 ± 0.19	7.06 ± 0.24	0.250	0.631	0.085	0.331	0.077	0.426	0.174
Arterial lactate (mmol/L)	10.50 ± 5.04	10.67 ± 4.51	11.02 ± 4.32	10.86 ± 7.14	10.18 ± 5.02	0.186	0.647	0.835	0.499	0.811	0.038	0.282
BUN (mg/dL)	25.7 ± 26.4	19.8 ± 10.2	25.1 ± 17.6	27.3 ± 32.5	26.4 ± 29.9	0.318	0.179	0.099	0.078	0.527	0.567	0.783
Creatinine (mg/dL)	2.4 ± 7.3	1.4 ± 1.2	3.3 ± 12.2	1.9 ± 2.0	2.1 ± 3.3	0.221	0.127	0.736	0.541	0.239	0.075	0.850
AST (IU/mL)	289 ± 753	168 ± 132	293 ± 863	283 ± 471	304 ± 781	0.686	0.288	0.397	0.225	0.923	0.869	0.828
ALT (IU/mL)	203 ± 594	127 ± 138	226 ± 779	164 ± 264	208 ± 564	0.684	0.287	0.730	0.362	0.438	0.720	0.558
Bilirubin (mg/dL)	0.68 ± 1.29	0.53 ± 0.39	0.75 ± 2.19	0.55 ± 0.46	0.68 ± 0.75	0.548	0.264	0.916	0.405	0.246	0.560	0.400
Albumin (g/dL)	3.68 ± 7.29	3.42 ± 0.67	4.40 ± 14.18	3.41 ± 0.67	3.42 ± 0.67	0.471	0.396	0.996	0.996	0.306	0.129	0.989
Glucose (mg/L)	285 ± 134	294 ± 148	282 ± 119	307 ± 128	281 ± 141	0.392	0.564	0.564	0.515	0.145	0.944	0.103
Total cholesterol (mg/dL)	142 ± 66	147 ± 38	149 ± 50	161 ± 152	136 ± 49	0.060	0.890	0.372	0.431	0.290	0.095	0.017
Survival discharge [n (%)]	471(50.21)	33(54.10)	119(50.21)	32(30.77)	287(53.54)	<0.001*	0.588	0.003**	0.935	0.001**	0.392	<0.001**
Good neurological outcome [n (%)]	302(32.20)	20(32.79)	84(35.44)	11(10.58)	187(34.89)	<0.001*	0.698	<0.001**	0.744	<0.001**	0.882	<0.001**

*P < 0.05, **P < 0.0083 (P value threshold after a Bonferroni correction for 6 comparisons).

Variables are expressed as mean ± SD for continuous variables or number (%) for categorical variables.

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; TTM, targeted temperature management; NTFD, TTM without temperature feedback devices; TFD, TTM with temperature feedback devices; ROSC, return of spontaneous circulation; CPR, cardiopulmonary resuscitation; PT(INR), Prothrombin time (international normalized ratio); BUN, blood urea nitrogen; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

In this study, survival and neurological outcomes were more favorable in the TFDs groups than in the NTFD groups. Substantial evidence corroborates the superior effectiveness of temperature feedback devices in achieving, maintaining, and rewarming targeted temperatures compared to the absence of such devices [10,11,17,18]. A recent systematic review reported that the use of temperature feedback systems in TTM was associated with a higher probability of favorable neurological outcomes compared to NTFD [17]. The concept of "high-quality TTM" has been proposed as a method to increase the effectiveness of TTM. The use of a high-quality TTM system equipped with automatic temperature feedback systems is recommended to manage targeted temperatures with minimal fluctuations [10]. If body temperatures are not adequately monitored and adjusted, the beneficial effects of TTM may be compromised due to delays in TTM induction, unintentional overcooling or hyperthermia, or spontaneous and rapid rewarming [10,19].

Nevertheless, issues of cost and availability of TFDs in real-world settings should be considered. In this study, 16.7% of post-cardiac arrest patients received TTM without temperature feedback devices. Commercial surface cooling or intravascular temperature management equipment and automated thermostat systems are often costly and not fully covered by health insurance programs [9]. Moreover, the high density of post-cardiac arrest patients in a few advanced hospitals results in the shortage of TTM equipment, and the demand for technologically sophisticated devices for TTM often exceeds their availability [11,12]. Advanced devices for TTM may not be readily available in clinical settings in developing countries [20]. Therefore, physicians often encounter clinical situations in which TFDs is unavailable. TTM without TFDs is cheaper and more readily available compared to TTM with TFDs, but the accuracy of temperature control is poor and may lead to unfavorable clinical outcomes [10,21]. Despite the significant association between NTFD and poor clinical outcomes, it remains unclear whether the association differs according to targeted temperature (33 °C vs. 36 °C).

The current study demonstrated that TTM at 33 °C was significantly associated with clinical deterioration compared to TTM at 36 °C when TFDs was not used. Adverse side effects have been associated with TTM at 33 °C. Casamento et al. reported similar adherence rates with temperature guidelines between 33 °C and 36 °C [22], but the occurrence of arrhythmias and cardiovascular dysfunction was higher in patients with TTM at 33 °C. Düggelin et al. reported that TTM at 36 °C was associated with higher adherence to precise temperatures and a lower rate of adverse effects, such as bradycardia [23]. Merchant et al. reported that maintaining accurate temperature control with conventional cooling methods (without TFDs) in TTM at 33 °C was difficult and was associated with unintentional overcooling episodes [21]. Further, they demonstrated that TTM at 33 °C using ice packs and conventional cooling blankets led to poorer clinical outcomes and lowered the threshold for adverse events. The authors suggested that accurate induction and maintenance in TTM at 33 °C was dependent on the selected cooling method and appropriate adjustments in response to ongoing temperature fluctuations [21]. Generally, TTM at 33 °C is more strongly associated with unintentional overcooling and adverse events, such as cardiac dysfunction and arrhythmias, whereas TTM at 36 °C is more strongly associated with a delayed start of TTM and hyperthermic episodes [13,14,22,23]. Given that the body's temperature control mechanisms for temperature maintenance operate optimally at 36 °C, TTM at 36 °C may be more likely to induce rebound hyperthermia [13,24]. Although the precise mechanisms underscoring poorer clinical outcomes in 33NTFD than in 36NTFD remain unclear, several factors, such as unintentional overcooling, hyperthermia, and a delayed start of TTM, may contribute, as they are associated with poor clinical outcomes [10]. Hyperthermic episodes and delayed induction may be prevented by adequate administration of neuromuscular blocking agents and implementation of standard TTM strategies [8,10]. Most participating hospitals in our study have implemented treatment protocols for patients receiving TTM according to international guidelines. No

Table 2
Interaction effect between TFD use and targeted temperatures in the multivariable logistic regression analysis of survival discharge (A) and good neurological outcome (B).

(A)

Variable	Survival discharge				P for interaction
	AOR (95% CI)	*P*	AOR (95% CI)	*P*	
Age	0.979(0.970–0.988)	<0.001*	0.979(0.970-0.988)	<0.001*	
Male sex	1.137(0.807–1.601)	0.463	1.121(0.797–1.578)	0.511	
Type of treating hospital		0.56		0.556	
Regional emergency center	Reference		Reference		
Local emergency center	0.914(0.676–1.237)		0.913(0.675–1.236)		
Arrest to ROSC duration	0.960(0.952–0.969)	<0.001*	0.960(0.952-0.969)	<0.001*	
Witnessed collapse	1.095(0.774–1.548)	0.608	1.073(0.760–1.517)	0.688	
Bystander CPR	1.066(0.786–1.446)	0.682	1.073(0.792–1.455)	0.65	
Initial shockable rhythm	2.338(1.679–3.254)	<0.001*	2.376(1.710-3.303)	<0.001*	
Provision coronary intervention	1.938(1.384–2.712)	<0.001*	1.907(1.357-2.680)	<0.001*	
TTM without TFD	Reference				0.013*
TTM with TFD	1.662(1.106–2.499)	0.015*			
TTM at 36 °C			Reference		
TTM at 33 °C			0.948(0.683–1.316)	0.749	

(B)

Variable	Good neurologic outcome				P for interaction
	AOR (95% CI)	*P*	AOR (95% CI)	*P*	
Age	0.967(0.956–0.978)	<0.001*	0.966(0.956–0.977)	<0.001*	
Male sex	0.945(0.615–1.452)	0.795	0.913(0.595–1.401)	0.676	
Type of treating hospital		0.254		0.362	
Regional emergency center	Reference		Reference		
Local emergency center	1.239(0.857–1.791)		1.186(0.822–1.711)		
Arrest to ROSC duration	0.946(0.935–0.958)	<0.001*	0.947(0.936–0.958)	<0.001*	
Witnessed collapse	1.845(1.185–2.873)	0.007	1.842(1.184–2.866)	0.007*	
Bystander CPR	1.187(0.818–1.723)	0.367	1.209(0.835–1.752)	0.315	
Initial shockable rhythm	6.263(4.243–9.245)	<0.001*	6.351(4.311–9.356)	<0.001*	
Provision coronary intervention	2.257(1.541–3.307)	<0.001*	2.098(1.429–3.081)	<0.001*	
TTM without TFD	Reference				0.036*
TTM with TFD	2.393(1.400–4.089)	0.001*			
TTM at 36 °C			Reference		
TTM at 33 °C			0.718(0.483–1.066)	0.1	

Abbreviations: ROSC, return of spontaneous circulation; CPR, cardiopulmonary resuscitation; TTM, targeted temperature management; TFD, temperature management devices with feedback systems; AOR, adjusted odds ratio (adjusted for age, sex, witnessed, bystander CPR, primary electrocardiogram rhythm, total arrest time, and provision of coronary intervention); CI, confidence interval.

* $P < 0.05$.

differences were observed in induction time between TTM at 33 °C and 36 °C in this study. Considerable research has attempted to identify the optimal approaches to prevent shivering and subsequent hyperthermia during TTM, and reliable protocols and guidelines have been published in this regard [8,25-29]. There have been significant improvements in treatment strategies and physicians' attention to minimize delays in induction, shivering, and hyperthermia based on evidence, such as the American Heart Association guidelines in the practice of resuscitation [29]. These advances may have contributed to improved prognosis in the 36NTFD group. In contrast, appropriate guidelines to prevent overcooling in TTM using non-feedback devices, such as ice bags and cooling blankets, are less common than those for preventing hyperthermic events [21]. There were no significant differences in patient outcomes among the 36TFD, 33TFD, and 36NTFD groups in our study. A recent large, prospective, randomized study in OHCA patients demonstrated that targeted hypothermia at 33 °C did not show significant benefit in clinical outcomes compared to targeted normothermia with early treatment of fever [30]. The combined results of our study and this recent trial imply that 36NTFD with active prevention of hyperthermia could achieve meaningful clinical improvement in OHCA patients with TTM as compared with 33NTFD.

There are several limitations to this study. First, the assignment of TTM devices and targeted temperatures could not be randomly allocated due to the observational nature of the study. Although we adjusted for potential confounders in the multivariable logistic regression model, unmeasured bias may have affected device selection and targeted temperatures. Second, in our study setting, the selection of TTM devices and targeted temperatures was determined according to the physicians' preference and family consent to pay the TTM fees. As such, the patient's socioeconomic and cultural background may have been sources of bias in the study. Third, the KoCARC registry does not collect data on adverse events and body temperature during TTM. Therefore, we were unable to evaluate the prevalence of adverse events, such as unintentional overcooling, hyperthermic episodes, arrhythmia, infection, and bleeding in each treatment group. Finally, an alternative explanation for the current results is the clinician's bias in selecting the TTM strategy. Several studies have reported that treating physicians are more likely to select TTM of 33 °C for patients whom they believe to have more severe hypoxic insults in order to maximize the protective effects of TTM against brain damage [10,31]. If a clinical judgment was made based on patient severity, the allocation of more severe patients to the TTM group at 33 °C would bias our results to favor 36NTFD. However, there were no significant differences in the baseline clinical characteristics between the individual treatment groups and the logistic regression analysis that was performed, was adjusted for severity and prognostic confounding factors. Nevertheless, data on signs of cerebral injury, such as malignant status myoclonus in patients, were not collected in the KoCARC registry, and the relatively small sample size of the 36NTFD group limits the generalizability of these results. Further well-designed trials are needed to clarify the clinical differences between the 36NTFD and TFD groups.

Table 3
Multivariable logistic regression for survival discharge and good neurological outcomes (A), and AOR comparisons of the four groups (B).

(A)

Variable	Survival discharge		Good neurological outcome	
	AOR (95% CI)	*P*	AOR (95% CI)	*P*
Age	0.979(0.970–0.989)	<0.001*	0.967(0.956-0.978)	<0.001*
Male sex	1.122(0.796–1.583)	0.51	0.928(0.602–1.433)	0.737
Type of treating hospital				
Regional emergency center	Reference		Reference	
Local emergency center	0.895(0.660–1.214)	0.475	1.170(0.806–1.698)	0.409
Arrest to ROSC duration	0.960(0.952–0.969)	<0.001*	0.947(0.936-0.958)	<0.001*
Witnessed collapse	1.077(0.760–1.526)	0.676	1.845(1.181–2.882)	0.007*
Bystander CPR	1.047(0.770–1.424)	0.769	1.197(0.821–1.745)	0.35
Initial shockable rhythm	2.331(1.673–3.250)	<0.001*	6.415(4.330-9.505)	<0.001*
Provision coronary intervention	1.965(1.392–2.774)	<0.001*	2.133(1.443-3.153)	<0.001*
33TTM without TFD	Reference		Reference	
36TTM without TFD	2.646(1.211–5.781)	0.015*	4.108(1.437-11.743)	0.008*
33TTM with TFD	2.514(1.478–4.276)	<0.001*	4.293(1.955-9.425)	<0.001*
36TTM with TFD	2.226(1.250–3.965)	0.007	5.269(2.289–12.127)	<0.001*

(B)

Variables	Survival discharge					Good neurological outcome				
	AOR (95% CI)	*P* vs 33NTFD	*P* vs 36NTFD	*P* vs 33TFD	*P* vs 36TFD	AOR (95% CI)	*P* vs 33NTFD	*P* vs 36NTFD	*P* vs 33TFD	*P* vs 36TFD
33 NTFD	Reference	Ref.	0.015*	0.001*	0.007*	Reference	Ref.	0.008*	<0.001*	<0.001*
36 NTFD	2.646(1.211–5.781)	0.015*	Ref.	0.875	0.616	4.108(1.437–11.743)	0.008*	Ref.	0.911	0.542
33 TFD	2.514(1.478–4.276)	0.001*	0.875	Ref.	0.612	4.293(1.955–9.425)	<0.001*	0.911	Ref.	0.354
36 TFD	2.226(1.250–3.965)	0.007*	0.616	0.612	Ref.	5.269(2.289–12.127)	<0.001*	0.542	0.354	Ref.

Abbreviations: ROSC, return of spontaneous circulation; CPR, cardiopulmonary resuscitation;; AOR, adjusted odds ratio; CI, confidence interval.
Abbreviations: 33NTFD, 36 °C TTM with TFD; 36NTFD, 33 °C TTM with TFD; 33TFD, 36 °C TTM without TFD; 36TFD, 33 °C TTM without TFD; AOR, adjusted odds ratio (adjusted for age, sex, witnessed, bystander CPR, primary electrocardiogram rhythm, total arrest time, and provision of coronary intervention); CI, confidence interval.
* $P < 0.05$.

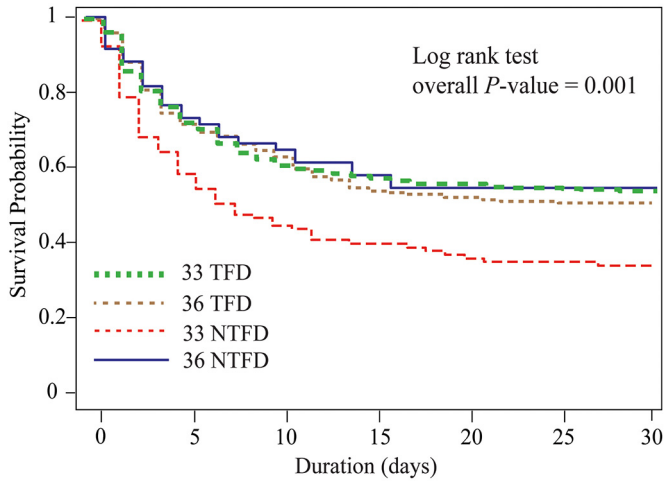

Fig. 2. Kaplan–Meier curves displaying the estimated survival probability for four different groups of OHCA patients with TTM. The study population was divided into four groups according to the targeted temperatures and implementation of TFD. The survival rate was most unfavorable for patients who received 33NTFD compared with other groups. (Additional file 1: Table S2).
Abbreviations: 36NTFD, 36 °C TTM without TFD; 36TFD, 33 °C TTM with TFD; 33NTFD, 33 °C TTM without TFD; 33TFD, 33 °C TTM with TFD.

5. Conclusions

In OHCA patients receiving TTM without automated devices using a temperature feedback system, the adjusted predicted probability of survival and favorable neurological outcomes at discharge was greater at 36 °C than at 33 °C. Moreover, the 36NTFD group displayed similar therapeutic effects as the TFD groups. This suggests that targeted temperature management at 36 °C shows therapeutic effectiveness if automated devices using a temperature feedback system is unavailable.

Ethics approval and consent to participate

This study was approved by the institutional review boards of each participating institute, and informed consent was waived due to the observational nature of the study. The study has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Consent for publication

All authors have read and approved the submission of the manuscript.

Availability of data and materials

Data are available on reasonable request. Data are available on request.

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Credit authorship contribution statement

Taeyoung Kong: Conceptualization, Data curation, Methodology, Writing – original draft, Writing – review & editing, Funding acquisition, Visualization. **Je Sung You:** Conceptualization, Data curation, Investigation, Funding acquisition. **Hye Sun Lee:** Data curation, Software, Validation, Visualization. **Soyoung Jeon:** Data curation, Formal analysis,

Software, Validation, Visualization. **Yoo Seok Park:** Conceptualization, Investigation, Methodology. **Sung Phil Chung:** Conceptualization, Methodology, Supervision, Writing – review & editing.

Declaration of Competing Interest

All authors declare no conflicts of interest.

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Appendix A. Supplementary data

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