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Comparison of hypothermic and normothermic targeted temperature management in out-of-hospital cardiac arrest patients with acute coronary syndrome: a nationwide retrospective study

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Abstract

Background Targeted temperature management (TTM) is considered a beneficial treatment for improving outcomes in patients with OHCA due to acute coronary syndrome (ACS). The comparative benefits of hypothermic TTM (32–34°C) versus normothermic TTM (35–36°C) are unclear. This study compares these TTM strategies in improving neurological outcomes and survival rates in OHCA patients with ACS.

Methods We conducted a retrospective analysis using data from the Japanese Association for Acute Medicine Out-of-Hospital Cardiac Arrest (JAAM-OHCA) registry, encompassing 68,110 OHCA patients between June 2014 and December 2020. After applying inclusion and exclusion criteria, 1,217 adult patients with ACS who received TTM were eligible for the study. Patients were categorized into two groups based on their TTM strategy: hypothermic TTM (32–34°C) and normothermic TTM (35–36°C). The primary outcome was 30-day favorable neurological outcome, defined by the Cerebral Performance Category (CPC) scale (CPC 1–2). Secondary outcomes included 30-day survival and adverse event incidence. Statistical analysis involved multivariable logistic regression and propensity score adjustments with inverse probability weighting (IPW) to account for potential confounders.

Results Of the 1,217 patients, 369 received normothermic TTM and 848 received hypothermic TTM. In both groups, most patients were male, with a median age in the 60s. Approximately 70% had a shockable rhythm at the scene, one-third had a shockable rhythm in-hospital, around 70% had ST segment elevation, and about half received extracorporeal membrane oxygenation. The proportions of patients with 30-day favorable neurological outcomes were 36.6% (135) in the normothermic group and 36.6% (310) in the hypothermic group. No difference in neurological outcomes was observed in the multivariable regression analysis (adjusted OR 1.14, 95% CI 0.84–1.54), and the result was consistent in the IPW analysis (OR 1.11, 95% CI 0.84–1.47). Other outcomes also showed no significant differences.

Conclusion In this nationwide, retrospective study using the JAAM-OHCA registry, we found no significant differences in 30-day favorable neurological outcome, 30-day survival, and adverse event incidences between hypothermic TTM (32–34°C) and normothermic TTM (35–36°C) in adult patients with OHCA due to ACS.

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Introduction

Acute coronary syndrome (ACS) is one of the primary causes of out-of-hospital cardiac arrest (OHCA) [1, 2]. Despite significant advancements in resuscitation science and the accumulation of evidence-based practices, high mortality rates persist in OHCA patients due to hypoxic-ischemic brain injury, which remains the leading cause of death even in this population. [3–5]. Targeted temperature management (TTM) is a standard treatment for post-cardiac arrest patients to mitigate the effects of reperfusion injury and improving neurological outcomes [6–8].

Current international cardiopulmonary resuscitation (CPR) guidelines do not recommend a specific target temperature for comatose patients after return of spontaneous circulation (ROSC) [3, 4]. However, there is still uncertainty regarding the benefit of mild therapeutic hypothermia (MTH) at 32–34°C. MTH has the potential to enhance hemodynamics by increasing myocardial contractility, cardiac output, and stroke volume [9–12]. It may also reduce the overall metabolic rate and myocardial metabolic demand, which positively influences reperfusion injury and increases the contractility of cardiac myocytes without elevating oxygen consumption [9–12].

The SHOCK-COOL trial, a small randomized study that examined the effects of MTH in patients who underwent primary PCI complicated by cardiogenic shock, found no significant improvement in cardiac power index at 24 h or in other hemodynamic parameters compared to normothermic controls [13]. Despite the potential mechanisms of MTH, these effects remain controversial, and the study had a limited sample size of only 40 patients, failing to provide conclusive evidence. Similarly, post-hoc analyses of the TTM1 (n = 920) and TTM2 (n = 1,135) trials, which evaluated different target temperatures in patients requiring vasopressors due to circulatory instability, showed no significant differences in outcomes [14, 15].

The Hyperion trial indicated potential benefits of MTH for specific subgroups, such as patients with nonshockable rhythms [16]. Previous studies did not specifically focus on ACS, which remains the most frequent cause of cardiac arrest. Given that ACS is a major driver of OHCA, it is crucial to investigate the optimal targeted temperature during TTM specifically in this population. Therefore, this study aims to assess the impact of hypothermic TTM compared to normothermic TTM using data from the JAAM-OHCA registry, a multicenter study in Japan, specifically targeting ACS patients. Identifying the optimal temperature management strategy could refine clinical guidelines and improve outcomes in this high-risk population.

Methods

Study design and setting

This study is a retrospective analysis of data from the Japanese Association for Acute Medicine Out-of-Hospital Cardiac Arrest (JAAM-OHCA) registry, a comprehensive nationwide database [17]. The registry collects detailed pre-hospital and in-hospital information and outcomes for OHCA patients transported to emergency departments of about 150 participating institutions in 2020. Data collection began in June 2014 and is ongoing. This study includes data from January 1, 2015, to December 31, 2020. Patients transferred from non-participating institutions, not resuscitated by a physician upon hospital arrival, or who refused registration were excluded. The study protocol was approved by the institutional review boards of the participating hospitals.

In this study, we included adult OHCA patients aged ≥ 18 years who experienced ACS and received TTM. Patients with unknown targeted temperatures were excluded. The diagnosis of ACS in this study was made by treating physician in charge. All resuscitation procedures, including PCI, TTM, and ECMO, were conducted according to the Japanese CPR guidelines, which are based on the CoSTR by ILCOR [18, 19]. However, the specific protocols used at each institution were unknown, and treatment decisions may have varied.

Data collection and quality control

The data collection process has been previously described [17]. Briefly, EMS personnel collected pre-hospital data according to the international Utstein-style guidelines [20, 21], while in-hospital data were collected by medical staff using a standardized format in an Internet-based system. The JAAM-OHCA registry committee integrated the pre-hospital and in-hospital information.

For this study, the collected data included: patient age, sex, day of the week, presence of a bystander witness, bystander CPR, use of public access automated external defibrillators (AED), first documented rhythm at the scene (shockable, non-shockable, or other), pre-hospital epinephrine administration, pre-hospital advanced airway management (the insertion of a supraglottic airway or tracheal tube in prehospital settings), time from EMS call to patient contact, time from call to hospital arrival, first documented rhythm after hospital arrival (shockable, non-shockable, or other [Presence of pulse]), ECG findings (ST segment elevation), PCI, TTM, targeted temperature during TTM (32–36°C), use of intra-aortic balloon pump (IABP), and extracorporeal membrane oxygenation (ECMO). The choice of TTM protocols was at the discretion of the treating physicians. The term 'Other' for the first documented rhythm after hospital arrival refers to the presence of a pulse following ROSC.

Main exposure

The main exposure was the targeted temperature during TTM, categorized into two groups [22]:

Hypothermic TTM: Target temperature of 32–34°C.

Normothermic TTM: Target temperature of 35–36°C.

Outcome

The primary outcome was 30-day favorable neurological outcome, assessed using the Cerebral Performance Category (CPC) scale, and 30-day survival. A favorable outcome was defined as CPC 1 or 2 [20, 21]. Secondary outcomes included the incidence of adverse events during TTM such as bleeding, hypotension, arrhythmias, infections, and others.

Statistical analysis

We evaluated the differences in characteristics and outcomes between the hypothermic TTM and normothermic TTM groups. Continuous variables were compared using the Mann–Whitney U test, while categorical variables were analyzed using Fisher's exact test.

First, to evaluate the impact of different targeted temperatures during TTM on outcomes, we calculated crude odds ratios (ORs) and adjusted odds ratios (AORs), along with their 95% confidence intervals (CIs), using univariable and multivariable logistic regression analyses. Normothermic TTM served as the reference group for all odds ratios. The factors adjusted for in the multivariable analysis included: age, sex, first documented rhythm at the scene, pre-hospital epinephrine administration, pre-hospital advanced airway management, time from EMS call to patient contact, first documented rhythm after hospital arrival, as well as the use of IABP and ECMO [22–25].

We also utilized propensity score analysis to mitigate confounding effects, performing inverse probability weighting (IPW) based on the propensity scores. Propensity scores were estimated using a logistic regression model that included age, sex, bystander witness, bystander CPR, use of public-access AEDs, first documented rhythm at the scene, pre-hospital epinephrine administration, pre-hospital advanced airway management, time from EMS call to patient contact, first documented rhythm after hospital arrival, PCI, IABP, and ECMO. The weights were derived from the inverse probability of receiving either hypothermic or normothermic TTM, and applied to create a weighted pseudo-population where the distribution of baseline covariates was balanced between the groups. The odds ratios were then calculated using univariable logistic regression analysis with IPW to assess the impact of different targeted temperatures.

To assess the robustness of our findings, sensitivity analyses were performed on the original cohort using univariable and multivariable logistic regression analyses. The sensitivity analyses included patients treated with ECMO, IABP, ECMO + IABP, patients who received ECMO either before or after ROSC, those treated with PCI, those with ST elevation, and those whose first documented rhythm at the scene was shockable.

All statistical analyses were performed using SPSS statistical package (version 26.0 J, IBM Corp. Armonk, NY, USA) or R (R Foundation for Statistical Computing, version 3.4.3). Two-sided p-values < 0.05 were considered statistically significant.

Results

Study population

Between June 2014 and December 2020, 68,110 OHCA patients were registered in the JAAM-OHCA registry. After excluding 1,637 patients in whom resuscitation was not attempted by physicians, 6,124 patients whose pre-hospital data were unavailable, 1,241 patients under 18 years old, 43,793 patients with no return of circulation, 12,682 patients whose cause of arrests was not ACS, 1389 patients who did not receive TTM, and 27 patients whose targeted temperature was unknown, a total of 1,217 adult OHCA patients with ACS who received TTM were eligible for our analysis Of the 1,217 patients, 369 (30.3%) were treated with normothermic TTM (35–36°C) and 848 (69.7%) with hypothermic TTM (32–34°C) (Fig. 1).

Baseline characteristics

Table 1 shows the baseline characteristics of the original cohort according to the targeted temperature. The majority of patients were male, with a median age in the 60s. The first documented rhythm at the scene was shockable in approximately 70% of cases for both groups. Upon hospital arrival, shockable rhythms were observed in about one-third of patients, while non-shockable rhythms were documented in approximately 30% of patients in both groups. Although there were some missing values, approximately 70% of the cases in both groups showed ST segment elevation. Additionally, approximately half of the patients in both groups received ECMO, with initiation occurring before ROSC in about 30% of cases in each group.

Outcomes

Table 2 presents the main outcomes of the study population according to targeted temperature. Among the normothermic TTM and hypothermic TTM groups, the proportions of patients with 30-day favorable

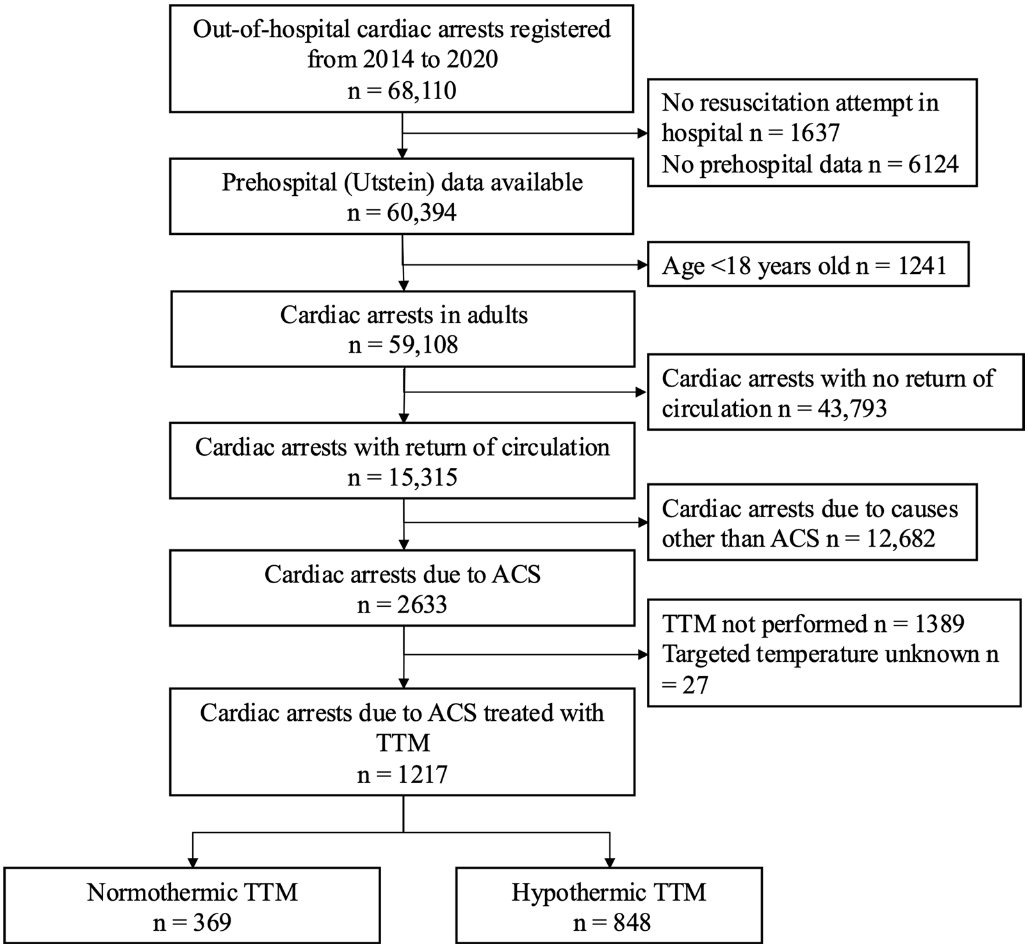

Fig. 1 Patient flow chart. ACS: Acute coronary syndrome, TTM: Targeted temperature management

neurological outcomes and 30-day survival, were 36.6% (135/369) vs 36.6% (310/848), and 61.8% (228/369) vs 58.7% (498/848), respectively.

Univariable logistic regression analyses, with normothermic TTM as the reference group, showed no significant differences between the groups in terms of favorable neurological outcomes (OR 1.00, 95% CI 0.78–1.29) and survival (OR 0.88, 95% CI 0.69–1.13). In the multivariable logistic regression analysis, using normothermic TTM as the reference, there were no significant differences in favorable neurological outcomes (adjusted OR 1.04, 95% CI 0.74–1.45) and survival (adjusted OR 0.92, 95% CI 0.68–1.24) between the normothermic TTM and hypothermic TTM groups.

This was consistent with the IPW analysis, which also used normothermic TTM as the reference group and showed no significant differences in neurological outcomes (36.0% [438/1216] in the normothermic TTM group vs 36.8% [448/1217] in the hypothermic TTM group, OR 1.11, 95% CI 0.84–1.47), and survival (60.9% [741/1216] vs 59.2% [720/1217], OR 1.15, 95% CI 0.88–1.51). Table 3 shows the occurrence of adverse events among the study population. No significant differences were observed between the two targeted temperature groups in terms of bleeding, hypotension, arrhythmias, infections, and other adverse events.

In the sensitivity analyses, no significant differences were observed between normothermic TTM and hypothermic TTM across all subgroups (Table 4).

Discussion

Summary of findings

Using the nationwide prospective JAAM-OHCA registry in Japan, we evaluated the impact of TTM on adult patients who experienced OHCA due to ACS. Approximately 70% of the patients in both groups showed ST segment elevation, and about half received ECMO. We found no significant differences in 30-day favorable neurological outcomes, 30-day survival, and adverse event incidence between hypothermic TTM and normothermic

Table 1 Patient characteristics and pre-/in-hospital information among OHCA patients by targeted temperature

Men	**Normothermic TTM**		**Hypothermic TTM**		***P* Values***
	N = 369		**N = 848**		
	329	**(89.2)**	**734**	**(86.6)**	**0.209**
Age, median (IQR) (Years)	65	(57–72)	64	(54–71)	0.553
Weekend	113	(30.6)	279	(32.9)	0.434
Prehospital information					
Bystander witness	286	(77.5)	662	(78.1)	0.829
Bystander CPR	202	(54.7)	438	(51.7)	0.321
Use of public-access AEDs	48	(13.0)	126	(14.9)	0.397
First documented rhythm at the scene					0.818
Shockable rhythm	250	(67.8)	590	(69.6)	
Non-shockable rhythm	79	(22.4)	171	(20.2)	
Other	40	(10.8)	87	(10.3)	
Prehospital Epinephrine	117	(31.7)	252	(29.7)	0.487
Prehospital Airway management	326	(88.3)	732	(86.3)	0.335
EMS resuscitation times, median (IQR), (minutes)					
EMS response time (call to contact with a patient)	8	(6–9)	8	(6–9)	0.890
Hospital arrival time (call to hospital arrival)	31	(24–38)	30	(25–38)	0.431
In-hospital information					
First documented rhythm after hospital arrival					0.177
Shockable rhythm	102	(27.6)	276	(32.5)	
Non-shockable rhythm	127	(34.4)	288	(34.0)	
Other	140	(37.9)	284	(33.5)	
Time from call to in-hospital ROSC, median (IQR), (minutes)*	46	(36–67)	48	(35–67)	0.546
ECG: ST segment elevation†	243	(68.6)	520	(67.8)	0.777
PCI	291	(78.9)	680	(80.2)	0.596
Time from call to PCI, median (IQR), (minutes)‡	145	(106–191)	124	(94–165)	< 0.001
IABP	197	(53.4)	511	(60.3)	0.025
ECMO	157	(42.5)	408	(48.1)	0.074
ECMO initiation before ROSC	109	(29.0)	287	(33.8)	0.831
Time from call to ECMO, median (IQR), (minutes)§	58	(49–80)	56	(46–68)	0.123

OHCA indicates out-of-hospital cardiac arrests; AED, automated external defibrillator; CPR, cardiopulmonary resuscitation

EMS, emergency medicine personnel, Extracorporeal Membrane Oxygenation and IQR, interquartile range

Values are presented as numbers (%) unless indicated otherwise

[*] Calculated from 223 normothermic TTM patients and 463 hypothermic TTM patients

[†] Calculated from 354 normothermic TTM patients and 767 hypothermic TTM patients

[‡] Calculated from 266 normothermic TTM patients and 610 hypothermic TTM patients

[§] Calculated from 156 normothermic TTM patients and 402 hypothermic TTM patients

TTM. Additionally, sensitivity analyses yielded consistent results, further reinforcing our overall conclusion.

Comparison to previous studies and strength

Three large-scale RCTs have examined the differential effects of hypothermic temperature management versus other targeted temperatures during TTM on post-cardiac arrest treatment [16, 26, 27]. The TTM trials one and two did not demonstrate a benefit for any specific targeted temperature, and as a result, the International Liaison Committee on Resuscitation (ILCOR) does not specify any target temperature during post-cardiac arrest treatment [28]. However, the Hyperion trial, which focused on patients with nonshockable rhythms, demonstrated the benefits of MTH [16]. Based on these results, ILCOR has identified the need for further research to discover subgroups that could benefit from MTH [28]. Conversely, the SHOCK-COOL trial, a small RCT that excluded post-cardiac arrest patients and investigated the effects of MTH in patients with ACS complicated by cardiogenic

Table 2 Outcomes according to the targeted temperature

	All patients	Original cohort		Crude analysis OR (95% CI)	Multivariable analysis† AOR (95% CI)	After adjustment of IPW		OR (95% CI)‡
		Normothermic TTM*	Hypothermic TTM			Normothermic TTM*	Hypothermic TTM	
	N = 1217	N = 369	N = 848			N = 1216	N = 1217	
Outcome measure								
30-day neurological favorable outcome	445 (36.6)	135 (36.6)	310 (36.6)	1.00 (0.78–1.29)	1.04 (0.74–1.45)	438 (36.0)	448 (36.8)	1.03 (0.80–1.34)
30-day survival	726 (59.7)	228 (61.8)	498 (58.7)	0.88 (0.69–1.13)	0.92 (0.68–1.24)	741 (60.9)	720 (59.2)	0.93 (0.79–1.09)

Values are expressed numbers (percentages) unless indicated otherwise

* Normothermic TTM serves as the reference group for all odds ratios

† Adjusted for age, sex, first documented rhythm by EMS personnel, prehospital adrenaline administration, prehospital advanced airway management, time from EMS call to contact with the patients, first documented rhythm after hospital arrival, PCI, IABP, and ECMO

‡ Shown is the odds ratio from the univariable logistic regression analysis with IPW

Table 3 Adverse events during TTM according to different targeted temperature

	Original cohort		Crude analysis OR (95% CI)	Multivariable analysis† AOR (95% CI)
	Normothermic TTM*	Hypothermic TTM		
	N = 369	N = 848		
Any adverse event of TTM	41 (11.1)	112 (13.2)	1.22 (0.83–1.78)	1.29 (0.88–1.90)
Bleeding	10 (2.7)	44 (5.2)	1.97 (0.98–3.95)	1.99 (0.98–4.03)
Arrythmia	10 (2.7)	44 (5.2)	1.97 (0.98–3.95)	1.99 (0.98–4.03)
Hypotension	25 (6.8)	70 (8.3)	1.24 (0.77–1.99)	1.33 (0.82–2.16)
Infection	6 (1.6)	24 (2.8)	1.76 (0.71–4.35)	1.94 (0.78–4.83)
Other	16 (4.3)	45 (5.3)	1.24 (0.69–2.22)	1.28 (0.71–2.31)

* Normothermic TTM serves as the reference group for all odds ratios

† Adjusted for age, sex, first documented rhythm by EMS personnel, prehospital adrenaline administration, prehospital advanced airway management, time from EMS call to contact with the patients, first documented rhythm after hospital arrival, PCI, IABP, and ECMO

Table 4 Sensitivity analyses: Favorable Neurological Outcomes according to patient characteristics, treatment and different targeted temperature

	All patients	Normothermic* TTM	Hypothermic TTM	Crude Odds ratio (95% CI)	Adjusted Odds ratio (95% CI) †
ECMO	89/565 (15.8)	23/157 (14.6)	66/408 (16.2)	1.12 (0.67–1.88)	1.31 (0.74–2.33)
IABP	188/708 (26.6)	47/197 (23.9)	141/511 (27.6)	1.22 (0.83–1.78)	1.18 (0.75–1.86)
ECMO + IABP	85/491 (17.3)	23/139 (16.5)	62/352 (17.6)	1.08 (0.64–1.82)	1.23 (0.69–2.19)
ECMO initiation before ROSC	56/396 (14.1)	11/109 (10.1)	45/287 (15.7)	1.66 (0.82–3.34)	1.72 (0.82–3.64)
ECMO initiation after ROSC	33/169 (19.5)	12/48 (25.0)	21/121 (17.4)	0.78 (0.40–1.52)	0.77 (0.36–1.66)
PCI	335/971 (34.5)	93/291 (32.0)	242/680 (35.6)	1.18 (0.88–1.58)	1.04 (0.70–1.53)
Presence of ST elevation	284/763 (37.2)	84/243 (34.6)	200/520 (38.5)	1.18 (0.86–1.63)	1.24 (0.84–1.94)
Shockable First Documented Rhythm at the scene	326/840 (38.8)	98/250 (39.2)	228/590 (38.6)	0.98 (0.72–1.32)	1.04 (0.70–1.53)

* Normothermic TTM serves as the reference group for all odds ratios

† Adjusted for age, sex, first documented rhythm by EMS personnel, prehospital adrenaline administration, prehospital advanced airway management, time from EMS call to contact with the patients, first documented rhythm after hospital arrival, PCI, IABP, and ECMO

shock, showed no significant differences in cardiac power index, other hemodynamic parameters, and 30-day mortality between patients randomized to mild therapeutic hypothermia and control [13]. Regarding previous observational studies with OHCA patients with varying degrees of circulatory compromise during TTM, post-hoc analyses of the TTM1 and TTM2 trials observed no significant differences in favorable outcomes [14, 15]. In TTM1, all arrests were presumed to be of cardiac etiology, with about 40% of patients having ST elevation, while in TTM2, 90% of arrests were presumed to be of cardiac etiology and about half of the patients had AMI. These findings align with our results.

Interpretations

Given that both hypothermic and normothermic TTM offer similar benefits in this patient population, normothermic TTM may be preferred due to lower costs and easier management. In fact, secondary analyses of two RCTs regarding TTM comparing these two Targeted temperature strategies in patients with circulatory instability showed no differences regarding long-term outcomes, although the use of vasopressors and the time to recovery of circulation were longer [14, 15]. Building on these findings, it is essential to recognize the change in temperature management strategies, shifting from specific target temperatures such as 33°C or 36°C to the broader goal of fever prevention (maintaining body temperature below 37.5°C) during the TTM period. Notably, while TTM inherently includes fever prevention during active temperature control, the emphasis on fever prevention as the primary objective has only recently been recognized as an important aspect of standard care. However, during our study period, such fever prevention strategies were neither explicitly recommended nor routinely implemented. This highlights a gap in historical practice and underscores the need for future research to evaluate the applicability of fever prevention specifically in ACS patients, including its impact on neurological outcomes, clinical management, and overall prognosis.

We also conducted analyses specifically focusing on patients with ST segment elevation, in addition to ACS as a whole, and found no differences in outcomes. While experimental studies suggest improvements in cardiac function for STEMI patients, human studies have consistently reported negative findings. The effects of MTH in cardiogenic shock are well-documented in experimental and animal studies, where MTH has been shown to improve myocardial contractility, reduce infarct size, and decrease myocardial oxygen consumption [29–31]. However, these theoretical benefits observed in animal models have not consistently translated into significant clinical improvements in human studies [13, 32]. One possible reason for this discrepancy is the difference in pathophysiological responses between animals and humans. Animal studies are often conducted in controlled environments, which may not replicate the complex and heterogeneous nature of human cardiac arrest and myocardial infarction [33, 34]. Additionally, factors such as timing, duration of ischemia, pre-existing comorbidities, and the use of inotropes and vasopressors can influence the outcomes in human studies, potentially diminishing the benefits of MTH [35, 36].

Furthermore, while this study's patients experienced transient cardiac arrest, not all of them may have continued to present with circulatory instability. For instance, only about 40% of STEMI patients were reported to be in shock [37]. Unfortunately, our registry does not include specific hemodynamic indicators, so we conducted sensitivity analyses for patients managed with IABP and ECMO, which also showed no significant differences. Notably, the proportion of patients treated with ECMO in our cohort was exceptionally high compared with international standards, highlighting the unique characteristics of our study population. Several recent studies have investigated the role of TTM in patients treated with ECMO, particularly in determining optimal target temperatures. Using the same JAAM-OHCA registry as this study, one analysis compared normothermic (35–36 °C) and hypothermic (32–34 °C) TTM in OHCA patients receiving ECMO and found no significant differences in neurological outcomes [22]. Similarly, a randomized trial in patients with cardiogenic shock treated with ECMO reported no significant survival benefit of moderate hypothermia (33–34 °C) compared with normothermia (36–37 °C) [38]. These findings collectively suggest that the choice of target temperature may not have a substantial impact on outcomes in ECMO-treated patients. With ECMO increasingly recognized as a standard treatment for its combined benefits of circulatory support and intra-arrest cooling, it may play a crucial role in improving outcomes for cardiac arrest patients. Given that ACS is one of the most common causes of cardiac arrest, further research is essential to determine the most effective TTM strategies for this specific population, ensuring that temperature management is optimally integrated into evolving standards of care.

Limitations

Several limitations need to be considered in this study. First, our study lacks detailed information on the culprit lesion of myocardial infarction, the size of the infarction, and specific cardiac function measures. Second, we do not have data on the patients' medical histories or regular medications prior to cardiac arrest, nor do we have information on the use of inotropes or vasopressors during resuscitation and intensive care. Third, the protocols for intensive care, including TTM, were not standardized, and the criteria for ACS diagnosis may have varied among clinicians. This could have introduced selection bias in determining which patients received normothermia versus hypothermia. For example, clinicians may have chosen normothermia for patients with more severe circulatory instability, potentially affecting outcomes. Additionally, it is important to acknowledge that this study was based on a nationwide, multicenter OHCA cohort rather than a dedicated ACS or AMI registry. As a result, detailed information specific to ACS or AMI, such as standardized diagnostic criteria and definitions for ACS or AMI (e.g., universal definition distinguishing between type 1 and type 2 MI), was not available. This limitation reflects the challenges of conducting a multicenter registry study focused on OHCA, where specific ACS-related protocols were not established. Fourth, as an observational study, there is the potential for unmeasured confounding factors that could have influenced the results. Although some key prognostic factors were not collected, we included major predictors known to impact OHCA outcomes and adjusted for these using multivariable logistic regression and propensity score analysis. we observed no significant differences in outcomes between the groups, regardless of the analytical method employed. While the absence of certain prognostic variables is a recognized limitation, we believe that the consistent findings across various analyses indicate that the risk of substantial residual confounding is minimal.

Conclusions

In this nationwide, retrospective study using the JAAM-OHCA registry, we found no significant differences in 30-day favorable neurological outcome, 30-day survival rates, and adverse event incidences between hypothermic TTM and normothermic TTM in adult patients who experienced OHCA due to ACS. Further research is warranted to confirm these findings and refine TTM protocols for this high-risk group.

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Author contributions
Matsuyama had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis. Study concept and design: Matsuyama, Kitamura, Watanabe. Acquisition, analysis, and interpretaton of data: All authors. Drafting of the manuscript: Matsuyama, Kitamura. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Matsuyama. Obtained funding: Matsuyama. Study supervision: Ohta.

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Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The Ethics Committee of each institution approved this study protocol. Because of the observational study and de-identification of personal data, each committee waived the need for informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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