

Comparison of in-hospital and out-of-hospital cardiac arrest patients receiving targeted temperature management: A matched case-control study

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Abstract

Background: Evidences that support the use of targeted temperature management (TTM) for in-hospital cardiac arrest (IHCA) are lacking. We aimed to investigate the hypothesis that TTM benefits for patients with IHCA are similar to those with out-of-hospital cardiac arrest (OHCA) and to determine the independent predictors of resuscitation outcomes in patients with cardiac arrest receiving subsequent TTM.

Methods: This is a retrospective, matched, case-control study (ratio 1:1) including 93 patients with IHCA treated with TTM after the return of spontaneous circulation, who were admitted to Partners HealthCare system in Boston from January 2011 to December 2018. Controls were defined as the same number of patients with OHCA, matched for age, Charlson score, and sex. Survival and neurological outcomes upon discharge were the primary outcome measures.

Results: Patients with IHCA were more likely to have experienced a witnessed arrest and receive bystander cardiopulmonary resuscitation, a larger total dosage of epinephrine, and extracorporeal membrane oxygenation. The time duration for ROSC was shorter in patients with IHCA than in those with OHCA. The IHCA group was more likely associated with mild thrombocytopenia during TTM than the OHCA group. Survival after discharge and favorable neurological outcomes did not differ between the two groups. Among all patients who had cardiac arrest treated with TTM, the initial shockable rhythm, time to ROSC, and medical history of heart failure were independent outcome predictors for survival to hospital discharge. The only factor to predict favorable neurological outcomes at discharge was initial shockable rhythm.

Conclusion: The beneficial effects of TTM in eligible patients with IHCA were similar with those with OHCA. Initial shockable rhythm was the only independent predictor of both survival and favorable neurological outcomes at discharge in all cardiac arrest survivors receiving TTM.

Keywords: Cardiac arrest; Cardiopulmonary resuscitation; Neurological outcome; Targeted temperature management; Therapeutic hypothermia

1. INTRODUCTION

Owing to the increasing growth of the population contributing to increased cardiovascular deaths worldwide, sudden cardiac arrest has become an increasing event and a global health issue.^{1,2} Many patients who survive from the cardiac arrest event have postcardiac arrest syndrome, a condition characterized by

ischemia-reperfusion injury leading to oxidative stress, neurological injury, myocardial dysfunction, and systemic inflammatory response.³ Targeted temperature management (TTM) has been associated with decreasing mortality and improving neurological function in patients with out-of-hospital cardiac arrest (OHCA) since the two original landmark studies in 2002.^{4,5} Advances in postcardiac arrest care incorporating TTM have emerged as the standard of care for OHCA in comatose adults to improve functional outcomes.⁴⁻⁷

As TTM benefits for patients with OHCA have been well described, those for patients with in-hospital cardiac arrest (IHCA) have been rarely reported. The varieties of physiology, comorbidities, and polypharmacy in patients with IHCA make intensive care substantially complex.⁸ However, majority of previous studies that focused on TTM paid paltry attention on the outcomes in patients with IHCA. Evidences that support the use of TTM for patients with IHCA are lacking, and evidences also showed that it might not improve the outcomes in this population.^{9,10} Therefore, clinicians should possess a thorough

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understanding of the factors affecting the outcomes of in-patient resuscitation and the disparate features between patients with IHCA and OHCA who received TTM.

The benefits of TTM remain increasingly debatable as recent studies have shown attenuated improvement in favorable neurological survival as TTM carried risks of bleeding, arrhythmias, and electrolyte derangements.^{11,12} This leads to the question of whether therapeutic hypothermia is appropriate as a “one-size-fits-all” therapy in the postresuscitation care for all patients with cardiac arrest. At present, which patients with cardiac arrest may benefit the most from TTM remains uncertain. Patients who experienced IHCA may be different from those who experienced OHCA^{13,14} Therefore, this study was conducted to examine the hypothesis that TTM benefits for patients with IHCA are similar to those for patients with OHCA and to determine the independent predictors of resuscitation outcomes in patients with cardiac arrest receiving subsequent TTM.

2. METHODS

2.1. Study design and setting

The electronic health record data from two large U.S. academic provider networks were linked with Medicare claims data.¹⁵ The first network consisted of 1 tertiary hospital (Massachusetts General Hospital), 2 community hospitals, and 17 primary care centers. The second network included 1 tertiary hospital (Brigham and Women’s Hospital), 1 community hospital, and 16 primary care centers. This retrospective matched case-control study (ratio 1:1) assessed all adult patients (aged ≥ 18 years) who were admitted from January 2011 to December 2018 and experienced a cardiac arrest event. Cardiac arrest was defined as the absence of a palpable central pulse, apnea, and unresponsiveness. Patients who survived the initial cardiac arrest and underwent therapeutic hypothermia were selected and classified into two groups: the case group including patients who experienced IHCA and the control group including those who experienced OHCA, with 1:1 ratio matched for age (within 3 years), Charlson score (within 3 points), and sex manually. The exclusion criteria included early mortality before the TTM was completed, missing data, or patients with “do not resuscitate” orders. Clinical, epidemiological, and resuscitation characteristics; possible TTM-related complications; and outcomes in cases and controls were compared. The local Ethical Committee of Partners HealthCare Institutional Review Board (Protocol Number: 2019P000111) approved the study and waived the requirement for informed consent.

2.2. TTM protocols

TTM protocols may vary from hospital to hospital but are accepted by the national academic societies and adhere to international guidelines. TTM refers to strict temperature control to target the core body temperature between 33°C and 36°C following the cardiac arrest. Patients who fulfilled the following criteria were eligible for the initiation of TTM: 1) time within 6–12 h following the return of spontaneous circulation (ROSC) after the cardiac arrest regardless of initial rhythm; 2) ability to maintain a mean arterial pressure (MAP) of ≥ 65 mmHg with or without inotropes, or circulatory support devices; 3) comatose state, defined as lack of a meaningful response to verbal commands. No absolute contraindications to TTM existed. The ultimate decision to begin TTM was based on an assessment of potential risks and benefits of hypothermia in each individual patient considering the complete clinical situation and possible comorbidities. Patients highly at risk of adverse events with hypothermia due to recent head trauma, active bleeding, major surgery within the last 14 days, severe sepsis, pregnancy,

or refractory hypotension received TTM targeted specifically toward reaching 36°C rather than the range of 33–36°C.

The cooling treatment was immediately initiated, and the protocol allowed up to 4 h to reach the target temperature. Patients were then maintained at the designated target temperature of 24 h and subsequently rewarmed to 37°C at a rate of 0.25°C per hour (not $>0.5^\circ\text{C}$ per hour) during a period of 12–16 h. Sedation and low-dose analgesia were mandatory throughout the cooling and rewarming phases to attain a Bedside Shivering Assessment Scale score of 0.¹⁶ A neuromuscular blockade agent was administered as necessary. Due to the pragmatic study design, no fixed standardized treatment regimens were applied. After TTM, active intervention to prevent fever was recommended for another 48 h.

2.3. Data collection and outcomes

Routine patient demographic data, event date, and time, medical history as recorded by the International Statistical Classification of Diseases and Related Health Problems (ICD-10) diagnostic code, physiologic measures, blood analysis data, and patient outcomes were retrospectively extracted and collected from the registry database and hospital records. These data were subsequently verified by two different attending physicians. In patients with multiple ensuing IHCAs in the same patient within 48 h, only data from the first episode were included to prevent confounding effects between events. The time to ROSC was defined as the time from collapse or alarm call until ROSC was established. The sequential organ failure assessment (SOFA) score within the first 24 h after admission was used to evaluate the severity of multiple organ dysfunction.¹⁷ Neurological outcome and survival at hospital discharge were the primary outcome measures. Subsequent hospital length of stay (LOS) after the cardiac arrest event was the secondary outcome. The neurological outcome was assessed using the Glasgow–Pittsburgh Cerebral Performance Categories (CPC) scale at discharge and recorded as CPC 1 (good performance), CPC 2 (moderate disability), CPC 3 (severe disability), CPC 4 (vegetative state), or CPC 5 (brain death or death).¹⁸ The neurological outcome at discharge was dichotomized by the CPC to good (1–2) or poor (3–5).

2.4. Statistical analysis

Results are expressed as n (%) for categorical variables. Descriptive statistics were reported as mean \pm SD or median interquartile range for continuous variables. The groups were compared using the Student’s t -test for numerical data and Pearson’s chi-squared test or Fisher’s exact test for categorical data, as appropriate. Logistic regression models were used to explore independent risk factors for in-hospital mortality and patients’ neurological outcomes. Univariate analyses were performed separately for each risk factor to ascertain the odds ratio and 95% CI. All biologically plausible variables with p value of <0.10 in the univariate analysis were considered for inclusion in the logistic regression model during the multivariate analysis. A backward selection process was used. All analyses were processed using the IBM SPSS Statistics software (version 20.0; IBM Corp., Armonk, NY USA). Differences were considered to have reached the significance level with a two-tailed $p < 0.05$.

3. RESULTS

During the study period, 400 eligible patients received TTM after the cardiac arrest (Fig. 1). Among them, 93 patients with IHCA were selected as the case group. The control group was identified by obtaining the same number of patients with OHCA, matched for age, Charlson score, and sex. Demographic data, underlying

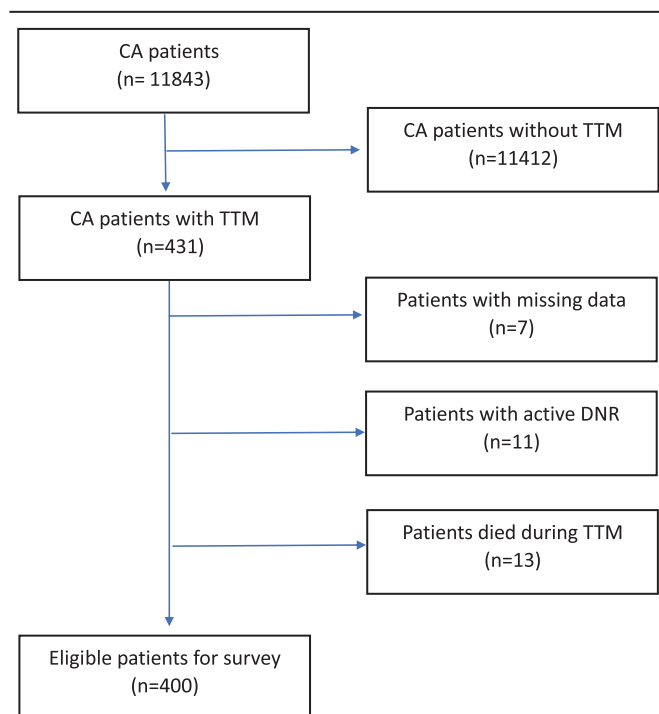


Fig. 1. A schematic diagram showing the selection process of patients for analysis (from 2011 to 2018). CA = cardiac arrest; TTM = targeted temperature management; DNR = do not resuscitate.

diseases, and resuscitation variables are displayed in Tables 1 and 2. No significant differences were detected in the body mass index, ethnicity, smoking status, coexisting conditions, initial rhythm, presumed cardiac cause, and coronary reperfusion with percutaneous coronary intervention. Patients with IHCA were more likely to have experienced a witnessed arrest (93.5% vs. 36.6%; $p < 0.001$), receive by-stander cardiopulmonary resuscitation (CPR) (93.5% vs. 36.6%; $p < 0.001$), larger total dosage of epinephrine (3.4 mg vs. 2.4 mg; $p < 0.045$), and extracorporeal membrane oxygenation (6.5% vs. 0%; $p = 0.013$). The time duration for ROSC was shorter in patients with IHCA (mean difference, 19.5–16.6 minutes = 174 seconds) than that in those with OHCA.

Patient characteristics after ROSC, TTM effects on coagulation and electrolyte parameters, and resuscitation outcomes at discharge are shown in Table 3. Overall, after ROSC, patients with IHCA had higher SOFA scores (9.5 vs. 8.4; $p = 0.004$), lower blood glucose levels (119.1 mg/dL vs. 259.6 mg/dL; $p = 0.002$), lower MAP (73.1 mmHg vs. 85.5 mmHg; $p < 0.001$), and longer subsequent LOS (19.7 days vs. 12.7 days; $p = 0.025$) than that in those with OHCA. The IHCA group was more likely to be associated with mild thrombocytopenia (platelet count, <150 K/ μ L) during TTM; however, neither the standard coagulation nor the electrolyte parameters showed any differences between the two groups. Finally, survival to discharge and favorable neurological outcomes did not differ between the IHCA and OHCA groups.

The univariate analysis showed that initial shockable rhythm, time to ROSC, total epinephrine dosage, presumed cardiac cause, coronary artery disease, heart failure, and SOFA within 24 hours after the event are predictors of survival at discharge among patients receiving TTM (Table 4). In the multivariate regression analysis, the initial shockable rhythm, time to ROSC, and past medical history of heart failure were independent outcome predictors for survival to hospital discharge. Factors that

Table 1.

Demographic data of patients with IHCA and OHCA receiving TTM

	IHCA (N = 93)	OHCA (N = 93)	<i>p</i>
Sex			
Male, N (%)	61 (65.6)	61 (65.6)	1.000
Female, N (%)	32 (34.4)	32 (34.4)	
Age, mean (SD)	65.5 (13.7)	65.5 (13.8)	0.977
BMI, mean (SD)	28.1 (5.7)	28.9 (6.7)	0.982
Ethnicity, N (%)			0.693
White	63 (67.6)	68 (73.0)	
Black	17 (18.3)	11 (11.8)	
Hispanic	8 (8.6)	6 (6.5)	
Asian	1 (1.1)	1 (1.1)	
Mixed	2 (2.2)	2 (2.2)	
Not recorded	2 (2.2)	5 (5.4)	
Smoking status, N (%)			
Former smoker	27 (29.0)	27 (29.0)	1.000
Current smoker	17 (18.3)	24 (25.8)	0.216
Nonsmoker	31 (33.3)	22 (23.7)	0.131
Unknown	18 (19.4)	20 (21.5)	0.716
Coexisting conditions, N (%)			
Hypertension	57 (61.3)	57 (61.3)	1.000
Diabetes mellitus	47 (50.5)	36 (38.7)	0.105
Chronic lung disease	27 (29.0)	26 (28.0)	0.871
Coronary artery disease	39 (41.9)	46 (49.5)	0.303
Heart failure	34 (36.6)	25 (26.9)	0.156
Arrhythmia	33 (35.5)	43 (46.2)	0.136
Peptic ulcer disease	19 (20.4)	18 (19.4)	0.854
Hepatic insufficiency	7 (7.5)	6 (6.5)	0.774
Renal insufficiency	39 (41.9)	35 (37.6)	0.549
Uremia under regular hemodialysis	13 (14.0)	6 (6.5)	0.090
Cerebrovascular disease	13 (14.0)	17 (18.3)	0.425
Dementia	1 (1.1)	4 (4.3)	0.368
Connective tissue disease	6 (6.5)	3 (3.2)	0.305
Solid tumor	18 (19.4)	23 (24.7)	0.376
Leukemia/lymphoma	7 (7.5)	1 (1.1)	0.064
Charlson score, mean (SD)	6.0 (2.9)	5.5 (2.5)	0.192
0–2	12 (12.9)	11 (11.8)	0.643
3 or 4	15 (16.1)	20 (21.5)	
≥ 5	66 (71.0)	62 (66.7)	

IHCA = in-hospital cardiac arrest; OHCA = out-of-hospital cardiac arrest; TTM = targeted temperature management; Age (in years); BMI = body mass index.

significantly predicted the favorable neurological outcome at discharge in the logistic regression analysis are shown in Table 5. The univariate analysis of predictors was an initial shockable rhythm, total epinephrine dosage, presumed cardiac cause, and SOFA within 24 hours after the event. Multivariate analysis revealed that the only factor to predict favorable neurological outcomes at discharge was the initial shockable rhythm. IHCA was not a pivotal factor affecting the resuscitation outcomes of patients after the cardiac arrest who received TTM.

4. DISCUSSION

Despite substantial improvements in resuscitation efforts over the last few decades, outcomes of OHCA and IHCA remain poor.^{19–22} In clinical scenarios, significant disparity was observed in the utilization of TTM. In contrast to OHCA patients with ROSC of whom at least 50% qualify for TTM,^{23,24} $<7\%$ of patients with IHCA qualify for therapeutic hypothermia.^{9,25} However, differences in TTM influence between IHCA and OHCA should be investigated because cardiac arrest still affects approximately 200,000 hospitalized individuals annually in the USA.²⁶

Table 2.
Event-associated parameters of IHCA and OHCA patients receiving TTM

	IHCA (N = 93)	OHCA (N = 93)	p
Initial rhythm, N (%)			
Shockable	24 (25.8)	36 (38.7)	0.060
Nonshockable	69 (74.2)	57 (61.3)	
Witnessed, N (%)	87 (93.5)	34 (36.6)	<0.001*
Bystander CPR, N (%)	87 (93.5)	34 (36.6)	<0.001*
Being transferred, N (%)	34 (36.6)	33 (35.5)	0.879
Presumed cardiac cause, N (%)	30 (32.3)	32 (34.4)	0.756
PCI, N (%)	27 (29.0)	31 (33.3)	0.527
Time to return for spontaneous circulation (min)			
Mean (SD)	16.6 (16.3)	19.5 (15.5)	0.034*
Median (IQR)	12 (7–23)	15 (10–25)	
<10	35 (37.6)	16 (17.2)	0.018*
10–19	29 (31.2)	40 (43.0)	
20–29	10 (10.8)	18 (19.4)	
30–59	17 (18.3)	15 (16.1)	
>60	2 (2.2)	4 (4.3)	
Cumulative dosage of epinephrine, N (%)			
0	15 (16.1)	29 (31.0)	
1	10 (10.8)	11 (11.8)	
2	27 (28.9)	14 (15.1)	
3	12 (12.9)	17 (18.3)	
4–6	12 (12.9)	17 (18.3)	
7–9	11 (11.9)	3 (3.3)	
≥10	6 (6.5)	2 (2.2)	
Total dosage of epinephrine, mean (SD)	3.4 (3.7)	2.4 (2.7)	0.046*
ECMO use, N (%)	6 (6.5)	0 (0.0)	0.013*

IHCA = in-hospital cardiac arrest; OHCA = out-of-hospital cardiac arrest; TTM = targeted temperature management; CPR = cardiopulmonary resuscitation; PCI = percutaneous coronary intervention; IQR = interquartile range; ECMO = extracorporeal membrane oxygenation.

* $p < 0.05$.

The use of TTM remains controversial in patients with IHCA, and the International Liaison Committee on Resuscitation makes a much weaker recommendation for TTM utilization in patients with IHCA than those with OHCA.²⁷ Contradictory to previous findings,^{9,10,14,28} the beneficial effects of TTM in IHCA regarding survival and neuroprotection were found to be similar to those in OHCA. The majority of patients with IHCA experienced a witnessed cardiac arrest and received bystander CPR. However, the IHCA group had higher SOFA scores and lower initial MAPs, which are associated with early in-hospital mortality.²⁹ The detrimental effect might be compensated by significantly shorter time duration to ROSC in the IHCA group. Time to ROSC possibly acts as a mortality marker and brain injury severity among cardiac arrest survivors and is inversely associated with the likelihood of neurological recovery.^{30–32} Effects of TTM may not be consistent over the full spectrum of the time to ROSC. Theoretically, time to ROSC may be further dichotomized into “no-flow time” and “low-flow time.” In 1987, Bulkley postulated a bimodal model of injury after a prolonged ischemia followed by reperfusion.^{33,34} Postresuscitation hypothermia treatment imparts beneficial effects by diminishing early excitotoxic and intermediate inflammatory reactions and later apoptotic cell death.^{35–37} The duration of resuscitation efforts, corresponding to the “low-flow time,” influences the TTM effectiveness.³⁸ A prolonged period of “low-flow time” with subphysiological perfusion worsens the reperfusion injury and therefore treating these processes, even with the TTM application, may no longer be possible. In this study, the exact “no-flow time” and “low-flow time” of each patient were not measured because of insufficient medical records. It should be pointed out that some

Table 3.
Characteristics after return of spontaneous circulation and outcome of patients receiving TTM

	IHCA (N = 93)	OHCA (N = 93)	p
SOFA within 24 hours after event			
Mean (SD)	9.5 (2.4)	8.4 (2.7)	0.004*
Median (IQR)	9 (8–11)	8 (7–11)	
Glucose (mg/dL), mean (SD)	199.1 (101.9)	259.6 (193.1)	0.002*
MAP (mmHg), mean (SD)	73.1 (16.1)	85.5 (24.0)	<0.001*
pH, mean (SD)	7.28 (0.17)	7.27 (0.16)	0.896
Lactate (mmol/L), mean (SD)	5.6 (5.3)	5.8 (3.9)	0.226
Creatinine (mg/dL), mean (SD)	2.3 (2.2)	1.8 (1.3)	0.413
Coagulopathy after TTM, N (%)			
Thrombocytopenia <150 K/μL	48 (51.6)	29 (31.2)	0.004*
Thrombocytopenia <50 K/μL	7 (7.5)	1 (1.1)	0.064
Thrombocytopenia <20 K/μL	0 (0.0)	0 (0.0)	...
Prolonged PT >14.4 s	62 (66.7)	57 (61.3)	0.276
Prolonged aPTT >36.6 s	36 (38.7)	31 (33.3)	0.549
Electrolyte imbalance after TTM, N (%)			
Hypernatremia, sodium >145 mmol/L	7 (7.5)	2 (2.2)	0.090
Hyponatremia, sodium <136 mmol/L	26 (28.0)	24 (25.8)	0.774
Hyperkalemia, potassium >5.0 mmol/L	9 (9.7)	13 (14.0)	0.344
Hypokalemia, potassium <3.4 mmol/L	4 (4.3)	6 (6.5)	0.502
Outcome			
Subsequent LOS, mean (SD)	19.7 (28.4)	12.7 (11.7)	0.025*
Acute kidney injury, N (%)	28 (30.1)	27 (29.0)	0.830
Survival to discharge, N (%)	50 (53.8)	42 (45.2)	0.241
Favorable CPC scale at discharge, N (%)	24 (25.8)	26 (28.0)	0.182

TTM = targeted temperature management; IHCA = in-hospital cardiac arrest; OHCA = out-of-hospital cardiac arrest; SOFA = sequential organ failure assessment; IQR = interquartile range; MAP = mean arterial pressure; PT = prothrombin time; aPTT = activated partial thromboplastin time; LOS = length of hospital stay; CPC scale = cerebral performance category scale.
* $p < 0.05$.

heterogeneity on the actual exposure to “no-flow time” must be expected, and thus, the time correlation to ROSC and the actual magnitude of the reperfusion injury may not be perfect. Nevertheless, a significantly shorter time to ROSC did play a major role in advantageously influencing the outcomes.

Aside from describing the comparisons of IHCA and OHCA, we sought to assess the prognostic implication of pertinent factors for patients with cardiac arrest who received TTM. With regard to outcome analysis, significant predictors of survival at discharge were the initial shockable rhythm and shorter time to ROSC. Interestingly, another significant predictor was a past medical history of heart failure. We assumed that these patients may have a certain degree of protective effect conferred upon them from the routine use of heart failure medications. The actual mechanism of this effect requires further holistic investigation.

Hypothermia itself can inhibit the cellular immune response; cause cardiac arrhythmias, decrease cardiac, renal, gastrointestinal, and cerebral function; and induce coagulopathy.³⁹ With the paucity of complete documentation, only platelet counts, prothrombin time, and activated partial thromboplastin time were presented, instead of actual bleeding or thrombosis complications, such as bleeding in critical organs or in-stent thrombosis after the percutaneous coronary intervention. The probability of hypothermia-related complications such as severe coagulopathy and renal dysfunction was not significantly different between the IHCA and OHCA groups.

In our study, detailed information regarding the targeted temperature and cooling method for each patient is shown. However, a previous trial published in 2013 showed that hypothermia at a target temperature of 33°C was not beneficial

Table 4.**Logistic regression analysis of predictors of survival at discharge among patients receiving TTM in this cohort**

	Univariable analysis		Multivariable analysis	
	Odds ratio (95% CI)	<i>p</i>	Odds ratio (95% CI)	<i>p</i>
IHCA	1.412 (0.793–2.514)	0.241		
Age	0.998 (0.978–1.020)	0.877		
Sex, male	1.419 (0.772–2.607)	0.260		
Charlson score	1.075 (0.966–1.196)	0.185		
Initial shockable rhythm	3.173 (1.657–6.078)	<0.001	3.876 (1.876–8.008)	<0.001*
Time to ROSC	0.966 (0.943–0.989)	0.004	0.966 (0.940–0.992)	0.011*
Witnessed cardiac arrest	1.687 (0.874–3.260)	0.119		
Bystander CPR	1.348 (0.736–2.470)	0.333		
Total dosage of epinephrine	0.855 (0.764–0.957)	0.006		
Presumed cardiac cause	1.857 (1.000–3.448)	0.050		
Coronary artery disease	2.195 (1.219–3.953)	0.009		
Arrhythmia	1.134 (0.632–2.035)	0.674		
Heart failure	2.202 (1.168–4.149)	0.015	2.589 (1.269–5.283)	0.009*
Cerebrovascular disease	1.203 (0.550–2.632)	0.644		
Thrombocytopenia (PLT < 150,000)	1.073 (0.584–1.972)	0.821		
Hypokalemia	0.413 (0.103–1.653)	0.211		
Glucose level after ROSC	0.998 (0.995–1.000)	0.114		
SOFA within 24 hours after event	0.901 (0.801–1.014)	0.083		
Mean arterial pressure	1.003 (0.989–1.017)	0.665		

TTM = targeted temperature management; IHCA = in-hospital cardiac arrest; ROSC = return of spontaneous circulation; CPR = cardiopulmonary resuscitation; PLT = platelet; SOFA = sequential organ failure assessment.

**p* < 0.05

Table 5.**Logistic regression analysis of predictors of favorable neurological outcome among survivors after TTM**

	Univariable analysis		Multivariable analysis	
	Odds ratio (95% CI)	<i>p</i>	Odds ratio (95% CI)	<i>p</i>
IHCA	0.568 (0.247–1.308)	0.184		
Age	1.015 (0.983–1.049)	0.364		
Sex, male	1.581 (0.647–3.863)	0.315		
Charlson score	1.027 (0.879–1.201)	0.734		
Initial shockable rhythm	5.221 (2.099–12.986)	<0.001	6.570 (2.435–17.728)	<0.001*
Time to ROSC	0.971 (0.933–1.010)	0.145		
Witnessed cardiac arrest	1.616 (0.597–4.380)	0.345		
Bystander CPR	0.631 (0.257–1.549)	0.315		
Total dosage of epinephrine	0.749 (0.600–0.934)	0.010		
Presumed cardiac cause	3.757 (1.524–9.257)	0.004		
Coronary artery disease	1.795 (0.781–4.126)	0.168		
Arrhythmia	1.155 (0.503–2.654)	0.733		
Heart failure	0.681 (0.294–1.575)	0.369		
Cerebrovascular disease	0.810 (0.275–2.382)	0.701		
Thrombocytopenia (PLT < 150,000)	1.182 (0.497–2.810)	0.706		
Hypokalemia	0.409 (0.036–4.696)	0.473		
Glucose level after ROSC	0.999 (0.995–1.003)	0.709		
SOFA within 24 hours after event	0.821 (0.686–0.982)	0.031		
Mean arterial pressure	1.017 (0.995–1.039)	0.130		

TTM = targeted temperature management; IHCA = in-hospital cardiac arrest; ROSC = return of spontaneous circulation; CPR = cardiopulmonary resuscitation; PLT = platelet; SOFA = sequential organ failure assessment.

**p* < 0.05.

compared with a target temperature of 36°C.¹² In addition, a nationwide multicenter analysis revealed no significant difference in the neurological recovery regarding the cooling methods for TTM.⁴⁰ Thus, we recruited all patients receiving TTM instead of categorizing with regard to the targeted temperature or cooling methods. TTM is largely attributed to intracellular shifts and increased potassium excretion from cold diuresis,^{41,42} although no tendency was observed toward developing

hypokalemia among the study population. Previous studies have demonstrated that extracorporeal cardiopulmonary resuscitation has favorable outcomes for the treatment of cardiac arrest, particularly with IHCA.^{43–45} However, pertinent data in our study were too limited to exhaustively assess its efficacy on patients receiving TTM.

Our study has the unique advantage by involving a large cohort of diverse population that included patients with IHCA

and OHCA from multiple centers, making our findings fairly generalizable. However, our study has limitations that should be addressed. First, this study was conducted using the registry data and was thus subject to limitations of any retrospective analysis, given that the causal relationship between variables could not be established although several associations were demonstrated. Second, a selection bias might have occurred, because the final decision to manage a patient was left by the clinical physician's discretion. Therefore, a higher proportion of patients with expected favorable outcomes would possibly receive TTM to optimize the prognosis. In addition, we do not have data on why patients did not receive TTM or the quality of TTM itself. Third, our study measured end points only at the time of hospital discharge, despite the knowledge that the neurological function can ameliorate for at least 6 months after resuscitation from cardiac arrest. Namely, long-term functional outcomes may be a more robust measurement of any treatment effect on patients recovering from cardiac arrest.⁴⁶ Good neurological outcome was defined as a CPC score of 1 or 2, which may be considered a rather crude measurement of neurological outcome. However, subtle differences in cognitive outcomes might not be recognized via CPC score, and a more detailed, thorough assessment of milder cognitive impairment is necessary in evaluating the potentially subtle treatment effects. Fourth, information regarding the usage and selection of sedation regimens was not collected, which are also considered to have an impact on outcomes in the postcardiac arrest care.⁴⁷ Furthermore, no record regarding the vasopressor use was observed among our study population; however, relevant complications, such as arrhythmia and decreased peripheral perfusion, could potentially have been unavoidably precipitated by a high dosage of vasopressors.⁴⁸ Rapid rewarming and longer preinduction time (the time from ROSC to TTM initiation) have been reported to have an adverse effect on outcomes;^{49,50} however, no pertinent data were found for that assessment. Fifth, clinical outcomes were only compared, not for medical costs or hospital resource utilization such as the workload and LOS in the intensive care unit. Finally, our observational period is 8 years and the intensive care treatment, especially the postresuscitation care standards, might have changed over the period.

In conclusion, similar beneficial effects of TTM were found in eligible patients with IHCA compared with those with OHCA in this matched cohort study. Initial shockable rhythm was the only predictor of both survival and favorable neurological outcomes at discharge in all cardiac arrest survivors receiving subsequent TTM.

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REFERENCES

- Arrich J, Holzer M, Havel C, Müllner M, Herkner H. Hypothermia for neuroprotection in adults after cardiopulmonary resuscitation. *Cochrane Database Syst Rev* 2016;2:CD004128.
- Roth GA, Forouzanfar MH, Moran AE, Barber R, Nguyen G, Feigin VL, et al. Demographic and epidemiologic drivers of global cardiovascular mortality. *N Engl J Med* 2015;372:1333–41.
- Neumar RW, Nolan JP, Adrie C, Aibiki M, Berg RA, Böttiger BW, et al. Post-cardiac arrest syndrome: Epidemiology, pathophysiology, treatment, and prognostication. A consensus statement from the International Liaison Committee on Resuscitation (American Heart Association, Australian and New Zealand Council on Resuscitation, European Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Asia, and the Resuscitation Council of Southern Africa); the American Heart Association Emergency Cardiovascular Care Committee; the Council on Cardiovascular Surgery and Anesthesia; the Council on Cardiopulmonary, Perioperative, and Critical Care; the Council on Clinical Cardiology; and the Stroke Council. *Circulation* 2008;118:2452–83.
- Bernard SA, Gray TW, Buist MD, Jones BM, Silvester W, Gutteridge G, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med* 2002;346:557–63.
- Hypothermia after Cardiac Arrest Study G. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med* 2002;346:549–56.
- Gaieski DF, Band RA, Abella BS, Neumar RW, Fuchs BD, Kolinsky DM, et al. Early goal-directed hemodynamic optimization combined with therapeutic hypothermia in comatose survivors of out-of-hospital cardiac arrest. *Resuscitation* 2009;80:418–24.
- Nolan JP, Soar J, Cariou A, Cronberg T, Moulart VR, Deakin CD, et al. European Resuscitation Council and European Society of Intensive Care Medicine Guidelines for Post-resuscitation Care 2015: section 5 of the European Resuscitation Council Guidelines for Resuscitation 2015. *Resuscitation* 2015;95:202–22.
- Wang CH, Huang CH, Chang WT, Tsai MS, Yu PH, Wu YW, et al. Associations among gender, marital status, and outcomes of adult in-hospital cardiac arrest: a retrospective cohort study. *Resuscitation* 2016;107:1–6.
- Arrich J; European Resuscitation Council Hypothermia After Cardiac Arrest Registry Study Group. Clinical application of mild therapeutic hypothermia after cardiac arrest. *Crit Care Med* 2007;35:1041–7.
- Kory P, Fukunaga M, Mathew JP, Singh B, Szainwald L, Mosak J, et al. Outcomes of mild therapeutic hypothermia after in-hospital cardiac arrest. *Neurocrit Care* 2012;16:406–12.
- Mahmoud A, Elgendy IY, Bavry AA. Use of targeted temperature management after out-of-hospital cardiac arrest: a meta-analysis of randomized controlled trials. *Am J Med* 2016;129:522–7.e2.
- Nielsen N, Wetterslev J, Cronberg T, Erlinge D, Gasche J, Hassager C, et al. Targeted temperature management at 33°C versus 36°C after cardiac arrest. *N Engl J Med* 2013;369:2197–206.
- Caltekin I, Savrun A, Gokcen E, Atik D, Demirtas E, Demir B, et al. Comparison of the factors affecting neurological outcome in out-of-hospital cardiac arrest cases. *J Pak Med Assoc* 2016;66:1412–7.
- Nichol G, Huszti E, Kim F, Fly D, Parnia S, Donnino M, et al. Does induction of hypothermia improve outcomes after in-hospital cardiac arrest? *Resuscitation* 2013;84:620–5.
- Hennessy S. Use of health care databases in pharmacoepidemiology. *Basic Clin Pharmacol Toxicol* 2006;98:311–3.
- Badjatia N, Strongilis E, Gordon E, Prescutti M, Fernandez L, Fernandez A, et al. Metabolic impact of shivering during therapeutic temperature modulation: the Bedside Shivering Assessment Scale. *Stroke* 2008;39:3242–7.
- Vincent JL, de Mendonça A, Cantraine F, Moreno R, Takala J, Suter PM, et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on “sepsis-related problems” of the European Society of Intensive Care Medicine. *Crit Care Med* 1998;26:1793–800.
- Booth CM, Boone RH, Tomlinson G, Detsky AS. Is this patient dead, vegetative, or severely neurologically impaired? Assessing outcome for comatose survivors of cardiac arrest. *JAMA* 2004;291:870–9.
- Bergum D, Nordseth T, Mjølstad OC, Skogvoll E, Haugen BO. Causes of in-hospital cardiac arrest—incidences and rate of recognition. *Resuscitation* 2015;87:63–8.
- Kolte D, Khera S, Aronow WS, Palaniswamy C, Mujib M, Ahn C, et al. Regional variation in the incidence and outcomes of in-hospital cardiac arrest in the United States. *Circulation* 2015;131:1415–25.
- Nichol G, Thomas E, Callaway CW, Hedges J, Powell JL, Aufderheide TP, et al; Resuscitation Outcomes Consortium Investigators. Regional variation in out-of-hospital cardiac arrest incidence and outcome. *JAMA* 2008;300:1423–31.

22. Sandroni C, Nolan J, Cavallaro F, Antonelli M. In-hospital cardiac arrest: incidence, prognosis and possible measures to improve survival. *Intensive Care Med* 2007;33:237–45.
23. Dumas F, Grimaldi D, Zuber B, Fichet J, Charpentier J, Pène F, et al. Is hypothermia after cardiac arrest effective in both shockable and nonshockable patients?: insights from a large registry. *Circulation* 2011;123:877–86.
24. Phelps R, Dumas F, Maynard C, Silver J, Rea T. Cerebral performance category and long-term prognosis following out-of-hospital cardiac arrest. *Crit Care Med* 2013;41:1252–7.
25. Mikkelsen ME, Christie JD, Abella BS, Kerlin MP, Fuchs BD, Schweickert WD, et al; American Heart Association's Get With the Guidelines-Resuscitation Investigators. Use of therapeutic hypothermia after in-hospital cardiac arrest. *Crit Care Med* 2013;41:1385–95.
26. Graham R, McCoy MA, Schultz AM. *Strategies to improve cardiac arrest survival: a time to act*. Washington, DC: National Academies Press; 2015.
27. Callaway CW, Soar J, Aibiki M, Böttiger BW, Brooks SC, Deakin CD, et al; Advanced Life Support Chapter Collaborators. Part 4: advanced life support: 2015 international consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. *Circulation* 2015;132(16 Suppl 1):S84–145.
28. Gueret RM, Bailitz JM, Sahni AS, Tulaimat A. Therapeutic hypothermia at an urban public hospital: development, implementation, experience and outcomes. *Heart Lung* 2017;46:40–5.
29. Huang CH, Tsai MS, Ong HN, Chen W, Wang CH, Chang WT, et al. Association of hemodynamic variables with in-hospital mortality and favorable neurological outcomes in post-cardiac arrest care with targeted temperature management. *Resuscitation* 2017;120:146–52.
30. Kjaergaard J, Nielsen N, Winther-Jensen M, Wanscher M, Pellis T, Kuiper M, et al. Impact of time to return of spontaneous circulation on neuroprotective effect of targeted temperature management at 33 or 36 degrees in comatose survivors of out-of hospital cardiac arrest. *Resuscitation* 2015;96:310–6.
31. Reynolds JC, Frisch A, Rittenberger JC, Callaway CW. Duration of resuscitation efforts and functional outcome after out-of-hospital cardiac arrest: when should we change to novel therapies? *Circulation* 2013;128:2488–94.
32. Wibrandt I, Norsted K, Schmidt H, Schierbeck J. Predictors for outcome among cardiac arrest patients: the importance of initial cardiac arrest rhythm versus time to return of spontaneous circulation, a retrospective cohort study. *BMC Emerg Med* 2015;15:3.
33. Bulkley GB. Free radical-mediated reperfusion injury: a selective review. *Br J Cancer Suppl* 1987;8:66–73.
34. González-Ibarra FP, Varon J, López-Meza EG. Therapeutic hypothermia: critical review of the molecular mechanisms of action. *Front Neurol* 2011;2:4.
35. Polderman KH. Application of therapeutic hypothermia in the ICU: opportunities and pitfalls of a promising treatment modality. Part 1: indications and evidence. *Intensive Care Med* 2004;30:556–75.
36. Webster CM, Kelly S, Koike MA, Chock VY, Giffard RG, Yenari MA. Inflammation and NFkappaB activation is decreased by hypothermia following global cerebral ischemia. *Neurobiol Dis* 2009;33:301–12.
37. Zhao H, Wang JQ, Shimohata T, Sun G, Yenari MA, Sapolsky RM, et al. Conditions of protection by hypothermia and effects on apoptotic pathways in a rat model of permanent middle cerebral artery occlusion. *J Neurosurg* 2007;107:636–41.
38. Wallmüller C, Testori C, Sterz F, Stratil P, Schober A, Herkner H, et al. Limited effect of mild therapeutic hypothermia on outcome after prolonged resuscitation. *Resuscitation* 2016;98:15–9.
39. Kirkpatrick AW, Chun R, Brown R, Simons RK. Hypothermia and the trauma patient. *Can J Surg* 1999;42:333–43.
40. Kim KH, Shin SD, Song KJ, Ro YS, Kim YJ, Hong KJ, et al. Cooling methods of targeted temperature management and neurological recovery after out-of-hospital cardiac arrest: a nationwide multicenter multi-level analysis. *Resuscitation* 2018;125:56–65.
41. Aibiki M, Kawaguchi S, Maekawa N. Reversible hypophosphatemia during moderate hypothermia therapy for brain-injured patients. *Crit Care Med* 2001;29:1726–30.
42. Clifton GL, Miller ER, Choi SC, Levin HS. Fluid thresholds and outcome from severe brain injury. *Crit Care Med* 2002;30:739–45.
43. Bednarczyk JM, White CW, Ducas RA, Golian M, Nepomuceno R, Hiebert B, et al. Resuscitative extracorporeal membrane oxygenation for in hospital cardiac arrest: a Canadian observational experience. *Resuscitation* 2014;85:1713–9.
44. Chen YS, Lin JW, Yu HY, Ko WJ, Jerng JS, Chang WT, et al. Cardiopulmonary resuscitation with assisted extracorporeal life-support versus conventional cardiopulmonary resuscitation in adults with in-hospital cardiac arrest: an observational study and propensity analysis. *Lancet* 2008;372:554–61.
45. Kagawa E, Inoue I, Kawagoe T, Ishihara M, Shimatani Y, Kurisu S, et al. Assessment of outcomes and differences between in- and out-of-hospital cardiac arrest patients treated with cardiopulmonary resuscitation using extracorporeal life support. *Resuscitation* 2010;81:968–73.
46. Smith K, Andrew E, Lijovic M, Nehme Z, Bernard S. Quality of life and functional outcomes 12 months after out-of-hospital cardiac arrest. *Circulation* 2015;131:174–81.
47. Paul M, Bougouin W, Dumas F, Geri G, Champigneulle B, Guillemet L, et al. Comparison of two sedation regimens during targeted temperature management after cardiac arrest. *Resuscitation* 2018;128:204–10.
48. Giraud R, Siegenthaler N, Bendjelid K. Cardiac index during therapeutic hypothermia: which target value is optimal? *Crit Care* 2013;17:214.
49. Lee BK, Jeung KW, Jung YH, Lee DH, Lee SM, Cho YS, et al. Relationship between timing of cooling and outcomes in adult comatose cardiac arrest patients treated with targeted temperature management. *Resuscitation* 2017;113:135–41.
50. Lu X, Ma L, Sun S, Xu J, Zhu C, Tang W. The effects of the rate of post-resuscitation rewarming following hypothermia on outcomes of cardiopulmonary resuscitation in a rat model. *Crit Care Med* 2014;42:e106–13.