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Clinical paper

Targeted temperature management at 33 versus 36 degrees after out-of-hospital cardiac arrest: A follow-up study

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Abstract

Aim: Targeted temperature management (TTM) is commonly used in the setting of out-of-hospital cardiac arrest (OHCA) to improve survival and functional outcomes. However, real-world evidence of effects and optimal temperature are limited. To help address this, we examined associations between TTM and neurologically-intact survival after non-traumatic OHCA across changing institutional TTM temperature goals.

Methods: We performed a single-site, retrospective, cohort study of adults with non-traumatic OHCA who arrived comatose to the emergency department and received TTM from 2010 to 2020. Primary exposure was TTM goal temperature. Institutional goal temperature changed from 33 °C (TTM33-1) to 36 °C (TTM36) in 2014 and back to 33 °C (TTM33-2) in 2017. The primary outcome was neurologically-intact survival at discharge, defined as Cerebral Performance Category score of 1 or 2. Secondary outcomes included survival to hospital discharge and care processes. Multivariable logistic regression analysis evaluated association between TTM goal and neurological outcome.

Results: Of 1,469 OCHA patients meeting inclusion criteria, 800 (54%) received TTM. TTM was initiated more frequently during TTM33-1 (60%) than TTM36 (52%) or TTM33-2 (52%). After adjustment for demographic and cardiac arrest characteristics, there was no significant association between TTM goal temperature of 33 °C and neurologically-intact survival, versus 36 °C (adjusted odds ratio 1.10, 95% confidence interval 0.76, 1.60).

Conclusion: TTM goal temperature was not significantly associated with neurologically-intact survival of adult OHCA patients who arrived comatose to the emergency department.

Keywords: Out-of-hospital cardiac arrest, Cardiac arrest, Targeted temperature management, TTM, Therapeutic hypothermia

Introduction

An estimated 350,000 people suffer out-of-hospital cardiac arrest (OHCA) each year in the US.[1] Neurologic injury after return of spontaneous circulation (ROSC) in cardiac arrest is mediated by several mechanisms including microcirculatory dysfunction, reperfusion injury, cerebral edema and elevated intracranial pressure, neuroinflammation, and impaired autoregulation.[2] Targeted temperature management (TTM) is a treatment aimed at reducing neurologic injury among patients who remain comatose after cardiac arrest; however, the literature on TTM highlights areas of controversy including patient selection, timing of initiation, duration, ideal target temperature, and TTM methods.[3–8]

Several recent randomized trials have raised questions about the appropriate goal temperature after OHCA. The Targeted Temperature Management (TTM) trial compared 33 °C to 36 °C in a cohort of patients with predominantly shockable initial rhythms and cardiac etiology of arrest and found no difference in all-cause mortality.[3] The subsequent HYPERION trial included only patients with non-shockable rhythms and a mix of in-hospital and out-hospital arrests and found improved neurologically-intact survival among patients

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treated with TTM to 33 °C compared with normothermia.[7] The much larger TTM2 trial compared 33 °C with normothermia and also found no difference in all-cause mortality, again in a population with predominantly shockable rhythms (70%) and cardiac etiologies of arrest.[5] Collectively, these trials led to updated treatment recommendations from the International Liaison Committee on Resuscitation (ILCOR), suggesting active fever prevention by targeting a temperature of below 37.5 °C for all patients, but raising uncertainty about whether sub-populations might benefit from a lower temperature goal.[9]

As these trials were published and international guidelines evolved, so did our institution's local guidelines. We previously reported a 10% decrease in neurologically-intact OHCA survival after an institutional change in TTM goal from 33 °C to 36 °C.[10] After this, our institution changed its goal temperature back to 33 °C while continuing to track care processes and outcomes. Since the time of our original publication, many of the previously discussed major trials were completed, adding to controversy about optimal goal temperature following OHCA.[5,7]

We conducted a multivariable logistic regression analysis to evaluate associations between TTM goal temperature and neurologic outcome using data from three distinct time periods during which our institution's TTM goal was changed from 33 °C (TTM33-1) to 36 °C (TTM36), and back to 33 °C (TTM33-2). We hypothesized that treatment during 33 °C periods would be associated with favorable neurological outcomes compared with treatment during the 36 °C period.

Methods

Ethics approval and setting

The study was approved by the University of Washington Office of Research, Human Subjects Division (STUDY00003641). Informed consent was waived by the regulatory body for all participants. This study took place in Seattle, Washington at Harborview Medical Center (HMC), a 413-bed urban, academic, Level 1 trauma center.

Study design and population

This was a retrospective cohort study of adult patients ($\geq$ 18 years) who suffered nontraumatic OHCA in the City of Seattle between 2010 and 2020, were transported to HMC, and remained comatose upon arrival. Patients were identified in the Seattle Fire Department cardiac arrest registry, which includes detailed prehospital and in-hospital variables cleaned and coded by a highly trained research staff. Race data were assessed by paramedics at the time of patient encounter and aggregated into only the categories that comprised more than 10% of the data and have been shown previously to have good concordance with hospital records (Black, White) or Other.[11] The same nurse collected all hospital data during the study period. Patients missing demographic or cardiac arrest data elements that were selected *a priori* to be used for modeling (<2%) were excluded from further description and analyses. Data were assumed to be missing at random based on the authors' clinical experience.

Exposure

Our primary exposure was institutional TTM goal temperature, which was set at 33 °C from the beginning of our study window, January 2010 to April 2014 (TTM33-1); updated to 36 °C from April 2014 to October 2017 (TTM36) and returned to 33 °C from October 2017 to the end of our study window, December 2020 (TTM33-2).[10] Our institution had a single TTM goal during each of the study periods with standardized guidelines and electronic order sets that defaulted to the recommended temperature goal.

Outcomes

The primary outcome was neurologically-intact survival at the time of hospital discharge, defined as Cerebral Performance Category (CPC) score of 1 or 2. Neurological outcome was adjudicated by a research nurse via comprehensive review of the medical record, including discharge summaries, physical and occupational therapy notes, and, when applicable, death records. Secondary outcomes included survival to hospital discharge. We also report care processes, including lowest temperature achieved, cardiac care, and diagnostic testing.

Statistical analysis

For descriptive analyses, unadjusted rates of initiation of TTM, cardiac care processes, and patient outcomes (mortality and neurologically-intact survival) were compared between the time periods using Chi-square analysis. Age and lowest temperature attained were compared between the time periods using Wilcoxon rank sum test.

Multivariable logistic regression was used to evaluate associations between TTM temperature goal (combining the TTM33-1 and TTM33-2 periods into TTM33) and outcomes of interest. Independent variables included in the model were patient age and sex, presence of a shockable initial cardiac rhythm, and whether the cardiac arrest was witnessed.

Subgroup analyses to specifically examine associations between TTM period and outcomes among patients with non-shockable initial cardiac rhythm were also performed via multivariable logistic regression, with the model as specified for the main cohort.

Finally, a sensitivity analysis using time series methodology was performed to evaluate whether secular time trends or cyclical patterns had an effect on our findings. Specifically, we used autoregressive integrated moving average (ARIMA) time series analyses (AR = 1 day; MA = 1 day). For this analysis, each period was compared to the previous period (e.g. TTM36 vs. TTM33-1), thus the two TTM33 periods were not combined. Goodness-of-fit was evaluated by Aikake information criterion (AIC), and autocorrelation was evaluated graphically. All statistical analyses were performed using Stata 15.1 (College Station, TX).

Results

Patient demographics and cardiac arrest characteristics

Of the 1,469 patients meeting inclusion criteria that were transported to the study hospital after OHCA, 800 (54%) received TTM (Fig. 1). Patients with OHCA were not eligible for TTM if they were following commands, had life threatening bleeding, or hemodynamic instability (669 patients, 45%). Patient characteristics for those who received TTM compared to those who did not are featured in Supplemental Table 1.

TTM was initiated somewhat more frequently during TTM33-1 (N = 257; 60.9% of patients), than during TTM36 (N = 244; 51.7%) or TTM33-2 (N = 299; 52.0%) (Supplemental Table 2); however, rate

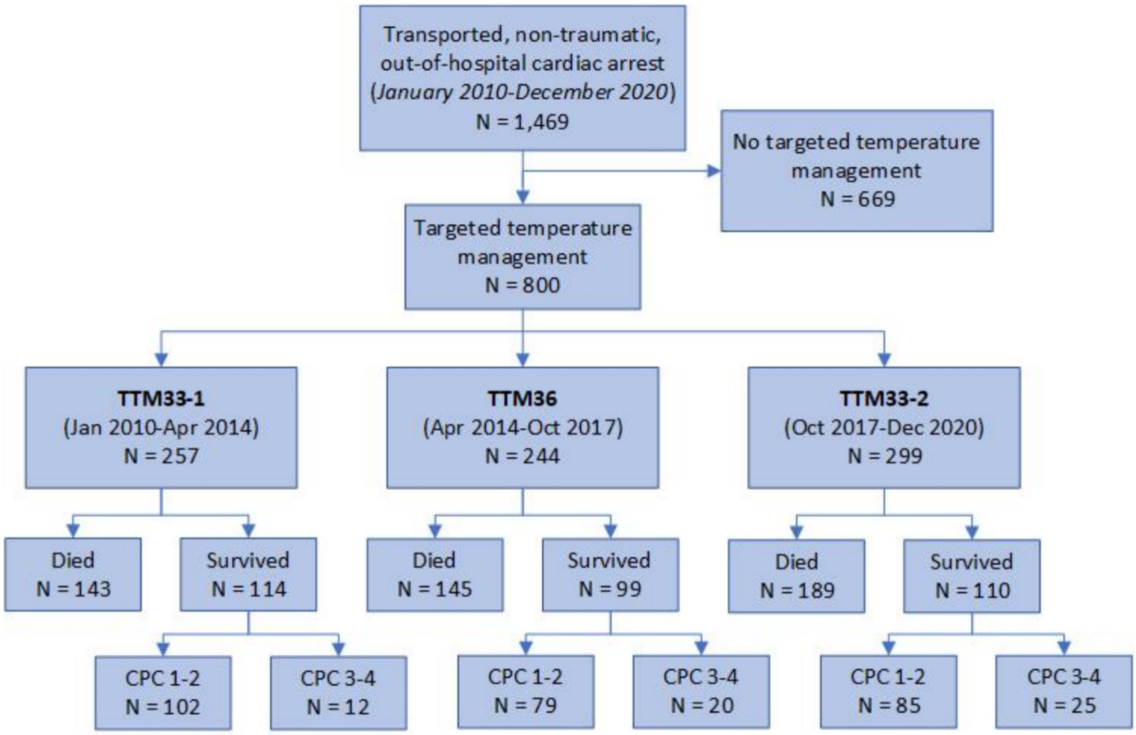

Fig. 1 – Cohort Diagram by TTM protocol (TTM33-1: January 2010–April 2014; TTM 36: April 2014–October 2017; October 2017–December 2020).

of TTM initiation across the combined TTM33 goal temperature periods was not significantly different from the TTM initiation in the TTM36 period ($p = 0.143$). Patients treated during TTM33 goal temperature periods were older than those in TTM-36 ($p < 0.001$), but otherwise patients in all TTM periods had similar baseline characteristics (Table 1).

Post-arrest-care practices and diagnostic testing

Unsurprisingly, median lowest temperature achieved was lower in the TTM33 goal temperature periods than TTM36 ($p < 0.001$; Table 2, Fig. 2). A practice change that occurred at HMC during the study period was that ECMO use began during TTM33-2, but this affected only 16 patients. Otherwise, there were no significant differences in

Table 1 – Baseline Patient and Cardiac Arrest Characteristics During Periods of Changing Institutional Goal Temperatures for Targeted Temperature Management (TTM). (TTM33: January 2010–April 2014 and October 2017–December 2020; TTM 36: April 2014–October 2017).

	TTM33 N (%)	TTM36N (%)	Total N (%)	Missing N (%)
Total N	556 (100)	244 (100)	800 (100)	
Age, years (Mean, SD)	58 (21)	54 (22)	57 (21)	0 (0)
Male Sex	378 (68)	173 (70.9)	551 (68.9)	0 (0)
Race				114 (14.3)
Black	89 (19.6)	39 (16.7)	128 (18.7)	
White	293 (64.7)	163 (70)	456 (66.5)	
Other	71 (15.7)	31 (13.3)	102 (14.9)	
Bystander witnessed	333 (59.9)	140 (57.4)	473 (59.1)	0 (0)
Bystander CPR	286 (51.6)	122 (50)	408 (51.1)	2 (0.3)
Initial rhythm ventricular fibrillation/ventricular tachycardia	220 (39.8)	88 (36.1)	308 (38.6)	3 (0.4)
Etiology–presumed cardiac	283 (52.9)	115 (49.8)	398 (52)	35 (4.3)
Pre-hospital endotracheal intubation	532 (95.7)	235 (96.3)	767 (95.9)	1 (0.1)
Disposition from ED				0 (0)
Admitted to ICU	385 (69.2)	182 (74.6)	567 (70.9)	
Transferred to catheterization laboratory	145 (26.1)	58 (23.8)	203 (25.4)	
Died in ED	10 (1.8)	0 (0)	10 (1.2)	
Other	16 (2.9)	4 (1.6)	20 (2.5)	

N (%) unless otherwise indicated. Abbreviations: SD – standard deviation, CPR – cardiopulmonary resuscitation, ED – emergency department, ICU – intensive care unit.

Table 2 – Post-Arrest Care and Outcomes. (TTM33: January 2010–April 2014 and October 2017–December 2020; TTM 36: April 2014–October 2017).

	TTM33 N (%)	TTM36 N (%)	Total N (%)	Missing N (%)
Total	556 (100)	244 (100)	800 (100)	
Lowest temperature in Celsius in first 48 h, median (IQR)	32.6 (0.9)	34.9 (1.4)	32.8 (2.4)	8 (1.0)
Survival to hospital discharge	224 (40.3)	99 (40.6)	323 (40.4)	0 (0.0)
Neurological Outcomes				0 (0.0)
Favorable neurological outcome	187 (33.6)	79 (32.4)	266 (33.2)	
Poor neurological outcome	369 (66.4)	165 (67.6)	534 (66.8)	
Neurological status at discharge				0 (0.0)
CPC 1 – Full neurologic recovery	132 (23.7)	49 (20.1)	181 (22.6)	
CPC 2 – Mildly impaired	55 (9.9)	30 (12.3)	85 (10.6)	
CPC 3 – Awake with severely impaired neurologic status	23 (4.1)	11 (4.5)	34 (4.2)	
CPC 4 – Comatose, vegetative, non-responsive	14 (2.5)	9 (3.7)	23 (2.9)	
CPC 5 – Died in hospital	332 (59.7)	145 (59.4)	477 (59.6)	
Cardiac care				
Coronary angiography	209 (37.6)	84 (34.4)	293 (36.6)	0 (0)
Diagnosis of myocardial infarction	79 (15.5)	29 (12.3)	108 (14.5)	54 (6.8)
Mechanical circulatory support (intra-aortic balloon pump, Impella, or ECMO)	59 (10.6)	11 (4.5)	70 (8.8)	1 (0.1)
ECMO only	16 (5.1)	0 (0)	16 (2.9)	0 (0)
Prognostic studies				
Head CT	451 (81.1)	210 (86.1)	661 (82.6)	0 (0.0)
Electroencephalogram	292 (52.6)	139 (57)	431 (53.9)	1 (0.1)
Lumbar puncture	94 (16.9)	54 (22.2)	148 (18.5)	2 (0.3)
MRI	144 (28.1)	84 (34.4)	228 (30.1)	43 (5.4)
End of life care				
In-hospital do not attempt resuscitation	316 (57)	146 (59.8)	462 (57.9)	2 (0.3)
Causes of death				0 (0)
Complications of cerebral anoxia	178 (53.6)	90 (62.1)	268 (56.2)	
Primary cardiac	40 (12)	9 (6.2)	49 (10.3)	
Other	114 (34.3)	46 (31.7)	160 (33.5)	

N (%) shown unless otherwise indicated. Abbreviations: IQR – interquartile range, CPC – cerebral performance category, ECMO – extracorporeal membrane oxygenation, MRI – magnetic resonance imaging.

cardiac care and diagnostic processes for the across the TTM33 periods versus the TTM36 period.

Associations between TTM goal period and neurologically-intact survival

Unadjusted rates of survival with favorable neurologic outcome at hospital discharge were not statistically different between the combined TTM33 periods and TTM36 period (p = 0.728). There were also no differences in survival to hospital discharge between TTM33 and TTM36 (p = 0.939) (Table 2).

After adjusting for demographic and cardiac arrest characteristics via logistic regression, it remained the case that no significant association was found between the combined TTM33 goal temperature period and favorable neurological outcome versus the TTM36 period (adjusted odds ratio, aOR: 1.10, 95% confidence interval, CI: 0.76, 1.60). Among model covariates, shockable initial cardiac rhythm and witnessed cardiac arrest were strongly associated with higher odds of favorable neurological outcome, and older age was associated with incrementally lower odds of favorable neurological outcome (Table 3).

Similarly, no significant association was found between the combined TTM33 goal temperature periods and survival to hospital discharge after adjustment (aOR 1.00, 95% CI 0.70, 1.43). However, shockable initial cardiac rhythm and witnessed cardiac arrest were strongly associated with higher odds of survival and age was associated with incrementally lower odds of survival.

In a sub-analysis focusing only on patients with non-shockable initial cardiac rhythm, findings were consistent with the main analyses, and TTM33 goal temperature was not associated with either neurologically-intact survival to discharge or overall survival when compared to TTM36 (Supplemental Table 3). Sensitivity analyses using time series methodology found no secular or periodic trends within the data and similarly found no associations between TTM time periods and outcomes of interest (Supplemental Table 4–5).

Discussion

We previously reported that a TTM goal temperature change from 33°C to 36 °C was associated with a decrease in favorable neurological status at hospital discharge, prompting our institution to change back to 33 °C.[10] This afforded us a unique opportunity to examine the effects of bi-directional goal temperature change within the same clinical environment. In this follow-up study, we found that changing the TTM goal temperature from 36°C back to 33 °C was not associated with improvement in neurological outcome or survival to hospital discharge even after adjusting for available patent and clinical characteristics. These findings remained when employing time series methods to account for secular changes. While the absolute differences between the findings in our original and current paper are small, the updated evaluation uses a more robust analysis with larger sample size and time series modeling to account for any secular

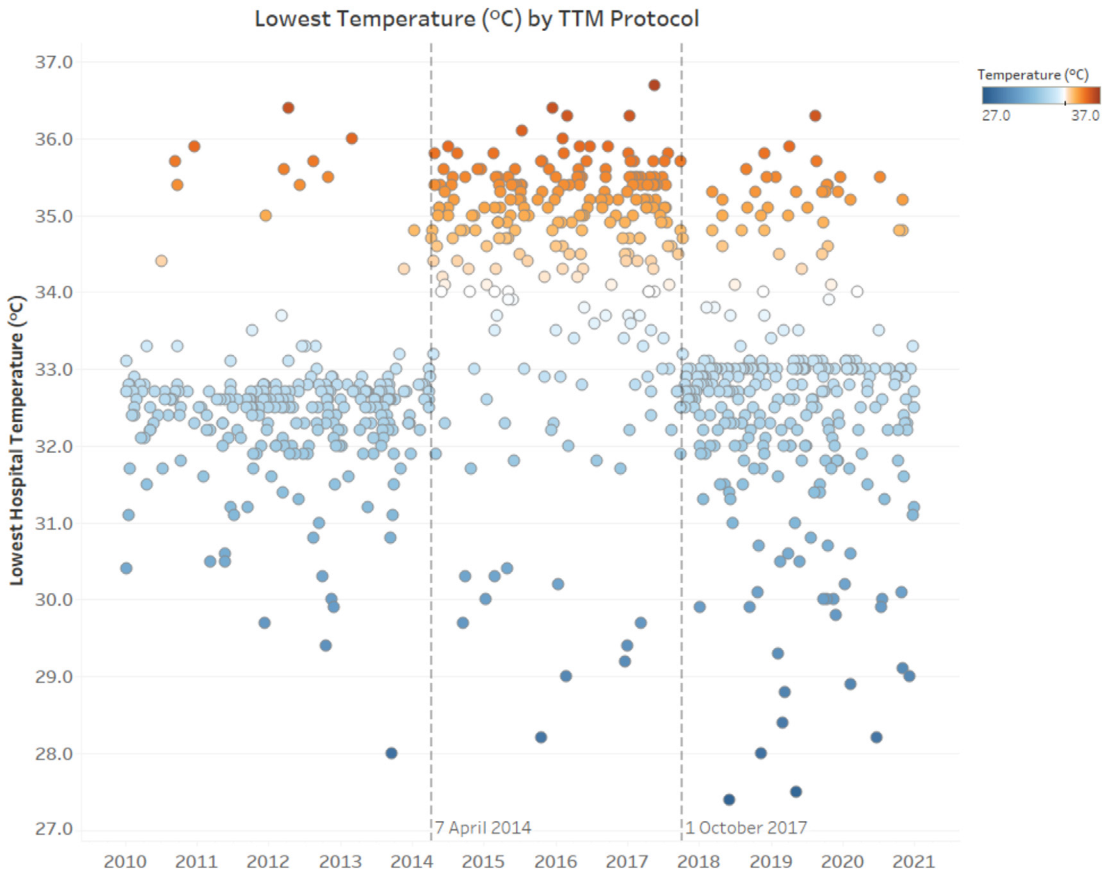

Fig. 2 – Lowest temperature over time by TTM protocol (TTM33-1: January 2010–April 2014; TTM 36: April 2014–October 2017; October 2017–December 2020).

Table 3 – Adjusted Associations Between Targeted Temperature Management Target Temperature Period and Outcomes (Main Cohort). – Adjusted odds ratios and 95% confidence intervals are shown. (TTM33: January 2010–April 2014 and October 2017–December 2020; TTM 36: April 2014–October 2017). Abbreviations: TTM – targeted temperature management.

	Favorable Neurological Outcome	Survival
TTM 33 (Baseline = TTM36)	1.10 (0.76, 1.60)	1.00 (0.70, 1.43)
Age	0.97 (0.96, 0.98)	0.97 (0.96, 0.98)
Female Sex (Baseline = Male Sex)	0.80 (0.55, 1.17)	0.76 (0.53, 1.09)
Shockable Initial Cardiac Rhythm (Baseline=Non-Shockable)	7.62 (5.36, 10.84)	7.40 (5.26, 10.4)
Witnessed Arrest (Baseline = Not Witnessed)	2.22 (1.53, 3.21)	1.96 (1.39, 2.76)

changes. As suggested by recent randomized trials, avoidance of hyperthermia may be as neuroprotective as hypothermic temperature control as it is currently deployed. It is also possible that patient characteristics or other aspects of cardiac arrest care evolved over the study period in ways that were difficult to measure.

Publication of the first TTM randomized controlled trial in late 2013 prompted practice changes in one-third of physicians who responded to an international survey of 11 countries.[3] Since then, multiple observational studies examined associated patient outcomes. For instance, Bray et al. demonstrated higher incidence of fever, less active temperature management, and worsening outcomes at a single institution that changed temperature goals from 33 °C to 36 °C.[12] A registry study in Australia and New Zealand demonstrated a slight increase in the lowest temperature achieved after publication of the TTM trial, an increase in fever, and notably, a change in slope of secular improvement in mortality.[13] A follow-up research letter also noted a widespread practice change with clinicians adopting higher temperature targets and slower decline in mortality rates over time since publication of the TTM trial, but appropriately urged caution about inferring causality from these retrospective data.[14] Our previous study noted a similar trend even after adjustment for baseline and cardiac arrest characteristics, but unmeasured confounders and secular change related to changes in patient characteristics or other care practices were likely, as we previously noted.[10] Additionally, in comparison to the largest randomized trial to date, the TTM2 trial, our cohort had predominantly non-shockable initial cardiac rhythm and other unfavorable cardiac arrest characteristics. However, a patient-level meta-analysis

combined patients with non-shockable initial rhythm from both TTM2 and HYPERION and demonstrated no improvement in survival or functional outcome with hypothermic temperature control to 33 °C.[15]

There continues to be significant debate about the optimal approach to post-arrest temperature management and international guidelines now recommend actively preventing fever by targeting a temperature of $\leq$ 37.5 °C but acknowledge uncertainty about whether some populations may benefit from lower temperatures.[9] Additionally, several observational studies have indicated that patients with markers of intermediate or severe hypoxic-ischemic brain injury might benefit from lower temperatures, though better stratification tools are needed.[16–18] Collectively, these studies and guidelines have raised whether an individualized approach to TTM based on brain injury severity warrants further study. Clinicians and health systems should attempt to mitigate potential unintended consequences of these practice changes, including increased incidence of fever and changes in diagnostic practices, via ongoing quality assurance, tracking of care processes and outcomes.

Limitations

As a retrospective study we assess association between target temperature and outcome, not causation, and potential unmeasured confounders cannot be ruled out. We adopted an "intention to treat" approach for each period, and our registry lacks granular temperature information for detailed TTM protocol adherence reporting. However, we can confirm that other than target temperature, the same TTM protocol and closed loop cooling devices were used throughout the study.

Our data set did not include specific clinicians' rationale for withholding TTM. Unpublished data from 2016 to 2018 at our institution indicate patients did not receive TTM for the following reasons: patient awoke/regained consciousness (29%), patient made comfort measures only (1%), patient expired (4%), bleeding/hemodynamically unstable (13%), with some percentage unknown. Long-term outcome data were unavailable, though data from our system indicate that CPC at hospital discharge predicts 1-year outcome.[19] Our unblinded data abstractor could have introduced bias in CPC rating. Conducted in a single high-performing, high-volume center, our findings may not be generalizable. We additionally considered whether our results may have been affected by changes and unmeasured covariates in the target population over the study time period, such as the ongoing opioid epidemic or COVID-19 pandemic. However, we did not find differences in percentages of opioids or other toxins as causes of OHCA between any of the time periods (Supplemental Table 6).

Conclusions

After adjusting for demographic and cardiac arrest characteristics, we found no difference in neurological outcome among adult OHCA patients who arrived comatose the emergency department when treated with two different TTM goals, 33 °C and 36 °C, across three time periods. Since target temperature does not seem to be associated with outcome across multiple time periods, future research might focus on identifying populations most likely to benefit from different target temperatures, earlier or more effective implementation of temperature control, and improving other aspects of the post-cardiac arrest care bundle.

Ethics approval and consent to participate

The initial study titled "outcomes of patients with out-of-hospital cardiac arrest treated with targeted temperature management at 33 and 36°" was approved by the University of Washington IRB Committee A Human Subjects Division on 12/1/2017 with IRB ID STUDY00003641. The continuing review was approved by the University of Washington IRB Committee A Human Subjects Division on 11/3/2020 with the same title and IRB ID. Informed consent was waived by the regulatory body for all participants, and procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and analyzed in the current study are not publicly available to preserve the privacy of health data, but anonymized elements may be made available from the corresponding author on reasonable request.

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Authors contributions

Nick Johnson conceptualized the study. Jane Hall, Catherine Counts, and Kyle Danielson performed data curation and formal analysis. Sue Scruggs performed data curation. Jane Hall, Robert Doerning, Kyle Danielson, and Nick Johnson drafted the manuscript. Michael R. Sayre, Sarah Wahlster, James A. Town, and David J. Carlbom reviewed and edited the manuscript. All authors read and approved of the final manuscript.

CRediT authorship contribution statement

Robert Doerning: Writing – review & editing, Writing – original draft, Supervision, Project administration. **Kyle R. Danielson:** Visualization, Formal analysis, Data curation. **Jane Hall:** Writing – original draft, Methodology, Formal analysis, Data curation. **Catherine R. Counts:** Formal analysis, Data curation. **Michael R. Sayre:** Writing – review & editing. **Sarah Wahlster:** Writing – review & editing. **James A. Town:** Writing – review & editing. **Sue Scruggs:** Data curation. **David J. Carlbom:** Writing – review & editing. **Nicholas J. Johnson:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Not applicable.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resplu.2025.100921.

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