Targeted Temperature Management Effectiveness in the Elderly: Insights from a Large Registry

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Targeted temperature management (TTM) is recommended for all comatose adult out-of-hospital cardiac arrest (OHCA) patients with shockable first documented rhythm. However, studies examining the use and benefits of TTM among patients aged 75 and older are lacking. Using the Cardiac Arrest Registry to Enhance Survival (CARES) dataset registry from 2013 to 2015. Study criteria included being 75 years of age or older, survival to hospital admission, and known in-hospital mortality and CPC (Cerebral Performance Categories Scale) Scores. The study outcomes were in-hospital mortality and poor neurologic outcomes (CPC Scores 3 or 4) at hospital discharge among survivors. Hierarchical logistic regression and propensity score matching were used for multivariable adjustment. Two thousand nine hundred eighty-two patients met study inclusion criteria. One thousand three hundred fifty-seven (45.5%) received TTM in the admitting hospital. Receipt of TTM was more likely among men, those with a shockable first documented rhythm, and those with their event witnessed. There was no significant association with TTM and in-hospital mortality among patients with ventricular fibrillation (odds ratio [OR]=0.88; 95% confidence interval [CI] [0.62–1.25]), $p=0.487$ within the cohort. However, patients with a nonshockable first rhythm receiving TTM had higher odds of in-hospital mortality ($p<0.001$). Propensity score results showed a modest association with TTM and increased mortality (OR)=1.22, 95% CI [1.01–1.47]; $p=0.036$ and no association with poor neurologic outcome (OR=1.18; 95% CI [0.82–1.69]; $p=0.379$) in the elderly. TTM is often provided to OHCA patients over age 75 though the benefits, particularly among nonshockable first documented rhythm patients are unclear. A randomized trial is needed to definitively answer who among OHCA event survivors aged 75 and older should receive this treatment.

Keywords: elderly, targeted temperature management, effectiveness, therapeutic, hypothermia

Introduction

EACH YEAR, AN ESTIMATED 350,000 out-of-hospital cardiac arrests (OHCA) occur in the United States (American Heart Association, 2017). Of those who receive attempted resuscitation, only 12.5% survive to hospital discharge. Many survivors have long-term neurologic disability as a result of cerebral reperfusion injury. Over the past 15 years, targeted temperature management (TTM) has emerged as the standard of care for comatose adult OHCA event survivors as early studies found improved neurologic outcomes in patients who received TTM (Bernard *et al.*, 2002; Hypothermia after Cardiac Arrest Study Group, 2002).

Based on evidence from two randomized trials, the American Heart Association (AHA) began recommending

TTM for patients successfully resuscitated after OHCA, with stronger recommendations in patients with a shockable rhythm compared with those with a nonshockable rhythm (AHA Guidelines, 2005). However, prior literature does not address the impact of TTM on the elderly OHCA patient, previously defined as being age 75 and older (Mader *et al.*, 2016). The elderly population may be more at-risk for the adverse effects of TTM including arrhythmia, circulatory instability, bleeding, and electrolyte derangement. Further, hospitalization charges have nearly doubled from a mean of \$43,425 in 2001 to \$81,002 in 2013 with no consistent change in survival and some postulate that this is a result of more technologic resources (Eid *et al.*, 2017). Moreover, elderly patients were excluded from one of the original studies (Hypothermia after Cardiac Arrest Study Group, 2002) and

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TABLE 1. VARIABLES STRATIFIED BY TARGETED TEMPERATURE MANAGEMENT STATUS

	<i>No TH in the hospital (N=1625)</i>	<i>TH in the hospital (N=1357)</i>	<i>p</i>
Age, median [25th, 75th]	82 [78, 86]	80 [77, 84]	<0.001
Age (%)			
75–84	65.6	76.5	
85–94	32.1	21.8	<0.001
95+	3.4	1.7	
Male, gender (%)	54.4	63.9	<0.001
Race (%)			
White	46.8	48.3	
Black	13.4	13.3	
Asian/other	4.9	5.5	0.210
Hispanic	7.4	5.3	
Unknown	27.5	27.6	
Location type (%)			
Home/residence	79.7	78.0	
Commercial/public building/industrial	10.6	12.2	0.475
Street/highway	4.9	5.4	
Recreation place/transport center/other	4.9	4.5	
Presumed etiology (%)			
Drowning	0.6	0.2	
Electrocution	0.0	0.1	
Other	1.5	1.0	0.044
Cardiac	88.2	91.1	
Respiratory	9.8	7.6	
Witnessed status (%)			
Unwitnessed	35.9	29.9	<0.001
Bystander witnessed	64.1	70.2	
Initiated CPR (%)			
Responding EMS	29.7	28.8	
Lay person-medical	5.3	3.8	
Lay person-family	21.0	23.7	0.174
Lay person	15.0	15.1	
First responder	29.0	28.6	
Missing/NA	0.1	0.0	
Was AED applied before EMS arrival (%)			
No	70.4	68.8	
Yes, without defibrillation	18.8	15.2	<0.001
Yes, with defibrillation	10.8	16.1	
Who applied AED (%)			
Not applicable	70.4	68.8	
First responder	25.2	28.0	0.140
Lay person-medical	1.7	1.1	
Lay person-other	2.7	2.1	
Who first defibrillated the patient (%)			
Not applicable	64.9	48.5	
First responder	7.6	13.6	
Lay person medical	0.9	0.7	<0.001
Lay person other	1.9	1.5	
EMS	24.0	35.0	
Missing	0.7	0.7	
First rhythm category (%)			
Ventricular fibrillation	17.9	30.9	
Ventricular tachycardia	1.5	1.4	
Unknown shockable rhythm	6.7	10.6	<0.001
Idiovent./PEA	29.8	22.6	
Asystole	29.4	26.3	
Unknown unshockable rhythm	14.7	8.2	
First rhythm type (%)			
Nonshockable	73.9	58.7	<0.001
Shockable	21.6	41.3	

(continued)

TABLE 1. (CONTINUED)

	No TH in the hospital (N=1625)	TH in the hospital (N=1357)	p
Was hypothermia provided in the field (%)			
No	78.4	58.7	<0.001
Yes	21.6	41.3	
Emergency room outcome (%)			
Admitted to ICU/CCU	9.1	9.2	0.001
Admitted to floor	1.1	0.1	
Admitted to hospital	89.9	90.7	
Was TH provided to patients at the transferred hospital (%)			
No/not applicable	98.8	95.1	<0.001
Yes	1.2	4.9	
Survived to hospital discharge (%)			
No	64.6	67.7	0.076
Yes	35.5	32.4	
CPC score (%)			
Died	64.6	67.7	0.094
CPC 3 or 4	7.4	7.8	
CPC 1 or 2	28.1	24.5	
Good CPC score for survivors only			
CPC 3 or 4	20.8% (N=120)	24.1% (N=106)	0.209
CPC 1 or 2 (good)	79.2% (N=456)	75.9% (N=333)	

CCU, critical care unit; CPC, Cerebral Performance Categories Scale; TH, therapeutic hypothermia.

were negligibly present in the other (Bernard *et al.*, 2002; Bernard 2012). A more recent trial demonstrating no difference in outcomes between patients randomized to standard hypothermia at 33°C compared with a more conservative, nearly normothermic group, at 36°C included patients over the age of 75 but did not have a control group that did not receive TTM (Winther-Jensen *et al.*, 2015). Thus, there is no existing literature on the association of TTM with survival in elderly patients suffering from an OHCA compared with standard therapy (ST).

In this study, using the Cardiac Arrest Registry to Enhance Survival (CARES) registry, we sought to determine the association of TTM on survival to hospital discharge after OHCA in the elderly population, defined as 75 years or older. As a secondary outcome, we aimed to determine the association of TTM on neurologically intact survival in this same elderly population.

Materials and Methods

Design, setting, and population

This study is a secondary analysis of existing prospectively collected and validated human data submitted to the CARES (<https://mycares.net>) dataset. The registry compiles data on key prehospital variables that can be objectively measured, clearly defined, and recorded easily. TTM became a mandatory reporting field in the registry on November 1, 2010 and data for this study ranged from 2013 through 2015 because a key terminology (“presumed cardiac” to “non-traumatic”) changed at the end of 2012.

Appendix Figure A1 details the exclusion criteria for the study. All patients were required to be age 75 or older, to have resuscitation attempted, and to survive to hospital admission. Briefly, we excluded the following additional records to create a more homogeneous dataset: patients with arrests

after 911 arrival, patients from hospitals that did not provide TTM in the hospital to any patients in the CARES dataset, patients whose arrest occurred in long-term care facilities (e.g., a skilled nursing facility or hospital) or in an unknown location, patients with missing CPC (Cerebral Performance Categories Scale) scores among those admitted to the hospital, patients with no sustained return of spontaneous circulation (ROSC), records with unknown hospital outcome data (including transfers), and patients with do not resuscitate orders. We only assessed in-hospital TTM, not TTM provided in the prehospital setting. The study was reviewed and deemed exempt from human subjects review by the Baystate Medical Center Institutional Review Board.

Statistical methods

Data analysis was performed using Stata/MP 13.1 for Windows (StataCorp LP, College Station, TX). For descriptive analyses, binary and categorical variables are presented as percentages and counts. Continuous variables are presented as medians with interquartile ranges. Inference tests comparing TTM to ST patients were chi-square tests for binary and categorical variables and if a cell count was <5, the Fisher’s exact test was used. For inferences on continuous variables, the Mann–Whitney test was used. The Wald test was used to compare adjusted marginal probabilities. All *p* values <0.05 were considered to be statistically significant.

For multivariable analyses, we used two approaches. First, we used a hierarchical logistic regression model with hospitals treated as random effects. This model was applied to all patients meeting our exclusion criteria. Next, we used propensity matching, with a 5 to 1 digit Greedy algorithm to create a matched subset of TTM and ST patients, matched on the propensity to receive TTM. The propensity matched results are thus comparing TTM patients to those ST patients most similar in their probability of receiving TTM.

A sensitivity analysis was also performed. To examine the consistency of the Greedy-matched propensity score results, we further compared patients using two different propensity matching algorithms. We matched with a one-to-many weighted (kernel) matching algorithm, and a caliper-matching algorithm with the caliper being 0.2 times the standard deviation of the logit of the propensity (Austin, 2011).

If we assume a priori 70% in-hospital mortality rate for TTM patients and a 75% in-hospital mortality rate for ST patients, a sample size of 1251 patients in each group would provide 80% to detect a difference this size or greater at $\alpha = 0.05$.

Results

There were 136,594 records available between 2013 and 2015. A total of 2982 patients from 538 hospitals met our a priori inclusion criteria (Appendix Figure A1). Baseline characteristics of the study population are in Table 1. Notably, patients who received TTM were more likely to be male, to have a first documented rhythm that was shockable (e.g., ventricular fibrillation or ventricular tachycardia), more likely to have their event witnessed by a bystander, and more likely to have received TTM in the field before hospital admission.

Figure 1 shows that the percent of patients with a shockable first documented rhythm decreased as the patient aged. For example, among patients aged 75 to 79, 44.3% had a shockable first documented rhythm compared to 19.8% among patients aged 90 and over ($p < 0.001$). Moreover, the percent of patients receiving TTM consistently exceeded the percentage of shockable patients (i.e., some nonshockable patients received TTM) and TTM usage in the hospital decreased as the patient aged from a rate of 50.3% among patients aged 75 to 79 to 37.1% among patients aged 90 and over ($p < 0.001$). Figure 2 further shows the rate of TTM use among shockable and nonshockable patients stratified by age.

The multivariable regression analysis assessed the association of TTM status on in-hospital mortality after adjustment for the baseline characteristics shown in Table 1. Initial modeling revealed a strong interaction effect between TTM and the variable of first rhythm category. Consequently, an interaction term for these two variables was added to the final model. The significant

FIG. 1. Percent of patients with shockable rhythms and receiving TTM stratified by age. TTM, targeted temperature management.

FIG. 2. Percent of patients receiving TTM by first rhythm category and age.

interaction term indicates that TTM does not have a constant association with in-hospital mortality. Instead, it varies depending on the first documented rhythm. This makes interpretation of the effect estimate of TTM on mortality more complex. The full model is provided in Appendix Table A1. For patients receiving TTM and who have a first documented rhythm of ventricular fibrillation (the baseline category), the odds ratio (OR) associated with TTM is 0.88; 95% confidence interval (CI) (0.62–1.25), $p = 0.487$ indicating no significant mortality difference between groups. An analysis of adjusted marginal probabilities of shockable patients showed no significant difference in in-hospital mortality by TTM status for shockable patients ($p = 0.924$) but a significant association with TTM and increased risk of in-hospital mortality among nonshockable patients ($p < 0.001$). Figure 3 depicts this graphically. Where the CIs in the figure overlap, the differences are nonsignificant.

The regression analysis assessing the secondary outcome of poor neurologic status (CPC Scores of 3 or 4 vs. CPC Scores of 1 or 2) among survivors found no significant interaction effect of rhythm category and TTM (Appendix Table A2). There was an association between receipt of TTM and poor neurologic status (OR = 1.61; 95% CI [1.07–2.41]; $p = 0.022$).

Table 2 presents the propensity score results. On the Greedy Matched sample 1054 TTM patients out of 1357 (77.7%) were successfully matched to the ST patients. The propensity score was constructed using the same predictors as the hierarchical regression model with TTM as the outcome and after matching all predictors were balanced (nonsignificantly different) by TTM status. For in-hospital mortality, the Greedy Matched analysis shows a small but significant association with TTM and increased odds of in-hospital mortality. Notably, the caliper matched sensitivity analysis showed the association was nonsignificant. For the poor neurologic status outcome among survivors, there was no significant association with TTM and this outcome. These findings were consistent in the sensitivity analysis as well.

Discussion

The results of this analysis indicate that TTM is not exclusively given to shockable patients among those patients aged 75 and older. However, TTM in the hospital was provided

FIG. 3. Adjusted probability of in-hospital mortality by TTM and first rhythm category.

more to patients with a first documented shockable rhythm and to patients who received TTM in the field. Additionally, as patients aged, they were less likely to receive TTM regardless of their first rhythm. This suggests a clear selection bias where some clinical decision making is being made as to who receives this treatment even within the same hospital.

The multivariable adjusted results need to be interpreted conservatively. We found that when examining all patients in the hierarchical regression model, there was no significant difference in in-hospital mortality among those patients with a shockable first rhythm but there was a small, significant increase in mortality risk among nonshockable patients receiving TTM. We stress that this does not mean that TTM should not be provided to patients over age 75, as these results cannot show a causal relationship. Rather, the results indicate that an associated benefit from TTM is not observable after adjusting for the available confounders.

The propensity score results also need to be interpreted with care. The propensity matched samples represent ST and TTM patients most like each other by their propensity for receiving TTM. In contrast, the regression results are based on all patients and are more representative of the entire OHCA population that met study criteria. The propensity results indicate a modest increase in in-hospital mortality risk and no difference in neurologic status among survivors. The two propensity matching algorithms in the sensitivity analysis differ from a 1:1 Greedy match in that they allow for multiple matching within a range of propensities (the Caliper match) or in the Kernel matching analysis, the ST patients in the dataset are all used and matched in weighted manner to each TTM patient. These subtle differences cause variation in the effect estimates though the findings were generally consistent with the Greedy matched results.

What our results do imply is that there is a clear need for a randomized clinical trial on the efficacy of TTM among elderly patients given the “real world” selection bias observed in who received this treatment in the hospital. We observed that patients with TTM and with nonshockable rhythms had higher mortality, which may be due to the worse prognosis of arrest with a nonshockable rhythm or alternatively because some doctors were using TTM as a measure of final resort for the sickest patients. It is possible that TTM in these patients may represent a “sicker” OHCA patient or that TTM is ineffective in this population with OHCA. The benefits of TTM have become increasingly controversial as more recent studies show mitigated improvement in favorable neurologic survival and TTM carries risks of bleeding, arrhythmias, and electrolyte derangements (Nielsen *et al.*, 2013; Mahmoud *et al.*, 2016).

Limitations

This study was conducted using registry data and is thus subject to the limitations in any retrospective analysis. The biggest limitation is that we do not have data on why patients

TABLE 2. PROPENSITY SCORE RESULTS

	OR for TTM	95% CI	p
In-hospital mortality; model type			
No adjustment (raw)	1.15	0.99–1.34	0.076
Propensity matched results			
Greedy matched	1.22	1.01–1.47	0.036
Caliper matched	0.99	0.79–1.25	0.954
Kernel matched	1.20	1.01–1.43	0.041
Poor CPC score (CPS=3 or 4 vs. scores of 1 or 2) among survivors; model type			
No adjustment (raw)	1.21	0.90–1.63	0.209
Propensity matched results			
Greedy matched	1.18	0.82–1.69	0.379
Caliper matched	1.18	0.72–1.95	0.506
Kernel matched	1.29	0.89–1.88	0.174

CPC, Cerebral Performance Categories Scale; OR, odds ratio.

did not receive TTM. For example, we were unable to identify cases where TTM was not indicated, such as those who were conscious following resuscitation. Odds of neurologically intact survival are increased in these patients, and they are included in the ST group. This information is now incorporated into CARES but was not a mandatory field during the study period. We also have unmeasured confounding. Missing in the CARES registry are measures of acuity, detailed measures of chronic disease burdens, and perhaps most importantly, the quality of the TTM. We do not know the degree of temperature management during their hospitalization, when TTM occurred during hospitalization, and the duration of TTM. It is possible that adjusting for these unmeasured confounders would change the association between TTM and neurologically intact survival. Lastly, the outcome of CPC at hospital discharge is an imperfect measure yet it is one of the most widely used measures in TTM research. Ideally, one would have long-term neurologic outcome data but these data are missing from this registry.

Conclusion

TTM is used in approximately half of OHCA survivors 75 years or older but the data in the CARES registry demonstrated no association between TTM and improved mortality in this population. These results are congruent with prior literature assessing the broader population (Mahmoud *et al.*, 2016). Given the risks and cost associated with TTM, further assessment of TTM compared with ST is warranted in this group.

Author Disclosure Statement

No competing financial interests exist.

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Appendix

*Surrogate for likely poor baseline function leading to decision for early palliative care.

**Surrogate for likely short arrest duration precluding need for aggressive post-resuscitative care.

#Missing key data elements (i.e., age, TTM treatment provision, and outcomes [includes hospital transfers]).

APPENDIX FIG. A1. Patient attrition diagram.

APPENDIX TABLE A1. HIERARCHICAL REGRESSION MODEL FOR THE OUTCOME = IN-HOSPITAL MORTALITY

<i>Variable</i>	<i>OR</i>	<i>95% CI</i>	<i>p</i>
TTM given in the hospital			
No	1		
Yes	0.88	0.62–1.25	0.487
First rhythm category			
Ventricular fibrillation	1		
Ventricular tachycardia	0.32	0.11–0.94	0.039
Unknown shockable rhythm	0.72	0.39–1.34	0.302
Idioventricular/PEA	2.26	1.45–3.52	<0.001
Asystole	5.00	3.16–7.93	<0.001
Unknown unshockable rhythm	0.82	0.49–1.37	0.442
Interaction terms			
TTM × ventricular fibrillation	1		
TTM × ventricular tachycardia	4.14	0.91–18.89	0.066
TTM × unknown shockable rhythm	1.26	0.61–2.61	0.535
TTM × idioventricular/PEA	2.20	1.31–3.70	0.003
TTM × asystole	2.01	1.13–3.57	0.017
TTM × unknown unshockable rhythm	2.94	1.52–5.70	0.001
Gender			
Female	1		
Male	0.89	0.73–1.08	0.234
Age, per year	1.04	1.02–1.06	<0.001
Presumed etiology			
Cardiac	1		
Respiratory	0.95	0.67–1.34	0.755
Other	1.33	0.62–2.86	0.465
Hypothermia provided in the field			
No	1		
Yes	1.46	1.15–1.84	0.002
Location type			
Home/residence	1		
Commercial place/public building	0.50	0.37–0.68	<0.001
Street/highway	0.58	0.39–0.88	0.010
Recreation place/other	0.41	0.24–0.68	0.001
Witnessed by a bystander			
No	1		
Yes	0.73	0.59–0.90	0.003
Who initiated CPR			
Responding Emergency Medical Services (EMS)	1		
Lay person-medical	0.96	0.57–1.63	0.889
Lay person-family member	1.09	0.83–1.44	0.529
Lay person-other	0.91	0.65–1.27	0.565
First responder	0.94	0.71–1.25	0.662
Was AED applied before EMS arrival?			
No/not applicable	1		
Yes, without defibrillation	2.57	0.75–8.81	0.133
Yes, with defibrillation	2.72	0.39–19.19	0.313
Who applied AED			
Not applicable	1		
First responder	0.56	0.16–1.92	0.353
Lay person-medical	0.41	0.07–2.25	0.302
Lay person-other	N/A		
Who first defibrillated the patient			
Not applicable	1		
First responder	0.88	0.19–4.00	0.868
Lay person-medical	0.22	0.02–2.29	0.207
Lay person-other	0.19	0.02–1.60	0.128
EMS	1.11	0.80–1.54	0.525
TTM provided to patients at the transferred hospital			
No/not applicable	1		
Yes	0.71	0.41–1.24	0.232

AED, automated external defibrillator; CI, confidence interval; EMS, emergency medical services; OR, odds ratio; PEA, pulseless electrical activity; TTM, targeted temperature management.

APPENDIX TABLE A2. HIERARCHICAL REGRESSION MODEL FOR THE OUTCOME = POOR CEREBRAL PERFORMANCE CATEGORIES SCALE SCORES AMONG SURVIVORS

<i>Variable</i>	<i>OR</i>	<i>95% CI</i>	<i>p</i>
TTM given in the hospital			
No	1		
Yes	1.61	1.07–2.41	0.022
First rhythm category			
Ventricular fibrillation	1		
Ventricular tachycardia	0.97	0.25–3.73	0.970
Unknown shockable rhythm	1.20	0.54–2.69	0.655
Idioventricular/PEA	4.70	2.30–9.59	<0.001
Asystole	9.14	4.35–19.20	<0.001
Unknown unshockable rhythm	1.94	0.83–4.53	0.127
Gender			
Female	1		
Male	0.78	0.55–1.13	0.191
Age, per year	1.04	1.00–1.08	0.065
Presumed etiology			
Cardiac	1		
Respiratory	1.34	0.71–2.55	0.371
Other	0.21	0.02–1.89	0.165
Hypothermia provided in the field			
No	1		
Yes	1.69	1.11–2.57	0.014
Location type			
Home/residence	1		
Commercial place/public building	0.49	0.27–0.91	0.023
Street/highway	1.39	0.70–2.78	0.352
Recreation place/other	0.30	0.09–0.98	0.047
Witnessed by a bystander			
No	1		
Yes	0.59	0.40–0.88	0.009
Who Initiated CPR			
Responding EMS	1		
Lay person-medical	0.64	0.21–1.95	0.428
Lay person-family member	0.89	0.53–1.48	0.648
Lay person-other	0.67	0.34–1.31	0.240
First Responder	0.85	0.51–1.42	0.536
Was AED applied before EMS arrival?			
No/not applicable	1		
Yes, without defibrillation	7.87	0.95–65.43	0.056
Yes, with defibrillation	NA		
Who applied AED			
Not applicable	1		
First responder	0.17	0.02–1.44	0.104
Lay person-medical	0.12	0.00–3.31	0.211
Lay person-other	NA		
Who first defibrillated the patient			
Not applicable	1		
First responder	NA		
Lay person-medical	NA		
Lay person-other	NA		
EMS	2.46	1.29–4.70	0.006
TTM provided to patients at the transferred hospital			
No/not applicable	1		
Yes	0.62	0.23–1.69	0.350