The role of targeted temperature management in 30-day hospital readmissions in cardiac arrest survivors: A national population-based study

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ABSTRACT

Background: Targeted temperature management (TTM) implementation following resuscitation from cardiac arrest is controversial. Although prior studies have shown that TTM improves neurological outcomes and mortality, less is known about the rates or causes of readmission in cardiac arrest survivors within 30 days. We aimed to determine whether the implementation of TTM improves all-cause 30-day unplanned readmission rates in cardiac arrest survivors.

Methods: Using the Nationwide Readmissions Database, we identified 353,379 adult cardiac arrest index hospitalizations and discharges using the International Classification of Diseases, 9th and 10th codes. The primary outcome was 30-day all-cause unplanned readmissions following cardiac arrest discharge. Secondary outcomes included 30-day readmission rates and reasons, including impacts on other organ systems.

Results: Of 353,379 discharges for cardiac arrest with 30-day readmission, 9,898 (2.80%) received TTM during index hospitalization. TTM implementation was associated with lower 30-day all-cause unplanned readmission rates versus non-recipients (6.30% vs. 9.30%, $p < 0.001$). During index hospitalization, receiving TTM was also associated with higher rates of AKI (41.12% vs. 37.62%, $p < 0.001$) and AHF (20.13% vs. 17.30%, $p < 0.001$). We identified an association between lower rates of 30-day readmission for AKI (18.34% vs. 27.48%, $p < 0.05$) and trend toward lower AHF readmissions (11.32% vs. 17.97%, $p = 0.05$) among TTM recipients.

Conclusions: Our study highlights a possible negative association between TTM and unplanned 30-day readmission in cardiac arrest survivors, thereby potentially reducing the impact and burden of increased short-term readmission in these patients. Future randomized studies are warranted to optimize TTM use during post-arrest care.

1. Introduction

Targeted temperature management (TTM) has historically been recommended for out-of-hospital (OHCA) and in-hospital cardiac arrest (IHCA) patients who remain unresponsive after return of spontaneous circulation, particularly in shockable rhythms [1–4]. However, in light of new evidence that questioned the utility of TTM, the latest society guidelines state there is not enough evidence to recommend for or against TTM after cardiac arrest and suggest to achieve "temperature control" rather than hypothermic states for immediate cardiac arrest survivors [5–8]. Furthermore, adherence to specific temperature targets has declined since the publication of the TTM trial [9–12]. Additionally, the decision to initiate TTM continues to be largely influenced by patient demographics, clinician uncertainty and varying adherence to protocols, availability of cooling devices at home institutions, and arrest circumstances [9–15].

While prior studies have addressed neurological outcomes and mortality in patients with cardiac arrest receiving TTM within their index hospitalization, less is known about the impact of TTM regarding the rates or risk factors of readmission among survivors or the effect of TTM on various organ systems. Readmission after cardiac arrest has been associated with subpar quality of care, poor patient outcomes, and increased costs [16,17]. Premature or recurrent hospitalization can further impair survivors' quality of life, recovery to baseline, and favorable neurologic evolution.

Our study sought to determine whether there is an association between rates of 30-day hospital readmission among out-of-hospital and in-hospital cardiac arrest survivors and the implementation of TTM during their index admission and ascertain possible impacts on other organ systems as well.

2. Methods

2.1. Database

The Nationwide Readmissions Database (NRD) is part of the Healthcare Cost and Utilization Project (HCUP) and is sponsored by the Agency for Healthcare Research and Quality (AHRQ) [18]. The NRD contains discharge data from 30 geographically dispersed states, accounting for 60.4% percent of all United States hospitalizations [19]. The NRD provides information on nationwide hospital inpatient discharges and readmissions (related or unrelated to most recent hospitalization) within a calendar year and inpatient mortality for all types of payers [19]. Each patient has a unique identifier code, which allows for tracing readmissions within each year and is randomly generated to protect patients' privacy [19]. The NRD relies on over 100 clinical and nonclinical variables per hospital stay [19]. All discharge diagnoses and procedures were identified using the International Classification of Diseases, 10th edition (ICD-10) codes. The AHRQ made these data available to author WW via the HCUP. Institutional Review Board (IRB) approval was pursued through HCA Healthcare (C.A.R.R.I.E. #ID 2023-151) but was granted an exemption due to the publicly available nature of this de-identified database without conducting research on human subjects.

2.2. Study design

We queried the NRD from January 1, 2010, to December 31, 2018, to identify a cohort of adult hospitalizations (>18 years) with cardiac arrest at index hospitalization using the International Classification of Diseases, 9th (ICD-9) and 10th (ICD-10) editions codes 427.5 and I46.9 respectively [20]. The ICD-9 codes for cardiac arrest have been well validated to have high sensitivity above 86% and a specificity of 99% [21]. Further admissions for each patient within the calendar year of index hospitalization were accounted for as readmission. Patients who expired during the index hospitalization, were readmitted to other facilities, or were identified as planned readmission ("ELECTIVE" variable in the HCUP database) were excluded from the final analysis in this study. Since the NRD patient identifiers are unable to be linked across different years, patients who were admitted during January or December were also excluded [19].

2.3. Variables of interest

Clinical variables were identified using ICD-9 and ICD-10 codes as entered by health providers caring for patients during their hospital stay. Variables were collected on patient demographics, social habits, median household income, hospital length-of-stay, hospital size, hospital type, comorbidities, the use of TTM during the index hospitalization, clinical outcomes during index hospitalization, including mortality, total charge at index hospitalization status, rate of readmission, time to readmission, and cause of readmission (using primary diagnostic categories). The

Elixhauser comorbidity index (use of 31 comorbid indicators to predict in-hospital mortality and 30-day readmission data) was calculated as a separate variable [22]. A list of the variables and their respective ICD-10 codes used in the study can be found in **Supplementary** Table 1.

2.4. Outcomes

The primary outcome of interest was 30-day all-cause unplanned readmission following cardiac arrest index hospitalization discharge. Secondary outcomes included 30-day readmission rates and reasons for readmission, including acute heart failure (AHF), implantable cardioverter defibrillator (ICD) implantation, respiratory complications, infectious complications, vascular complications, prosthetic device complications, venous thromboembolism, acute kidney injury (AKI), gastrointestinal bleed, stroke, and death due to any cause during readmission. We also collected data on whether TTM implementation was associated with non-routine discharges, total hospital charge, and hospital length-of-stay.

2.5. Statistical analysis

National estimates were obtained using the discharge-level weight variable (DISCWT) provided by the HCUP. Weighted discharges provide national estimates versus unweighted discharges, which are simply the number of observations in the database. Categorical variables were described using frequency (percentage) and analyzed for significance using Chi-Squared Test. Continuous variables were described using mean ($\pm$SD) and analyzed using student's t-Test. Multivariable logistic regression analysis, stratified by hospital region and year, was conducted to assess the covariates' association with all previously specified endpoints. Multivariable logistic regression results are represented as odds ratios (ORs) and their respective 95% CIs. Multivariable linear regression analysis was conducted to assess covariates' association with LOS and non-routine discharge. Prior to performing our main analysis for the intended outcome, we performed a sensitivity analysis intending to identify any possible confounding effects of mortality on admissions receiving TTM. We then excluded these patients (n = 244,375) from our analysis to conduct our primary analysis (n = 353,379). Variables used in the regression model building were either selected from the dataset as provided variables or abstracted with the ICD-10 codes or from the Elixhauser comorbidity index. The variables used for the regression model include age, sex, primary payer status, hospital bed size, socioeconomic stratum, hospital teaching status, prior permanent pacemaker, prior ICD, prior percutaneous coronary intervention, prior coronary artery bypass graft, prior stroke, hyperlipidemia, tobacco usage, prior myocardial infarction, coronary artery disease, previous cardiac surgery, morbid obesity, obstructive sleep apnea, supraventricular tachycardia, ventricular tachycardia, atrial fibrillation, other premature beats, other cardiac arrhythmias, Wolff-Parkinson White syndrome, Lown-Ganong-Levine syndrome, and 31 variables derived from the Elixhauser comorbidity index. Variables were selected into the multivariable regression model if they were statistically significant (p < 0.20) in the univariate analysis screening. We forced variables that are well known to be associated with the outcome of interest based on prior research. Linear regression results are represented as beta coefficients (Coef.) and their respective 95% CIs. Additionally, to further mitigate bias, we performed a 1:1 propensity score matching (PSM) for age, gender, insurance type, hospital type, quartile for median household income, and the Elixhauser comorbidity index. We then conducted our multivariable regression model in this population to further validate the association between TTM and 30-day unplanned readmission. In addition, since the majority of readmissions occurred on day 1 after discharge, we conducted the same multivariable regression model after the exclusion of those patients readmitted on day 1 after discharge. Finally, to identify any confounding relationship between the index admission acute kidney or AHF with the same reason for readmission,

Table 1

Baseline characteristics at index hospitalizations of patients who had a cardiac arrest with and without implementation of targeted temperature management.

Baseline characteristics	Targeted Temperature Management Present	Targeted Temperature Management Absent	Total	p-value[b]
Total, n (%)	9,898 (2.80%)	343,481 (97.20%)	353,379	<0.001
Age, mean (SE)	59.1 (0.21)	64.5 (0.95)	64.3 (0.09)	<0.001
Female Gender, n (%)	3,138 (31.70%)	136,739 (39.81%)	139,878 (39.58%)	<0.001
Male Gender, n (%)	6,760 (68.30%)	206,742 (60.19%)	213,502 (60.42%)	<0.001
Social habits, n (%)				
Alcohol abuse	1,158 (11.70%)	28,030 (8.16%)	29,188 (8.26%)	<0.001
Illicit drug use	1,018 (10.28%)	22,624 (6.59%)	23,642 (6.69%)	<0.001
Smoking	3,313 (33.47%)	104,857 (30.53%)	108,171 (30.61%)	<0.050
Median household income, n (%)				<0.001
0-25th percentile	1,380 (23.56%)	71,058 (31.19%)	72,438 (30.99%)	
26th-50th percentile	1,529 (26.10%)	60,866 (26.71%)	62,396 (26.70%)	
51st-75th percentile	1,598 (27.28%)	54,167 (23.77%)	55,765 (23.86%)	
75th-100th percentile	1,350 (23.05%)	41,766 (18.33%)	43,116 (18.45%)	
Primary expected payer, n (%)				<0.001
Private insurance	2,015 (34.03%)	57,956 (25.09%)	59,971 (25.31%)	
Medicare	2,287 (38.63%)	122,583 (53.06%)	124,870 (52.70%)	
Medicaid	1,005 (16.97%)	31,611 (13.68%)	32,616 (13.77%)	
Self-pay	290 (4.90%)	9,214 (3.99%)	9,504 (4.01%)	
Length of hospital stay, mean (SE)	9.62 (0.39)	10.2 (0.92)	10.1 (0.09)	<0.001
Bed size of hospital, n (%)				<0.001
Small	765 (7.73%)	36,029 (10.49%)	36,794 (10.41%)	
Medium	2,345 (23.69%)	84,798 (24.69%)	87,143 (24.66%)	
Large	6,788 (68.58%)	222,654 (64.82%)	229,442 (64.93%)	
Teaching status, n (%)				<0.001
Urban non-teaching	2,954 (29.84%)	97,123 (28.28%)	100,077 (28.32%)	
Urban teaching	6,670 (67.39%)	226,179 (65.85%)	232,849 (65.89%)	
Rural	275 (2.78%)	20,179 (5.87%)	20,454 (5.79%)	
Comorbidities, n (%)				
Uncomplicated diabetes	1,514 (15.30%)	64,316 (18.72%)	65,830 (18.63%)	<0.001
Complicated diabetes	868 (8.77%)	43,529 (12.67%)	44,397 (12.56%)	<0.001
Hyperlipidemia	2,185 (22.08%)	82,875 (24.13%)	85,060 (24.07%)	<0.050
Uncomplicated hypertension	242 (2.44%)	12,659 (3.27%)	12,091 (3.65%)	<0.001
Complicated hypertension	5,249 (53.03%)	158,644 (46.19%)	163,893 (46.38%)	<0.001
Obstructive sleep apnea	786 (7.94%)	26,640 (7.76%)	27,426 (7.76%)	0.680
Prior MI	539 (5.45%)	20,986 (6.11%)	21,525 (6.09%)	0.140

Table 1 (*continued*)

Baseline characteristics	Targeted Temperature Management Present	Targeted Temperature Management Absent	Total	p-value[b]
Prior CABG	6,109 (61.72%)	182,222 (53.05%)	188,331 (53.29%)	<0.001
Ischemic cardiomyopathy	426 (4.30%)	15,655 (4.56%)	16,081 (4.55%)	0.460
Prior PCI	7,886 (79.67%)	231,416 (67.37%)	239,303 (67.72%)	<0.001
Cardiogenic shock	2,349 (23.73%)	42,180 (12.28%)	44,529 (12.60%)	<0.001
Atrial fibrillation	2,226 (22.49%)	82,185 (23.93%)	84,411 (23.89%)	0.050
Atrial flutter	428 (4.32%)	17,348 (5.05%)	17,777 (5.03%)	0.070
Supraventricular tachycardia	274 (2.50%)	8,641 (2.52%)	8,888 (2.52%)	0.950
Ventricular tachycardia	954 (9.64%)	29,403 (8.56%)	30,357 (8.59%)	<0.050
Ventricular fibrillation	5,605 (56.63%)	82,730 (24.09%)	88,335 (25.00%)	<0.001
Wolff-Parkinson-White	38 (0.38%)	511 (0.15%)	549 (0.16%)	<0.050
Prior PPM	112 (1.13%)	6,730 (1.96%)	6,842 (1.94%)	<0.001
Prior ICD	236 (2.38%)	6,377 (1.86%)	6,613 (1.87%)	<0.050
Prior stroke	435 (4.39%)	20,191 (5.88%)	20,626 (5.84%)	<0.001
Congestive heart failure	4,960 (50.11%)	140,433 (40.89%)	145,394 (41.14%)	<0.001
Valvular disease	1,195 (12.07%)	51,310 (14.94%)	52,505 (14.86%)	<0.001
Chronic pulmonary disease	2,290 (23.14%)	87,371 (25.44%)	89,661 (25.37%)	<0.050
HIV/AIDS	16 (0.16%)	1,008 (0.29%)	1,025 (0.29%)	0.090
Metastatic cancer	75 (0.76%)	6,168 (1.80%)	6,243 (1.77%)	<0.001
Renal failure	1,433 (14.48%)	77,426 (22.54%)	78,859 (22.32%)	<0.001

[a] Note: As per HCUP guidelines, all frequencies less than 11 are represented as "<11" to adhere to HIPAA laws. Therefore, corresponding total frequency is masked.

[b] All p values < 0.05 were rounded and reported as p < 0.05 and all p values < 0.001 were rounded and reported as p < 0.001 Definitions of above elements may found at: https://www.hcup-us.ahrq.gov/db/nation/nis/nisdde.js. SE = Standard error. BMI = Body mass Index, MI = Myocardial infarction. CABG = Coronary artery bypass graft. PCI = percutaneous coronary intervention. PPM = permanent pacemaker placement. ICD = Implantable cardiac defibrillator. AIDS = Acquired immunodeficiency syndrome.

we conducted an interaction term analysis between AKI (and AHF) and TTM during the index admission and their relationship with 30-day unplanned readmission for AKI and AHF, respectively. Statistical analysis was performed using STATA 17 (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC.). P-values < 0.05 were considered statistically significant. The checklist for working with the NRD was used to ensure the appropriateness of data analysis as recommended by AHRQ [23].

3. Results

3.1. Sensitivity analysis

Admissions with TTM deployed were associated with higher odds of mortality during hospitalization (OR: 1.24; 95% CI: 1.17–1.33; p < 0.001). These patients (n = 244,735) were subsequently excluded from our primary analysis (**Supplementary** Table 2). Baseline characteristics

Table 2
Clinical outcomes at index admission.

Outcomes	Targeted Temperature Management Present	Targeted Temperature Management Absent	All	p-value[a]
Acute heart failure, n (%)	1,992 (20.13%)	59,411 (17.30%)	61,403 (17.38%)	<0.001
Acute kidney injury, n (%)	4,070 (41.12%)	129,206 (37.62%)	133,276 (37.71%)	<0.001
Ischemic stroke, n (%)	551 (5.57%)	21,387 (6.23%)	21,938 (6.21%)	0.13
Hemorrhagic stroke, n (%)	110 (1.11%)	5,344 (1.56%)	5,454 (1.54%)	<0.05
Vascular complication, n (%) [b]	54 (0.55%)	3,910 (1.14%)	3,964 (1.12%)	<0.001
Pneumothorax or hemothorax, n (%)	310 (3.13%)	10,150 (2.96%)	10,460 (2.96%)	0.58
Hematoma or hemorrhage, n (%)	654 (6.61%)	33,605 (9.78%)	34,258 (9.69%)	<0.001
Sepsis, n (%)	1,675 (16.92%)	69,522 (20.24%)	71,197 (20.15%)	<0.001

[a] All p values < 0.05 were rounded and reported as p < 0.05 and all p values < 0.001 were rounded and reported as p < 0.001 [b] Definitions of complications can be found in Supplementary Table 1.

of those patients with a diagnosis of cardiac arrest who died at index admission compared with patients who lived at index admission are provided in the **Supplementary** Table 3.

3.2. Population characteristics and clinical outcomes at index hospitalization

Of 522,775 hospital index admission discharges due to cardiac arrest, 353,379 weighted discharges with readmission within the database met the inclusion criteria and were included in the analysis. Of those, 9,898 (2.80%) admissions had TTM present during index hospitalization (Fig. 1).
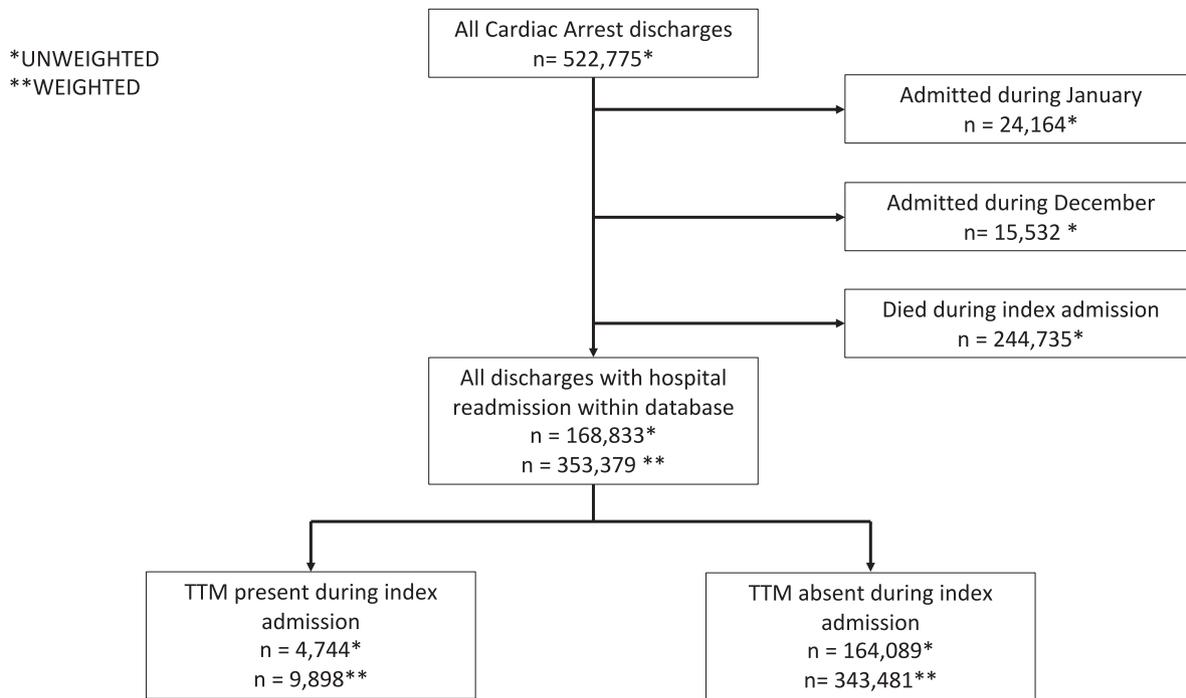
The population characteristics at index hospitalization between admissions with TTM and without TTM are shown in Table 1. Admissions with TTM deployed during their index hospitalization were younger (59.1 ± 0.21 vs. 64.5 ± 0.95 years, p < 0.001), experienced higher male gender admissions (68.30% vs. 60.19%, p < 0.001), higher rates of illicit drug use (10.28% vs. 6.59%, p < 0.001), a higher percentage of household income > 75 percentile (23.05% vs. 18.33%, p < 0.001), lower percentage of household income of 0–25 percentile (23.56% vs. 31.19%, p < 0.001), higher percentage of private insurance (34.03% vs. 25.09%, p < 0.001) and lower Medicare insurance rates and (38.63% vs. 53.06%, p < 0.001), lower length of hospital stay (9.62 ± 0.39 vs. 10.2 ± 0.92 days, p < 0.001), and lower percentage of rural teaching status hospital (2.78% vs. 5.87% p < 0.001) compared to admissions without TTM.

Admissions with TTM also carried lower rates of complicated diabetes (8.77% vs. 12.67%, p < 0.001) and renal failure (14.48% vs. 22.54%, p < 0.001) and higher rates of prior CABG (61.72% vs. 53.05%, p < 0.001), PCI (79.67% vs. 67.37%, p < 0.001), cardiogenic shock (23.73% vs. 12.28%, p < 0.001), ventricular fibrillation (56.63% vs. 24.09%, p < 0.001) and congestive heart failure (50.11% vs. 40.89%, p < 0.001) than admissions without TTM implementation.

During index hospitalization, admissions with TTM were associated with higher rates of AHF (20.13% vs. 17.30%, p < 0.001), AKI (41.12% vs. 37.62%, p < 0.001) and lower rates of hemorrhagic stroke (1.11% versus 1.56%, p < 0.001), vascular complications (0.55% vs. 1.14%, p < 0.001), hematoma or hemorrhage (6.61% vs. 9.78%, p < 0.001), and sepsis (16.92% vs. 20.24%, p < 0.001) compared with admissions without TTM. No differences in ischemic stroke complications were observed (Table 2).

3.3. Readmission rates and outcomes

Admissions receiving TTM were associated with lower 30-day all-cause unplanned rates compared with admissions without TTM (6.30% vs. 9.30%, p < 0.001) (Table 3). The days to readmission among index admissions with and without TTM are illustrated in Fig. 2. Most readmissions occurred within the first day following index admission and discharge decreased over the 30-day period following discharge.

Table 3
Rates and Reason for Readmission at 30 Days.

Condition of Interest	Targeted Temperature Management Present	Targeted Temperature Management Absent	All	p-value[a]
All-cause 30-day readmission rates, n (%)	627 (6.30%)	31,928 (9.30%)	32,555 (9.21%)	<0.001
Cardiac readmissions, n (%)				
Acute heart failure	71 (11.32%)	5,738 (17.97%)	5,809 (1.64%)	0.05
Atrial fibrillation/ flutter	160 (25.52%)	9,658 (30.25%)	9,818 (2.78%)	0.11
Paroxysmal ventricular tachycardia	41 (6.54%)	2,115 (6.62%)	2,156 (0.61%)	0.91
Iatrogenic cardiac complication	17 (2.71%)	811 (2.54%)	920 (0.26%)	0.87
Heart block	<11	428 (1.34%)	–	0.09
PPM implantation	<11	298 (0.93%)	–	0.20
ICD implantation	34 (5.42%)	885 (2.77%)	919 (0.26%)	<0.05
Respiratory complications, n (%)	<11	86 (0.27%)	–	0.92
Infectious complications, n (%)	49 (7.81%)	3,062 (9.59%)	3,111 (0.88%)	0.39
Vascular complications, n (%)	<11	39 (0.12%)	–	0.57
Prosthetic devices complications, n (%)				
Device issue	<11	153 (0.48%)	–	0.36
Device infection	75 (11.96%)	4,704 (14.73%)	4,779 (1.35%)	0.25
Device thrombosis	<11	344 (1.08%)	–	0.40
Venous thromboembolism, n (%)				
Deep venous thrombosis	33 (5.26%)	1,161 (3.64%)	1,194 (0.34%)	0.26
Pulmonary embolism	24 (3.83%)	1,006 (3.15%)	1,031 (0.29%)	0.56
Acute kidney injury, n (%)	115 (18.34%)	8,773 (27.48%)	8,888 (2.52%)	<0.05
Gastrointestinal bleed, n (%)	51 (8.13%)	2,134 (6.68%)	2,185 (0.62%)	0.52
Stroke, n (%)	12 (1.91%)	539 (1.69%)	551 (0.16%)	0.82
Mortality during readmission, n (%)	34 (5.42%)	2,768 (8.67%)	2,803 (0.79%)	0.25

[a] As per HCUP guidelines, all frequencies less than 11 are represented as "<11" to adhere to HIPAA laws. Therefore, corresponding total frequency is masked (-).
[b] All p values < 0.05 were rounded and reported as p < 0.05 and all p values < 0.001 were rounded and reported as p < 0.001.
[c] Definitions of complications can be found in Supplementary Table 1.
PPM = Permanent pacemaker placement. ICD = Implantable cardiac defibrillator.

Fig. 1. Sample selection and study design; *Unweighted Data; **Weighted Data; Weighted discharges provides national estimates vs unweighted are simply the number of observations in the database. More information can be found at: https://www.hcup-us.ahrq.gov/tech_assist/nationalestimates/508_course/508course_2018.jsp#nisdischovertime.
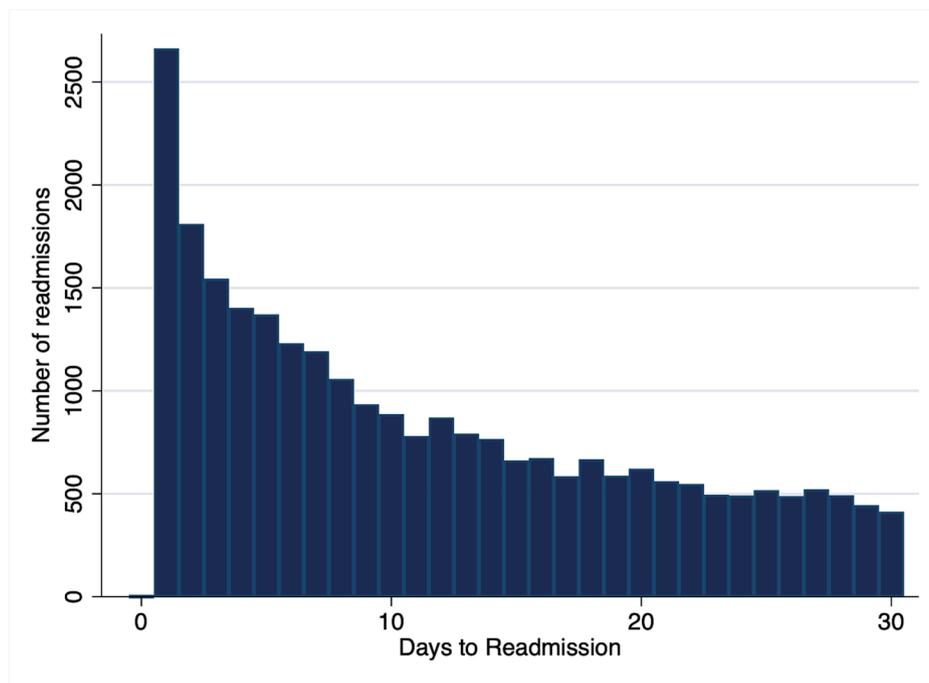
Fig. 2. Histogram demonstrating days to readmission for our study cohort. The majority of readmissions occurred between 1 and 5 days following index admission with a steady decrease over the 30-day study period of interest.

There was a trend toward lower AHF readmission (11.32% vs. 17.97%, p = 0.05) among admissions who had received TTM. There was also a lower association between AKI readmission in the TTM group (18.34% vs. 27.48%, p < 0.001).

3.4. Multivariable regression analysis

After excluding admissions who expired during index hospitalization from further analysis, admissions with TTM deployed during index hospitalization were associated with lower odds of unplanned all-cause readmission at 30 days (OR: 0.81; 95% CI: 0.69–0.95; p < 0.05). We identified several variables associated with increased odds of 30-day

unplanned readmission, including chronic heart failure (OR: 1.27; 95% CI: 1.22–1.32; p < 0.001), complicated diabetes (OR: 1.19; 95% CI: 1.12–1.25; p < 0.001), cardiogenic shock (OR: 1.14; 95% CI: 1.08–1.22; p < 0.001), and atrial fibrillation/flutter (OR: 1.13; CI: 1.04–1.23; p < 0.05). Ventricular fibrillation was associated with lower odds of unplanned readmission (OR: 0.86; 95% CI: 0.81–0.90; p < 0.001). The remaining findings are displayed in Fig. 3. Additional predictor variables for readmission are shown in **Supplementary Table 4**. We found no association between TTM and non-routine discharge, total charge, or hospital length of stay (**Supplementary Table 5**). Additionally, since the majority (n = 5,463) of readmissions occurred on the first day after the index hospitalization, we conducted the same multivariate regression model after excluding those readmissions that occurred on the first day after discharge. After the exclusion of these patients, TTM was associated with a lower all-cause unplanned 30-day readmission (OR: 0.78, 95% CI: 0.66–0.93, p = 0.005). The complete results of the multivariable regression are shown in **Supplementary Table 6**.

3.5. Inverse probability treatment weighting

IPW showed that TTM had a lower average treatment effect (ATE) for all-cause unplanned 30-day readmission by 2.38% (ATE: −0.0238, 95% CI: −0.039 to −0.008, p = 0.002).

3.6. Propensity score matching

A 1:1 propensity score matching accounting for age, gender, insurance type, hospital type, quartile for median household income, and Elixhauser comorbidity index was conducted to corroborate the results

of the multivariable regression analysis. Admissions with TTM were associated with lower odds of all-cause unplanned 30-day readmission rates (OR: 0.80, 95% CI 0.66–0.99, p = 0.036) after adjusting for multiple confounders. The complete results of the multivariable regression analysis in the propensity-matched cohort are shown in **Supplementary Table 7**.

3.7. Interaction term analysis

We found no interaction of index AKI and TTM regarding 30-day unplanned readmissions for AKI (OR: 0.98, 95% CI 0.58–1.63, p = 0.935) and no interaction of index AHF and TTM regarding 30-day unplanned readmissions for AHF (OR: 1.2, 95% CI 0.58–2.51, p = 0.607) (**Supplementary Table 8**).

4. Discussion

Our study revealed that cardiac arrest survivors who received TTM during their index hospitalization were associated with lower rates of all-cause readmissions at 30 days when compared with cardiac arrest survivors who did not receive TTM. These admissions who received TTM were associated with lower readmission rates for AKI and trended towards lower AHF readmission rates at 30 days. These admissions were associated with a higher rate of readmissions for ICD implantation at 30 days. Initial sensitivity analysis demonstrated an association between TTM implementation and early mortality at index admission, although this was addressed by removing these patients from our main analysis. The implementation of TTM during index hospitalization was not associated with non-routine discharge, total hospital charge, or length of
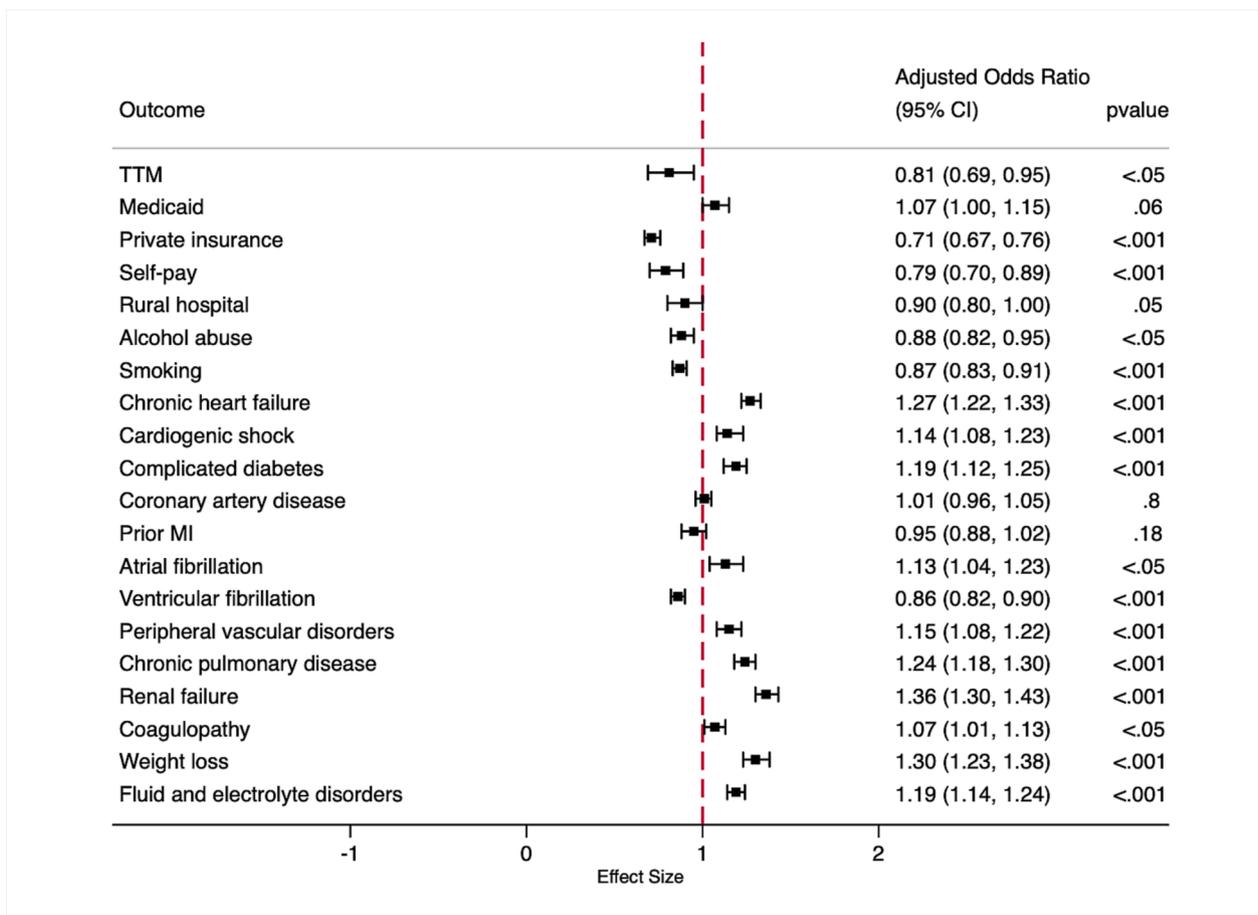

Outcome		Adjusted Odds Ratio (95% CI)	pvalue
TTM		0.81 (0.69, 0.95)	<.05
Medicaid		1.07 (1.00, 1.15)	.06
Private insurance		0.71 (0.67, 0.76)	<.001
Self-pay		0.79 (0.70, 0.89)	<.001
Rural hospital		0.90 (0.80, 1.00)	.05
Alcohol abuse		0.88 (0.82, 0.95)	<.05
Smoking		0.87 (0.83, 0.91)	<.001
Chronic heart failure		1.27 (1.22, 1.33)	<.001
Cardiogenic shock		1.14 (1.08, 1.23)	<.001
Complicated diabetes		1.19 (1.12, 1.25)	<.001
Coronary artery disease		1.01 (0.96, 1.05)	.8
Prior MI		0.95 (0.88, 1.02)	.18
Atrial fibrillation		1.13 (1.04, 1.23)	<.05
Ventricular fibrillation		0.86 (0.82, 0.90)	<.001
Peripheral vascular disorders		1.15 (1.08, 1.22)	<.001
Chronic pulmonary disease		1.24 (1.18, 1.30)	<.001
Renal failure		1.36 (1.30, 1.43)	<.001
Coagulopathy		1.07 (1.01, 1.13)	<.05
Weight loss		1.30 (1.23, 1.38)	<.001
Fluid and electrolyte disorders		1.19 (1.14, 1.24)	<.001

Fig. 3. Forest plot depicting various outcomes and their association with readmission at 30 days, expressed as adjusted odds ratio and 95% confidence interval; p-value < 0.05 considered statistically significant.

hospital stay during all-cause 30-day readmissions.

Landmark trials and prior studies have underscored conflicting evidence for the benefit of TTM on neurological outcomes and mortality in recipients, which has influenced the clinical decision for TTM deployment [5–7]. Recent data from the TTM-2 trial [7] challenges the clinical benefits of initial observations and suggests for the emphasis of "temperature control" of less than 37.7 °C over hypothermic protocols in survivors of cardiac arrest, which remain the current guidelines for post-arrest care [8]. Nonetheless, the literature is scarce regarding readmission rates and causes among cardiac arrest survivors who receive TTM, a quality-of-care metric related to assess hospital performance and predictions of patient outcomes [24,25]. Furthermore, little is known on the short and long-term effect of TTM on other organs and systems and its relationship with organ-specific readmissions.

Our study results provide meaningful information regarding the potentially protective role of TTM on readmission by finding an association between cardiac arrest survivors being 19% less likely to be readmitted at 30 days if TTM was implemented during index hospitalization. These results were consistent even after accounting for possible bias by performing IPW and propensity score matching to reduce bias from heterogeneity of baseline characteristics among study groups. A study by Yeo et al. [26] assessing 30-day readmission in cardiac arrest survivors demonstrated an increase in all-cause readmission rates among patients who survived cardiac arrest, and similarly noted these protective effects of TTM for 30-day readmission in shockable cardiac arrest rhythms without effect on non-shockable rhythm, regardless of the occurrence of arrest (out-of-hospital or in-hospital). Unlike Yeo et al, we did not differentiate cardiac arrest by rhythm type so to directly assess the influence of TTM implementation, accounting for potential practice cofounders as follows. First, there is higher perceived benefit of instituting TTM in shockable rhythms over non-shockable rhythms as was identified in the HACA trial [5], while further trials extend its benefit to non-shockable rhythms for in- and out-of-hospital cardiac arrest, however emphasizing neurologic outcomes rather than readmissions [27]. Second, healthcare system-based challenges may limit timely TTM implementation in patients whose clinical presentation supports TTM initiation [9–15]. Third, the literature identifies variability in TTM temperature targets based on initial cardiac arrest rhythm [9–12]. Thus, we aimed for a more inclusive analysis to capture different TTM practices around the country including timing of cooling and targeted temperature, while accounting for the evolution of the literature on TTM during the study period and its immediate impact on practice, and addressing any potential association of TTM on sequelae to other organs during the readmission period.

By revealing that close to one of ten cardiac arrest survivors experienced higher readmissions within 30 days, our study supports the persistently high healthcare system burden [29] in managing cardiac arrest patients. Readmission rates for cardiac arrest survivors remain significantly high, with prior estimates of 19–35%, of which non-shockable rhythms and older age relate most to higher rates [26,28]. Different from Chan et al. [28] who studied a cohort of Medicare-eligible patients (with an average age of 75), our cohort at index admission was younger overall (average age of 64.3). Variability in the implementation of TTM and institutional resources may also account for these findings as our cohort is inclusive of a wide range of healthcare practices and expected primary payers.

Our study revealed that most of the unplanned readmissions occurred within the first day following discharge. However, even after excluding those patients who were readmitted on day 1 after discharge, there was minimal change to our results, suggesting that the effect of TTM on readmissions persists beyond the 1st day after discharge. Early readmissions, defined as readmissions between Day Zero and Day Seven following discharge, continue to carry a significant economic burden on the healthcare system and patient outcomes [29]. We propose that heterogeneity ofhospital factors, including physician decision-making, differences in the optimization of post-arrest critical care among a robust patient population, improper discharge planning, and preventable medical errors may account for these findings in our cohort. Our hypotheses support prior studies that contend that early readmissions may be preventable due to these hospital-related factors [30,31].

Receiving TTM was associated with higher rates of AHF and AKI during index hospitalization, but lower rates during readmission within 30 days. Following cardiac arrest, acute organ damage results from anoxic injury via cardiogenic shock and ischemic-reperfusion injury [32,33]. AKI is another well-known sequela of cardiac arrest [34,35], but the literature remains unclear as to whether TTM offers renal protection [35–38] or if it is an expected progression of renal function recovery once moving away from the initial insult. Similarly, patients often experience AHF secondary to myocardial dysfunction and shock [39]. A possible bias for these results would be that since there were higher rates of acute kidney injuries and AHF at the index hospitalization, these patients might have received optimal treatments for these conditions at their admissions, thus decreasing their risk of readmission for the same reason. To attempt to uncover if this possibility was leading the decrease in readmissions seen with TTM, we conducted an interaction term analysis between index admission AKI and AHF and TTM with their relationship to readmission for the same condition, and we found no interaction. Thus suggesting that the development of AKI and AHF during patients' index admission has no effect on 30-day unplanned readmission due to the same condition. We propose that benefits from enhanced post-arrest critical care, including closer telemetry monitoring, medical optimization of comorbidities, temperature control, minimization of recurrent cardiac rate and rhythm events, and reversal of underlying etiologies for arrhythmias may result in mitigation of acute anoxic injury, resulting in a positive index of hospital outcome, and this may be associated with decreased readmissions in the shorter term [40,41].

We also sought to determine whether TTM was associated with protective effects on other organ systems, thereby decreasing readmission rates for these reasons. Although we did not identify a statistically significant association between deployment of TTM and readmissions due to respiratory causes, findings by Karnatovskaia et al. [42] suggest TTM may contribute to improved survival and decreased hospital length of stay in patients experiencing acute respiratory distress syndrome following cardiac arrest. We did not establish an association between TTM implementation and gastrointestinal hemorrhage, similar to findings reported by Zou et al. [43]. Future randomized trials are warranted to determine if TTM offers protective effects in modifying organ injury during post-cardiac arrest care.

After accounting for the potential impact of TTM on mortality by removing these patients from our study cohort, our regression model supports TTM implementation as a potential protective variable during index admission for lower odds of 30-day readmission. As expected, most readmissions in cardiac arrest survivors were due to cardiac causes including heart failure, cardiogenic shock, and atrial fibrillation or flutter. Heart failure and cardiogenic shock are known sequela and causes of readmission following cardiac arrest, with and without TTM [26]. Moreover, in a randomized controlled trial, Thomsen et al. [44] identified atrial fibrillation as an independent predictor of complications and mortality during post-cardiac arrest care, even in the setting of TTM. Future randomized studies may be considered to assess the potential benefit of mitigating tachyarrhythmias during post-cardiac arrest care and long-term outcomes.

A diagnosis of ventricular fibrillation paradoxically decreased the odds of 30-day readmission in our cohort, which may result from ICD placement for this shockable rhythm during index admission. This may confound these findings since patients with initially shockable rhythms often experience improved clinical outcomes, are more likely to receive an ICD and be administered TTM during index admission compared to patients with non-shockable rhythms [45]. Additionally, these patients who experience ventricular fibrillation due to sequela of acute coronary syndrome, may benefit from interventions including early PCI,

especially when combined with TTM, thereby augmenting future risk of readmission [46].

Lastly, our results highlighted that the presence of tobacco and ethanol use was associated with lower odds of 30-day unplanned readmission. However, we believe these results do not represent an accurate association. As this is counterintuitive, there is no biological explanation for this association but likely rather a Table 2 fallacy [47]. Furthermore, tobacco and ethanol use ICD-10 diagnosis codes are known for having a very low sensitivity [48–50]. As a result, responder bias might be a possible explanation for these results, as patients who admitted to use tobacco and ethanol might have other factors that made them less likely to be readmitted.

Study Limitations

Our study carries several limitations that relate to the data sampling methodology. First, data pertaining to clinical symptoms, laboratory results, vital signs, and medications are not available. Second, the database does not qualify or quantify the clinical and process details of TTM, including the targeted temperature of cooling, how long admissions received TTM, or for how long cooling was achieved. Lastly, the accuracy of the diagnosis directly depends on the medical provider's coding, and certain diagnoses may be erroneously coded or undercoded. These limitations impact our conclusions because of the uncertainty of how TTM was implemented. However, the ICD codes used for cardiac arrest have been shown to have a sensitivity of 86% and specificity of 99% [21]. In contrast, ICD codes for certain variables like tobacco, ethanol, or illicit drugs are known to have very low sensitivity although high specificity due to underreporting [48–50]. In our cohort, we found that tobacco and ethanol use were associated with lower readmission. These results might be related to responder bias, as patients who admitted using these substances might have other factors that made them less likely to be readmitted. Nonetheless, we recognize that many confounding variables, including heterogeneity of the patient population, protection of other organs, cardiovascular optimization during post-arrest care, and rehabilitation status following discharge may lead to decreased readmissions in our cohort. Second, mortality at index admission appears to be a confounder for decreased readmission rates, though we accounted for this by first determining the association between TTM and mortality, and then excluding these patients from our study cohort. Third, each year of the NRD should be considered as a separate sample as the patient linkage numbers (NRD_VisitLink) is unable to follow the same patient across different years. Furthermore, patients hospitalized in one state and readmitted or transferred to a hospital in another state cannot be tracked, as each state uses different coding for their patient linkage numbers.

5. Conclusion

The implementation of Targeted Temperature Management during index hospitalization of survivors of cardiac arrest is associated with lower odds of 30-day unplanned all-cause readmissions. These findings are hypothesis-generating and may inform the development of randomized studies to evaluate the mechanisms, causes, and effects of comorbidities impacting readmission rates.

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7. Funding information

CRediT authorship contribution statement

Justin Mark: Conceptualization, Methodology, Formal analysis, Writing – original draft, Writing – review & editing, Visualization, Project administration. **Jose Lopez:** Formal analysis, Writing – original draft, Writing – review & editing, Visualization, Supervision. **Waseem Wahood:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Visualization. **Joshua Dodge:** Conceptualization, Methodology, Writing – original draft. **Miguel Belaunzaran:** Writing – original draft, Visualization. **Fergie Losiniecki:** Writing – review & editing. **Yelixa Santos-Roman:** Writing – review & editing. **Mauricio Danckers:** Writing – original draft, Writing – review & editing, Supervision, Project administration.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2023.101207.

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