



Original Article

Targeted Temperature Management After Cardiac Arrest: The Montreal Heart Institute Experience

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ABSTRACT

Background: Targeted temperature management (TTM) has been associated with an improvement in neurological function and survival in patients with cardiac arrest (CA) and an initially shockable rhythm. We report the Montreal Heart Institute (MHI) experience using TTM to evaluate mortality and neurological outcome in patients remaining in coma after CA, regardless of the initial rhythm.

Methods: We performed a retrospective review of all patients receiving TTM at the MHI between 2008 and 2015. Primary outcome was a composite of mortality and poor neurological outcome at hospital discharge. We also evaluated the long-term outcomes of those who initially survived to hospital discharge.

Results: A total of 147 patients (120 men, mean age 59.5 ± 12.5 years) underwent TTM at the MHI during the study period. Overall

RÉSUMÉ

Contexte : Le contrôle ciblé de la température (CCT) a été associé à une amélioration de la fonction neurologique et de la survie chez les patients en arrêt cardiaque ayant un rythme initialement choquable. Nous présentons l'expérience d'utilisation du CCT à l'Institut de Cardiologie de Montréal (ICM) pour évaluer la mortalité et l'issue neurologique chez les patients qui demeurent comateux après un arrêt cardiaque, indépendamment du rythme initial.

Méthodologie : Nous avons effectué une analyse rétrospective de tous les patients ayant fait l'objet d'un CCT à l'ICM entre 2008 et 2015. Le paramètre d'évaluation principal se composait de la mortalité et d'une évolution neurologique défavorable à la sortie de l'hôpital. Nous avons aussi évalué le devenir à long terme des patients ayant initialement survécu après leur congé.

Prolonged cardiac arrest (CA), especially when occurring out of hospital, is associated with poor survival and high morbidity. In 2016, approximately 360,000 individuals presented to emergency departments in the United States after out-of-hospital cardiac arrest (OHCA),¹ with an overall survival to hospital discharge regardless of neurological status of only 10.6%.¹ Since the early 1960s, many efforts to improve this dismal prognosis have been attempted, including the use of therapeutic hypothermia for neuroprotection after CA,

which showed improved survival.²⁻⁵ This term later evolved to “targeted temperature management” (TTM) when similar outcomes between hypothermia (temperature target of 33°C) compared with TTM (36°C) were reported.⁵ Consequently, in patients with return of spontaneous circulation (ROSC) after CA who remain comatose, TTM is currently recommended by guidelines,⁶⁻⁸ with temperature targets ranging between 33°C and 36°C. Of note, a recent trend for clinicians to switch toward milder hypothermia and temperature target of 36°C has been observed.⁹

Nevertheless, many aspects of TTM after CA remain unknown. First, although the randomized studies included only witnessed CA with shockable rhythms, TTM is commonly used in other situations such as unwitnessed CA but with a presumed low “downtime” or patients with nonshockable rhythm (NSR).^{10,11} In addition, the debate on the ideal targeted temperatures is still ongoing.^{10,12} Data on long-term benefits of this therapy in terms of survival and neurological status are lacking.

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Ethics Statement: The research reported has adhered to the relevant ethical guidelines.

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survival to hospital discharge with good neurological outcome was 45.6%. Shockable rhythm was associated with a better outcome (mortality odds ratio, 0.212; 95% confidence interval, 0.068-0.664; $P = 0.008$). Of the 11 initial survivors with a poor neurological status (Cerebral Performance Category ≥ 3), 4 died rapidly (within 1 month of hospital discharge), but 6 (54.5%) markedly improved their neurological status to Cerebral Performance Category 1. Long-term survival (mean follow-up of 38 ± 26 months) for those alive at hospital discharge ($n = 76$ patients) was 81.9%.

Conclusion: Our retrospective analysis of CA survivors treated with TTM at MHI showed good survival, similar to the published results from the landmark randomized controlled trials, despite enrolling patients with nonshockable rhythms. A significant proportion of survivors with poor neurological outcome at discharge improved at follow-up.

We aim to present our clinical experience of all consecutive patients who underwent TTM at the Montreal Heart Institute (MHI). Our objectives are 4-fold: (1) to evaluate the outcomes in terms of mortality and neurological sequelae in a retrospective analysis setting; (2) to identify factors associated with worse prognosis; and (3) to assess the long-term consequence for these patients. In addition, we aimed to perform an exploratory analysis comparing results between eras of targeted temperature: between our earlier experience (33°C) and the more recent one (36°C).

Methods

Study design

We conducted a retrospective observational study. The medical charts of all patients who underwent TTM after CA between February 5, 2008, and December 29, 2015, at MHI were reviewed. We also conducted open-ended telephone interviews for specific data points (vital and neurological status) with patients or their relatives to assess their long-term outcome.

Setting and TTM protocol

The MHI is a large cardiology centre in Canada and as such receives referrals from other hospitals across the province. After ROSC, many patients are transferred for advanced care, including coronary angiography, and TTM is performed when appropriate. Our hospital's protocol suggests the following criteria for TTM consideration: (1) remaining comatose (Glasgow Coma Scale < 8); (2) witnessed CA; (3) ROSC within 60 minutes; and (4) reasonable life expectancy otherwise. Contraindications include noncardiac cause of arrest, severe hemodynamic instability, severe coagulopathy, or bleeding. The presence of an initial shockable rhythm (ventricular fibrillation/ventricular tachycardia) is not required, and the final decision whether to institute TTM or not is left at the discretion of the treating physician.

Résultats : Au total, 147 patients (120 hommes, âge moyen de $59,5 \pm 12,5$ ans) ont fait l'objet d'un CCT à l'ICM pendant la période d'étude. Le taux de survie globale jusqu'à la sortie de l'hôpital avec évolution neurologique favorable a été de 45,6 %. Un rythme choquable a été associé à une meilleure issue (rapport de cotes pour la mortalité = 0,212; intervalle de confiance à 95 % : de 0,068 à 0,664; $p = 0,008$). Chez les 11 survivants initiaux dont l'état neurologique était altéré (score CPC [Cerebral Performance Category] ≥ 3), 4 sont décédés peu après (dans le mois suivant leur congé), mais 6 (54,5 %) ont vu leur état neurologique s'améliorer considérablement jusqu'à un score CPC de 1. La survie à long terme (durée moyenne du suivi de 38 ± 26 mois) pour les patients vivants à leur sortie de l'hôpital ($n = 76$ patients) a été de 81,9 %.

Conclusions : Notre analyse rétrospective des survivants d'un arrêt cardiaque traités par CCT à l'ICM a montré une bonne survie, comparable aux résultats publiés d'essais contrôlés phares à répartition aléatoire, malgré l'inscription de patients ayant des rythmes non choquables. Au moment du suivi, une amélioration a été observée chez une forte proportion des survivants dont l'état neurologique était altéré à leur sortie de l'hôpital.

Patients are cooled for 24 hours, initially targeting a temperature of 32°C to 34°C , which was modified to 35°C to 36°C in December 2013 after the TTM publication by Nielsen and colleagues.⁵ After the first 24 hours, patients undergo a slow rewarming to 37°C , which is maintained for 24 hours by keeping the cooling system in place to avoid the potential deleterious effects of rebound hyperthermia. TTM is achieved using the Arctic Sun external cooling system (Medivance, Louisville, CO), a noninvasive system consisting of conductive gel pads with a feedback control mechanism allowing rapid reaching of targeted temperature and precise temperature maintenance.¹³

Outcomes

The primary end point was a composite of all-cause mortality to hospital discharge or poor neurological outcome, measured using the Cerebral Performance Category (CPC) scale (Table 1) in all patients with CA who underwent TTM at MHI.^{14,15}

The CPC score at hospital discharge was assessed a posteriori by chart review, using all information available, including clinical and neurological assessment, physical and occupational therapists' evaluations, and social service and nursing notes. The CPC score at follow-up was obtained through telephone interviews, either with the patient or a family member, assessing activities of daily living, including driving and working capacities.

Statistical analysis

Data are presented as mean \pm standard deviation. Continuous variables were analyzed as such, and categorical variables were divided by quartiles. Differences between groups were tested using chi-square with 95% confidence intervals ($P < 0.05$). Potential factors associated with worse outcome (age, male sex, high blood pressure, hyperlipidemia, diabetes, coronary artery disease, lactate level, creatinine level, and time to ROSC) were first entered into a univariate model,

and those with $P < 0.20$ were included in a multivariate analysis using a stepwise approach, with $P < 0.05$ being considered significant. Kaplan–Meier survival analysis curves were used to assess outcomes.

Results

A total of 147 patients (120 men, mean age 59.5 ± 12.5 years) underwent TTM at MHI during the study period. Patients were cooled for an average of 23.4 ± 6.4 hours, with an average time to reach target temperature (from ROSC to target) of 259 ± 124 minutes (Table 2). There were 133 patients in the earlier cohort and only 14 patients in the more recent era. Overall, 80 patients (54.4%) reached the primary end point of mortality or poor neurological outcome, 74 (55.6%) in the 33°C protocol and 6 (42.9%) in the recent era, without any significant difference between eras (odds ratio [OR], 0.598; 95% confidence interval [CI], 0.197–1.819; $P = 0.3649$) (Table 3). A total of 78 of 147 patients (53.1%) survived to hospital discharge, regardless of their CPC score. Of the 69 patients who died, 64 were in the 33°C target group and 5 were in the 36°C cohort. The cause of death was presumed to be related to neurological outcome for the majority of those patients ($n = 66$); they all had a CPC score of 4 or 5. The remainder died of shock and multiorgan failure (3% and 20%, respectively).

Interventions and prognostic factors

Urgent coronary angiography was performed in 115 patients, mainly for ST-elevation myocardial infarction (STEMI) or suspected ischemia causing the arrest, with a mean time from ROSC to coronary intervention of 213 ± 714 minutes (Tables 3 and 4). Of those undergoing angiography, percutaneous revascularization was performed in 85, for STEMI ($n = 79$), chronic total occlusion ($n = 1$), involvement of the left main or left anterior descending artery ($n = 3$), or extensive disease ($n = 2$). The decision to perform a coronary intervention or not was left at the treating physician's discretion and individualized. Early revascularization by percutaneous coronary intervention (PCI) was not associated with a better outcome (OR, 1.054; 95% CI, 0.485–2.292; $P = 0.8935$), even for the STEMI subgroup (OR, 6.617; 95% CI, 0.739–59.277; $P = 0.2525$).

As expected, the presence of shockable rhythms at presentation was associated with a better outcome than NSR (mortality OR, 0.212; 95% CI, 0.068–0.664; $P = 0.0078$); on the other hand, age and gender were not associated with poor outcome. By multivariate analysis, higher lactate and serum creatinine levels and prolonged resuscitation (longer time to ROSC) were all associated with worse outcome (Table 3). Every increase of 1 mmol/L of lactate was associated with worse outcome (OR, 1.210; 95% CI, 1.044–1.403; $P = 0.0113$).

Long-term outcomes

Long-term neurological outcome and mortality data were available for 76 patients (92%), with 2 patients lost to follow-up. Among the 78 survivors to discharge from our hospital, 11 (14.1%) had a poor neurological status (CPC 3 or 4); of those, 4 died early afterward (36.3%), mainly upon return to their referring hospital, whereas the

Table 1. Cerebral performance category scale*

Score	Outcome
1	Good cerebral performance: conscious, alert, able to work, might have mild neurologic or psychologic deficit.
2	Moderate cerebral disability: conscious, sufficient cerebral function for independent activities of daily life. Able to work in sheltered environment.
3	Severe cerebral disability: conscious, dependent on others for daily support because of impaired brain function. Ranges from ambulatory state to severe dementia or paralysis.
4	Coma or vegetative state: any degree of coma without the presence of all brain death criteria. Unawareness, even if appears awake (vegetative state) without interaction with environment; may have spontaneous eye opening and sleep/awake cycles. Cerebral unresponsiveness.
5	Brain death: apnea, areflexia, electroencephalogram silence.

*Adapted from Jennett and Bond.¹⁵

majority of the remainder (6, 54.4%) improved their neurological status to a CPC score of 1. Neurological recovery with CPC improvement was obtained in 6 patients in the 33°C group and 2 patients in the 36°C cohort. Furthermore, all the patients with good neurological status at discharge remained neurologically stable throughout follow-up (Fig. 1).

In patients surviving to hospital discharge, the late mortality was 17.1% ($n = 13$) after a mean follow-up of 38 ± 26 months between CA and last clinical encounter (Fig. 2). A Consolidated Standards of Reporting Trials (CONSORT) flow diagram is shown in Figure 3.

Discussion

We performed a retrospective analysis of our institutional TTM experience after CA and showed that approximately half of patients (45.6%) survived to hospital discharge without significant neurological disability. Our findings are similar to the results of the 3 main studies published in the field, ranging from 46% to 55% survival.^{3–5} In contrast to these randomized controlled trials, we present our clinical experience, regardless of initial rhythm or location of the arrest, and with approximately half of the events being unwitnessed. Our results are important, because these variables have been associated with worse outcomes,¹⁶ and TTM is not strongly recommended in the current guidelines for these situations.⁶ The choice to proceed with TTM in our cohort was ultimately left at the discretion of the treating physician.

The earliest targeted temperature era trended toward higher mortality (54.4% vs 42.9%, respectively), but this difference was not statistically significant ($P = 0.3649$). Although our numbers are small in the contemporary era, this trend toward better outcomes has also been raised by Buick et al.,¹⁷ who recently showed improved survival over time from OHCA within the Toronto area; their factors associated with improved outcome over time include improved bystander cardiopulmonary resuscitation rate (CPR) rate and increased TTM use.¹⁷ It is possible that the improved results from recent experience encompass a bundle of modern intensive care rather than solely the targeted temperature itself, but our setting has not changed significantly over time. On the other hand, the TTM trial⁵ also had some selection bias because of its randomized controlled design, and it is possible

Table 2. Patient characteristics at baseline

	All (N = 147)
Demographics	
Age, y	59.5 (12.5)
Male sex (%)	120 (81.6)
Medical history	
Hypertension (%)	62 (42)
Dyslipidemia (%)	68 (46)
Diabetes (%)	23 (15.6)
CAD (%)*	37 (25)
Chronic renal failure (%)	9 (6)
Previous stroke or TIA (%)	17 (11.5)
Family CAD (%)	23 (15.6)
Active smoker (%)	47 (31.9)
Clinical characteristics on admission	
STEMI (%)	92 (62.5)
Early coronary angiography (%)	115/147 (78.2)
Time (min) to early PCI	213 (714)
First measured body temperature (°C)	35.8 (1.2)
Serum lactate (mmol/L)	4.9 (4)
Serum creatinine (µmol/L)	126 (41)
Serum glucose (mmol/L)	13.3 (5.4)
Circulatory shock (%)†	52 (35.8)
Characteristics of the CA	
Location of CA (outside of hospital) (%)	135 (91.8)
Bystander performed CPR (%)	86 (58.5)
First monitored rhythm	
VF/VT (%)	113 (83)
Electromechanical dissociation/asystole (%)	23 (16.9)
Time to ROSC (min)	26.3 (17.6)
Time to hypothermia (min)	259 (124)
TTM duration (h)	23.4 (6.4)

Data are presented as % or mean ± standard deviation.

CA, cardiac arrest; CAD, coronary artery disease; CPR, cardiopulmonary resuscitation; PCI, percutaneous coronary intervention; ROSC, return of spontaneous circulation; STEMI, ST-segment elevation myocardial infarction; TIA, transient ischemic attack; TTM, targeted temperature management; VF/VT, ventricular fibrillation/ventricular tachycardia.

* Defined as previous PCI, coronary artery bypass grafting, or ischemic disease requiring treatment.

† Defined as persistent hypotension causing end-organ hypoperfusion or necessitating vasopressor support or intra-aortic balloon pump.

that some OHCA survivors did not undergo screening for the trial, as suggested by the rather small numbers of patients assessed for eligibility, namely, 1431 for 36 centers.⁵ Furthermore, all centers enrolling in the TTM trial had an established therapeutic hypothermia protocol as standard of care before entry into the trial. Consequently, clinicians might

have been reluctant to enroll patients, given the possibility of not receiving hypothermia. Also, a longer time to reach target temperature and a somewhat hurried rewarming in the 33°C group may have negatively influenced the outcome in this group.^{18,19} By contrast, achieving a milder target of 36°C was associated with less active cooling, a shorter period at target temperature, and higher rebound fever rates,¹² which might lead to worse outcomes. Therefore, setting an appropriate temperature target remains challenging as reflected by the American and Canadian guidelines, which do not recommend a specific target but rather a range of temperature.^{6,8}

As expected, having a shockable initial rhythm was associated with better outcome at hospital discharge in our cohort as well.¹⁶ It still remains unclear whether TTM offers a benefit for NSR. Although it seems appealing to provide neuroprotection regardless of the initial rhythm, the benefit of TTM in NSR has not been clearly demonstrated. Several factors can explain this apparent incongruity. First, the shockable rhythm population includes mostly men presenting with a cardiac cause of arrest, mainly acute myocardial infarction.²⁰ In contrast, the NSR subgroup is more heterogeneous, both in terms of characteristics and cause of arrest;²⁰ they are generally older, have more comorbidities, and are more prone to severe complications.²¹ Furthermore, confounding factors such as a witnessed CA, which is an independent predictor of better outcome, is less commonly found in NSR.²² Therefore, it is possible that a larger sample size would be required to demonstrate benefit of TTM in an NSR population. Despite this lack of evidence, guidelines currently recommend TTM for any initial rhythm,⁶ based on the belief that TTM is not harmful and may provide some benefit as suggested by observational studies.^{23,24} The Therapeutic Hypothermia After Cardiac Arrest in Non Shockable Rhythm trial (HYPERION; NCT01994772) is ongoing to definitely answer the question of whether TTM after CA is beneficial for NSR.²⁰

Early revascularization through PCI was not associated with a better outcome, despite the majority of our revascularized patients (79/85) having a STEMI. There is conflicting evidence on the benefit of early coronary angiography and PCI in patients without STEMI,²⁵⁻²⁸ and our results do not support an aggressive universal PCI approach. Current guidelines do not recommend urgent coronary angiography for all CA survivors but rather in selected situations, with high suspicion of acute coronary event and few comorbidities.⁶

Table 3. Outcomes following TTM after CA

Primary outcome	
Mortality or CPC ≥ 3 at discharge, n (%)	80 (54.5%)
Secondary outcomes	
Mortality at hospital discharge, n (%)	69 (46.9%)
VT/VF as first monitored rhythm	OR, 0.212 (95% CI, 0.068-0.664), <i>P</i> = 0.0078
Early PCI	OR, 1.054 (95% CI, 0.485-2.292), <i>P</i> = 0.8935
Early PCI in STEMI	OR, 6.617 (95% CI, 0.739-59.277), <i>P</i> = 0.2525
Exploratory outcomes: survival and CPCS ≥ 3 at discharge according to temperature	
33°, n (%)	74 (55.6%)
35°-36°, n (%)	6 (42.9%)
33° vs 35°-36°	OR, 0.598 (95% CI, 0.197-1.819), <i>P</i> = 0.3649

Data presented as OR (95% CI, *P* value).

CI, confidence interval; CPCS, cerebral performance category scale; OR, odds ratio; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; TTM, targeted temperature management; VF/VT, ventricular fibrillation/ventricular tachycardia.

*Statistical significance set for *P* < 0.05.

Table 4. Potential factors associated with mortality or poor neurological outcome

	Univariate analysis*	Multivariate analysis†
Age	2.136 (0.834-5.466), $P = 0.2976$	
Male sex	1.069 (0.460-2.483), $P = 0.877$	
High blood pressure	1.782 (0.911-3.486), $P = 0.097$	-
Hyperlipidemia	1.684 (0.864-3.281), $P = 0.1259$	-
Diabetes	2.635 (0.966-7.183), $P = 0.0584$	-
Coronary artery disease	1.104 (0.519-2.347), $P = 0.7973$	
Lactate level	1.281 (1.132-1.451), $P \leq 0.0001$	1.210 (1.044-1.403), $P = 0.0113$
Creatinine level (mmol/L)	11.494 (3.826-34.528), $P \leq 0.0001$	9.141 (1.843-45.325), $P = 0.0432$
Time to ROSC	1.079 (1.045-1.115), $P \leq 0.0001$	1.061 (1.024-1.098), $P = 0.0010$

Data presented as OR (95% CI), P value.

ROSC, return of spontaneous circulation.

*Variables were included in the multivariate model if $P < 0.20$ by univariate analysis.

†Statistical significance set for a $P < 0.05$.

Limited information is available on the long-term prognosis of CA survivors after TTM, including evolution of neurological function over time, the published literature focusing on short-term end points such as survival and neurological status at hospital discharge. Of note, we showed that after more than 3 years of follow-up, survivors with a bad neurological outcome at hospital discharge (CPC = 3 and 4) significantly improved their neurological function over time, returning to an independent level of activity (CPC = 1), or died rapidly after discharge from our tertiary care hospital, suggesting that a bad neurological status at hospital discharge does not predict long-term outcome. Therefore, clinicians should be cautious about early prognostication in a given patient, and the benefit of TTM should be assessed longitudinally. To date, only one study assessed long-term neurological outcome in OHCA survivors, irrespective of TTM use, and showed no improvement in neurological outcome over time.²⁹ Many differences could explain the apparent discrepancy between the findings of Kim and colleagues²⁹ and ours. First, despite reviewing 279 patients, their 1-month survival was only 30.1%, which is lower than in the published literature and the 53.1% at discharge in our cohort. Notably, only 14.7% had an initially shockable rhythm and TTM was used in only 16.1%, which might reflect differences in baseline characteristics and management of the population studied. Nevertheless, they also showed that some of their early

survivors (16.7%) with poor outcome do improve within 6 months of follow-up, even though the proportion of their patients improving is less than our 54.4%. We believe that the greater proportion of shockable rhythms and universal use of TTM in our contemporary cohort favoured improvement in neurological outcome over time.

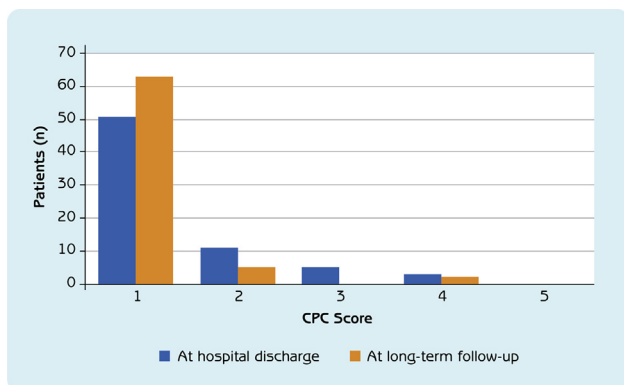


Figure 1. Neurological outcome over time. Shown are the Cerebral Performance Category (CPC) scores of patients at hospital discharge (blue) and at follow-up (red) with average follow up of 38 ± 26 months. Six of the 8 patients who had a bad outcome at hospital discharge (CPC ≥ 3) improved to a functional neurological outcome at follow-up.

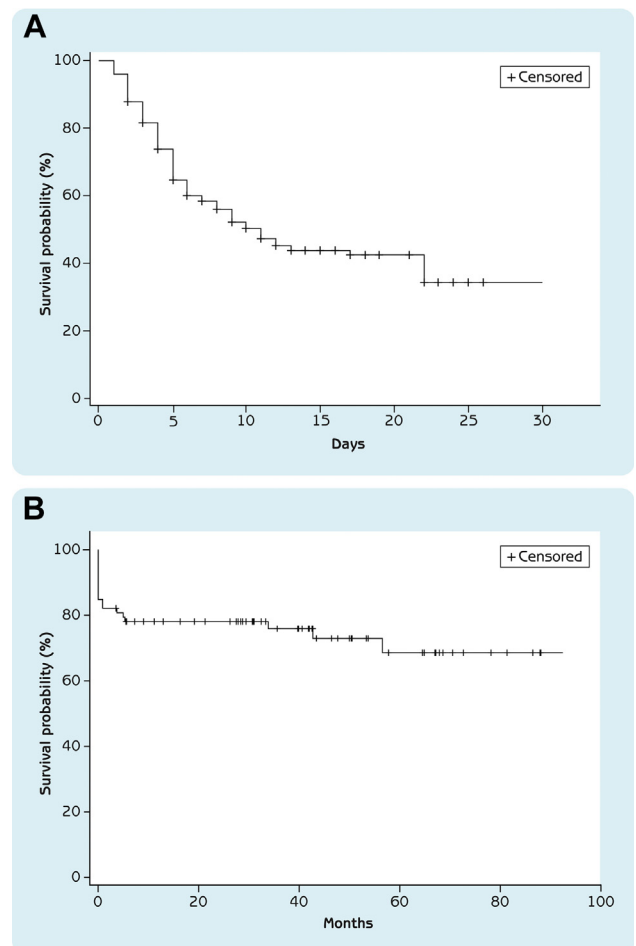


Figure 2. Probability of survival in patients with cardiac arrest (CA) treated with targeted temperature management (TTM). Kaplan–Meier estimates of the probability of survival from hospital admission (A) and hospital discharge (B).

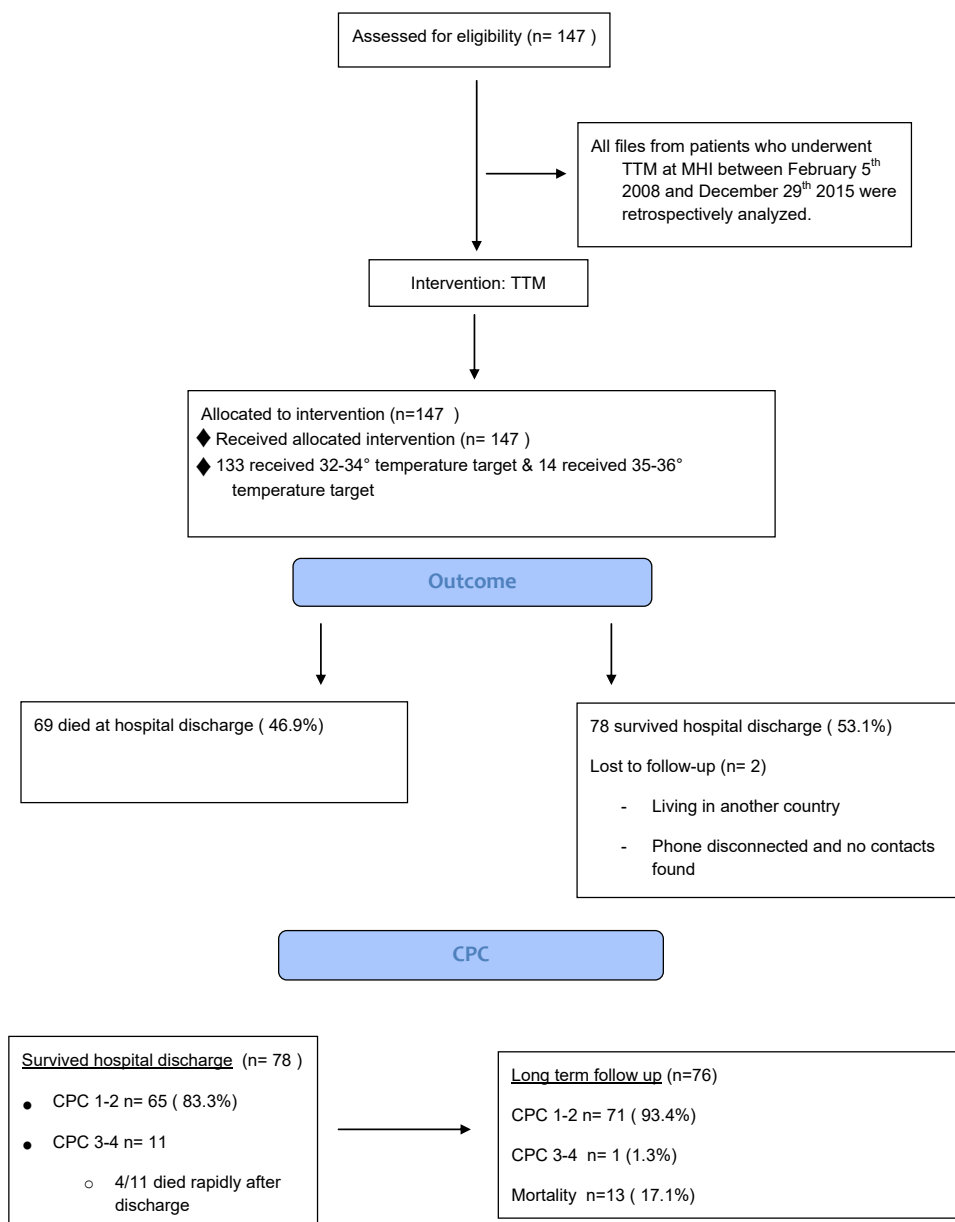


Figure 3. Consolidated Standards of Reporting Trials (CONSORT) flow diagram.

Limitations

Our study has limitations, the majority being inherent to its retrospective design. First, it is important to mention that the population of patients with OHCA who were assessed for TTM at MHI represent only a small subset of all the OHCA occurring in the general population, those who were pre-screened for aggressive management. Further, we do not have all the information regarding the quality of CPR performed in the OHCA setting, and some relevant information as to whether it was witnessed/unwitnessed with bystander CPR is incomplete. Also, our numbers are relatively small, which may have led to reduced power to identify a potential difference between temperature groups or a small benefit of TTM in NSR. To compare our data with published literature, we used the commonly used CPC scale, which has some inherent

limitations and has been criticized because of limited correlation with subjective quality of life and other functional scores.³⁰ In addition, neuro-prognostication was not standardized in our institution at the time of our study. Finally, the retrospective nature of our findings may limit their generalizability to other patient populations.

Conclusion

Consecutive survivors of CA who underwent TTM at the MHI have similar overall outcomes as those in the major randomized controlled trials, despite having included unwitnessed events and patients with nonshockable initial rhythm. Having a shockable rhythm was associated with a better prognosis, whereas longer time to ROSC, higher lactate, and creatinine levels were associated with worse outcome, and

temperature target treatment eras (33°C vs 36°C) showed similar outcomes. Furthermore, approximately two-thirds of the patients with initially poor neurological outcomes at tertiary care hospital discharge improved significantly to return to a functional level of independence, suggesting that a poor neurological outcome at hospital discharge does not necessarily predict long-term outcome.

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Disclosures

The authors have no conflicts of interest to declare.

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