

## Clinical paper

# Clinical predictors of survival in patients treated with therapeutic hypothermia following cardiac arrest<sup>☆</sup>

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## ABSTRACT

**Introduction:** Therapeutic hypothermia has been shown to provide neuroprotection and improved survival in patients suffering a cardiac arrest. We report outcomes of consecutive patients receiving therapeutic hypothermia for cardiac arrest and describe predictors of short and long-term survival.

**Methods:** Eighty patients receiving therapeutic hypothermia between January 2005 and December 2008 were identified and categorized as those who survived and died. Outcomes and predictors of survival were determined.

**Results:** Forty-five patients (56%) survived to hospital discharge and were alive at 30 days and among survivors 41 (91%) were alive 1 year after discharge. Survivors were younger, were more likely to present with VF, required less epinephrine during resuscitation, were more likely to have preserved renal function, and were less likely to be taking beta-blockers and ACE inhibitors. Predictors of survival included VF on presentation (OR 14.9, CI 2.7–83.2,  $p=0.002$ ), pre-cardiac arrest aspirin use (OR 9.7, CI 1.6–61.1,  $p=0.02$ ), return of spontaneous circulation <20 min (OR 9.4, CI 2.2–41.1,  $p=0.003$ ), absence of coronary artery disease (OR 5.3, CI 1.1–24.7,  $p=0.002$ ) and preserved renal function.

**Conclusion:** Therapeutic hypothermia is useful in the treatment of patients suffering a cardiac arrest. Several clinical factors may aid in predicting patients who are likely to survive after a cardiac arrest.

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## 1. Introduction

Sudden cardiac death is an important public health problem and remains the leading cause of mortality in the developed world.<sup>1–4</sup> Development and early deployment of emergency medical response systems and the wider public availability of defibrillators has led to improvements in resuscitation of patients suffering a cardiac arrest.<sup>5,6</sup> However, neurologic outcome in resuscitated patients remains abysmal despite aggressive and invasive measures. Therapeutic hypothermia has emerged as the single most neuroprotective intervention for patients suffering a cardiac arrest.<sup>7,8</sup> The benefit of mild hypothermia may be attributed to a decrease in: cerebral oxygen demand, production of excitatory neurotransmitters (i.e. glutamate excitotoxicity), neuronal apoptosis with blunting of cell-death signaling pathways and oxidative stress with resulting decrease in free radical formation.<sup>9–11</sup> We

report our outcomes of consecutive patients receiving therapeutic hypothermia for cardiac arrest and describe clinical predictors of survival.

## 2. Methods

The study protocol was approved by the University of Rochester Medical Center Research Subjects Review Board. Medical records of all patients for whom therapeutic hypothermia was instituted between January 2005 and December 2008 were reviewed. Data abstraction included detailed review of documentation provided by first responders and also of the hospital record. Data collected included: age, sex, cardiac rhythm on initial presentation, time from arrest to initiation of CPR, time from arrest to ROSC, time from arrest to first defibrillation and time from arrest to achieve target temperature. Other data collected included Glasgow Coma scale (GCS) on arrival and discharge, vital signs on admission, presence of comorbidities, medications, history of tobacco use, left ventricular ejection fraction (LVEF), dose of epinephrine, type of anti-arrhythmic and dose administered, laboratory data on admission, electrocardiographic findings on admission and discharge, administration of Coenzyme Q10 and whether or not patients required revascularization. Information was also collected for GCS

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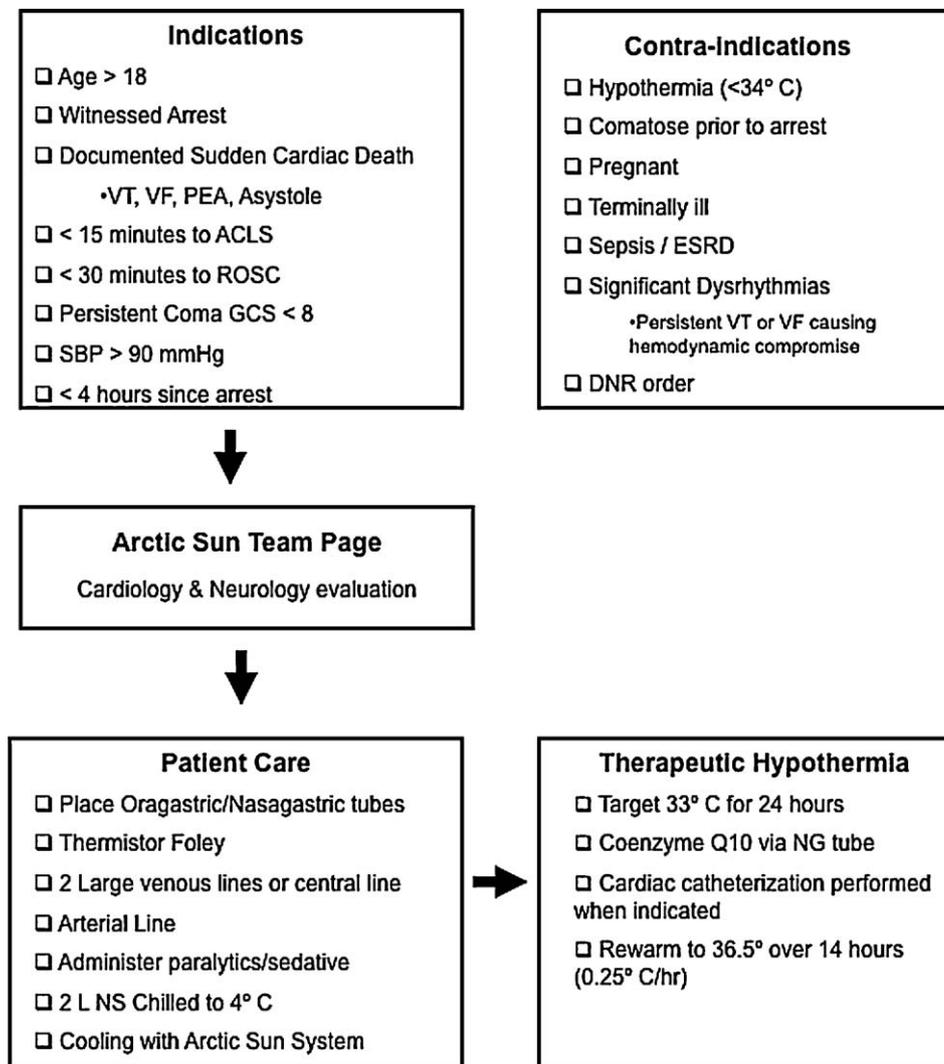


Fig. 1. Outline of Arctic Sun protocol.

1 day after sedation was weaned, GCS at discharge, survival to discharge after 30 days, survival at 1 year, and discharge disposition. A glomerular filtration rate less  $\leq 60$  ml/min/1.73<sup>2</sup> was used as a cut-off to represent at least a moderate degree of kidney dysfunction. Social Security Death Index was queried to determine survival at 1 year.

At our institution therapeutic hypothermia is achieved using the Arctic Sun system (Medivance Inc., Louisville, CO). Once a patient is identified as a candidate for therapeutic hypothermia an "Arctic Sun" alert is made overhead and also by a pager system, alerting staff from the coronary care unit as well as the neurology intensive care unit. Patients without hemodynamic and/or electrical instability and without evidence of severe or permanent neurologic deficits are chosen for induction of hypothermia (Fig. 1). Patients are incubated (if not already done so by emergency medical services), sedated with fentanyl and midazolam drips and paralyzed with atracurium to prevent shivering. Hypothermia is established by way of Arctic Gel Pads (Medivance Inc., Louisville, CO) which are applied to the patients' torso and legs. A thermistor foley catheter is placed to monitor core body temperature. During the hypothermia induction period, 2 L of chilled (4 °C) normal saline is infused to quickly reach targeted hypothermia of 33 °C, which is then maintained for a period of 24 h. Coenzyme Q10 150 mg thrice daily is administered through a nasogastric tube. Upon completion of 24 h of hypothermia the rewarming phase begins, and patients are

rewarmed over 14 h at a rate of 0.25 °C/h. Once rewarmed, serial assessment of neurologic function is made as sedation and paralytics are weaned and the patients Glasgow Coma scale is determined.

In this study cohort patients presenting with acute coronary syndromes particularly those with ST elevations were taken emergently to the cardiac catheterization laboratory as therapeutic hypothermia was being induced. When feasible coronary revascularization was established with percutaneous coronary intervention (PCI). In patients with severe coronary artery disease in whom PCI could not be performed an intra-aortic balloon pump was placed and a decision to proceed with coronary artery bypass grafting was made based on neurologic recovery once therapeutic hypothermia was completed.

### 3. Statistical methodology

Patients were divided into those who survived and those who died at release/discharge from hospital. For continuous measures, the results between survivors and non-survivors were compared using the nonparametric Wilcoxon rank sum test and are presented as mean  $\pm$  standard deviation (SD). The results for dichotomized variables were compared using the chi-square test and are presented as count (%). Multivariate logistic regression analysis was used to analyze the survival endpoint and the all-subsets

**Table 1**  
Baseline demographics.

Variable	Total (n = 80)	Survived (n = 45)	Died (n = 35)	p-Value
Age (years)	61 ± 14	57 ± 14	66 ± 12	<b>0.01</b>
Male gender	59 (74%)	35 (78%)	24 (69%)	0.35
Left ventricular ejection fraction (%)	41 ± 17	42 ± 16	38 ± 18	0.3
Ventricular fibrillation at presentation	56 (71%)	39 (87%)	18 (51%)	<b>0.001</b>
Epinephrine dose	1.8 ± 1.8	1.3 ± 1.8	2.6 ± 1.6	<b>0.001</b>
Admission QTc (s)	0.5 ± 0.1	0.5 ± 0.1	0.5 ± 0.1	0.2
Stroke	12 (15%)	6 (13%)	6 (17%)	0.6
Diabetes	18 (23%)	7 (16%)	11 (31%)	0.09
Current smoker	37 (47%)	23 (50%)	14 (41%)	0.4
History of coronary artery disease	34 (43%)	15 (33%)	19 (54%)	0.06
Stroke	12 (15%)	5 (13%)	7 (17%)	0.64
Acute coronary syndrome on presentation	61 (76%)	33 (73%)	28 (80%)	0.78
ST elevation myocardial infarction	24 (30%)	13 (29%)	11 (31%)	
Non-ST elevation myocardial infarction	37 (46%)	20 (44%)	17 (49%)	
Current smoker	38 (47%)	23 (50%)	15 (42%)	0.5
Aspirin use	30 (38%)	20 (44%)	10 (29%)	0.15
Beta-blocker use	36 (45%)	15 (33%)	21 (60%)	<b>0.02</b>
ACE inhibitor use	28 (35%)	11 (24%)	17 (49%)	<b>0.03</b>
Statin use	32 (40%)	16 (46%)	16 (36%)	0.4
Admission glucose (mg/dl)	257 ± 105	233 ± 97	287 ± 108	<b>0.01</b>
Admission creatinine (mg/dl)	1.3 ± 0.9	1.1 ± 0.9	1.5 ± 0.9	<b>0.002</b>
Estimated glomerular filtration rate (ml/min/1.73 <sup>2</sup> )	75 ± 31	85 ± 30	61 ± 28	<b>&lt;0.001</b>

approach was used to develop a clinical model, which allowed adjustment for all significant baseline covariates. A receiver-operating-characteristic (ROC) curve based on the multivariate logistic regression model was derived with the corresponding Area Under the Curve (AUC) to show the utility of the model. For illustrative purposes, survival to hospital discharge graphs were developed using the Kaplan–Meier methodology. For all tests, a *p*-value of <0.05 was considered statistically significant. Statistical Analysis was performed with SAS, version 9.2 (SAS Institute Inc., Cary, NC).

#### 4. Results

A total of 80 patients were included in the study of whom 45 (56%) survived to hospital discharge and were alive at 30 days. Forty-one (91%) of the survivors were alive 1 year after discharge. Baseline demographics for patients receiving therapeutic hypothermia and comparison between those who survived and died are shown in Table 1. Several significant differences were noted between the groups. Survivors were younger, were more likely to present with VF, needed less epinephrine during resuscitation, were more likely to have preserved renal function, more likely to be taking aspirin, and less likely to be taking beta-blockers and ACE inhibitors. The time from ROSC to goal temperature of 33 °C was similar between those who survived and those who died (410 ± 178 min versus 420 ± 199 min, respectively, *p*-value 0.992).

Table 2 shows the time sequence of events starting from time to arrival of emergency medical services to the time of ROSC. Survivors had shorter times for all time-based interventions including shorter times to initiation of CPR, defibrillation and ROSC. Nineteen survivors (42%) suffered a cardiac arrest at home, 19 (42%) in a public place, and 7 were while in the hospital. Among those who died 24 (69%) suffered a cardiac arrest at home, 5 (14%) in a public place, and the remainder suffered a cardiac arrest while in the hospital.

**Table 2**

Time sequence of events during cardiac resuscitation. Anchor time taken as time of cardiac arrest when documented. Otherwise time of cardiac arrest was extrapolated from the time when emergency medical services was called.

Variable	Total (n = 80)	Survived (n = 45)	Died (n = 35)	p-Value
Time to arrival of emergency medical services (min)	7 ± 5	6 ± 5	8 ± 5	<b>0.028</b>
Time to cardiopulmonary resuscitation (min)	3 ± 4	3 ± 3	5 ± 5	<b>0.031</b>
Time to defibrillation (min)	9 ± 6	8 ± 4	13 ± 2	<b>0.027</b>
Time to return of spontaneous circulation (min)	22 ± 13	17 ± 10	28 ± 15	<b>0.001</b>

Urgent percutaneous coronary intervention was performed in 17 (38%) of those who survived and 5 (14%) of those who died (*p*-value 0.02). The Glasgow Coma scale on arrival was similar between those who survived and those who died (3.3 ± 0.9 versus 3.1 ± 0.5, respectively, *p*-value 0.28). Upon rewarming and once sedation was weaned, the Glasgow Coma scale was 11 ± 5 for the total group, and was significantly higher in the subset of patients who survived to hospital discharge when compared to those who died (13 ± 2 versus 4 ± 2, *p*-value <0.001). Twenty-nine survivors (64%) were eventually discharged to home and the remainder was transferred to a rehabilitation facility.

Coenzyme Q10 administration was added later into our Arctic Sun protocol and was given to 62 of 80 patients (78%) in this study cohort. In the 62 patients receiving Coenzyme Q10, 37 (60%) survived to hospital discharge and 25 (40%) died (*p*-value 0.25). Coenzyme Q10 administration was not a predictor of survival to hospital discharge.

Significant univariate predictors to hospital discharge using Kaplan–Meier analysis are shown in Fig. 2. Using multivariate logistic regression analysis a clinical model of predictors to survival to hospital discharge was developed. All significant baseline variables were included in the model. The following variables were significantly associated with survival to hospital discharge: Ventricular fibrillation as presenting rhythm, pre-cardiac arrest aspirin use, time of cardiac arrest to ROSC less than 20 min, absence of coronary artery disease and preserved renal function (Table 3). An area under the ROC curve for our clinical model to predict survival to hospital discharge is shown in Fig. 3.

#### 5. Discussion

While significant improvements have been achieved over the last three decades for the acute care of patients suffering a car-

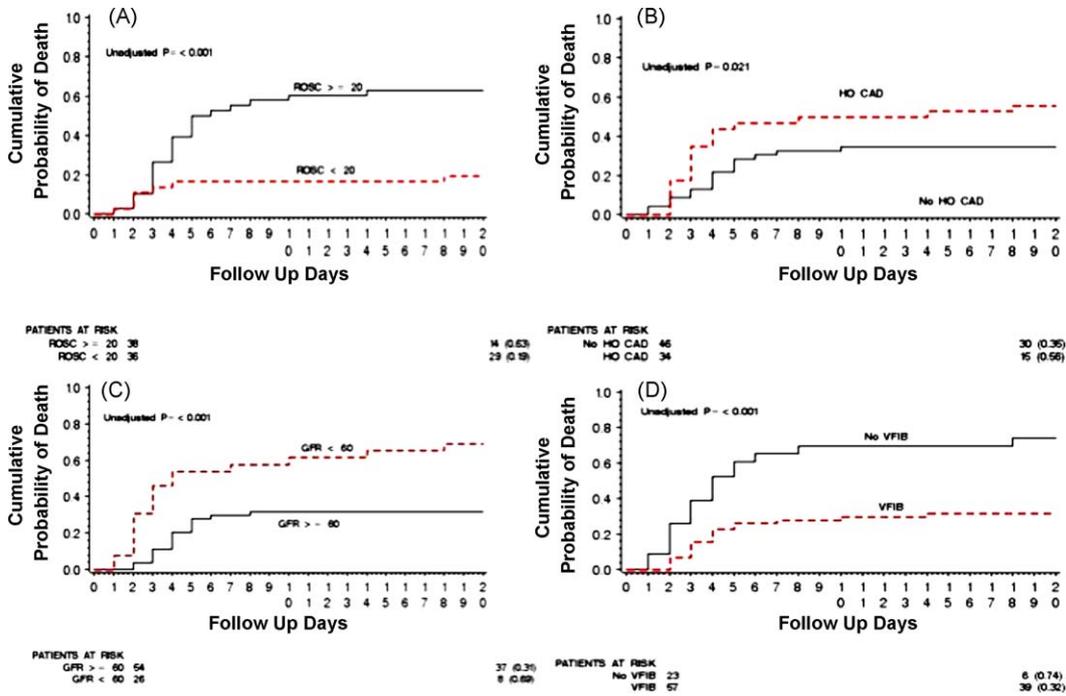


Fig. 2. Kaplan–Meier estimates of survival to hospital discharge.

diac arrest, survival rates remain disappointing largely due to poor neurological outcome after resuscitation. Cardio-cerebral resuscitation of patients suffering a cardiac arrest emphasizes neurological protection and encompasses aggressive post-resuscitation care including therapeutic hypothermia.<sup>12–14</sup> In 2002, two prospective randomized trials showed benefit of mild hypothermia compared to normothermia in survivors of cardiac arrest, with VF or non-perfusing VT as the initial rhythm, who had impaired neurologic function after ROSC.<sup>7,8</sup>

In our case series of 80 patients receiving therapeutic hypothermia whose presenting rhythms included VF, pulseless VT and PEA, 56% survived to hospital discharge which is similar to prior

reports.<sup>15,16</sup> In the study by the Hypothermia After Cardiac Arrest study group (HACA) 55% of the patients who presented in VF randomized to hypothermia had a favorable neurological outcome as compared to 39% of the patients randomized to the normothermia group.<sup>7</sup> Bernard et al. reported that 49% of patients who presented in VF randomized to hypothermia survived and had a favorable neurological outcome as compared to 26% of patients randomized to normothermia.<sup>8</sup>

With multivariate regression analysis several factors were identified as predictors of survival to hospital discharge some of which have been described in prior studies. Patients who presented with VF ( $n = 58$ , 73%) had a higher chance of survival (67%) as compared

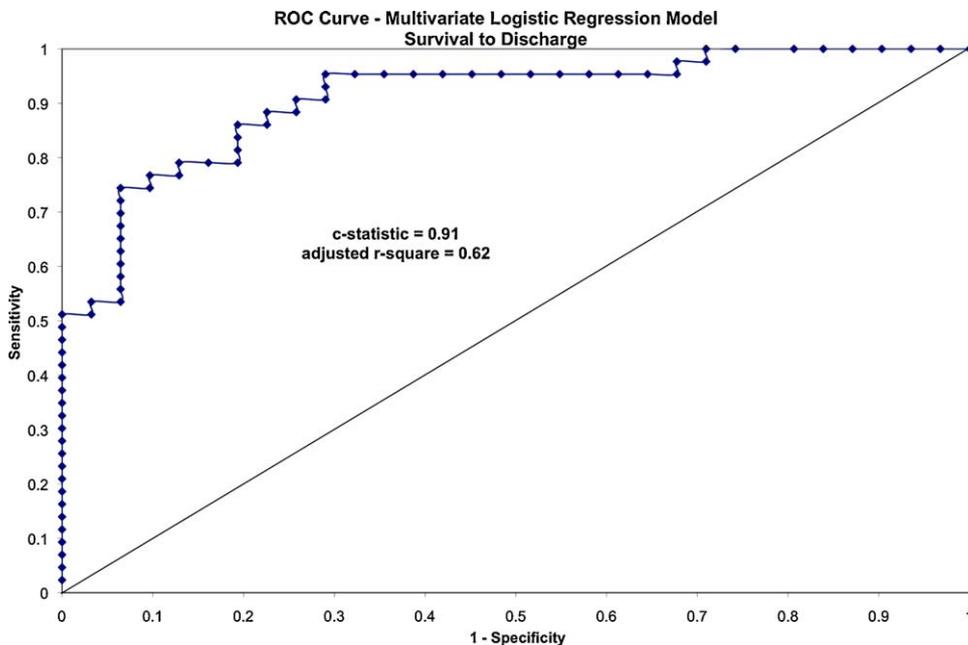


Fig. 3. Area under the ROC Curve (C Statistic) for clinical model predicting survival to hospital discharge.

**Table 3**

Multivariate logistic regression analysis of clinical predictors of survival to hospital discharge. Factors included into the model included age, gender, left ventricular ejection fraction, presenting rhythm, aspirin use, beta-blocker use, ace-inhibitor use, statin use, coronary artery disease, smoking status, diabetes, time to ROSC and glomerular filtration rate.

	Odds ratio	95% CI	p-Value
Ventricular fibrillation on presentation	14.9	2.7–83.2	<b>0.002</b>
Pre-cardiac arrest aspirin use	9.7	1.6–61.1	<b>0.02</b>
Arrest to return of spontaneous circulation <20 min	9.4	2.2–41.1	<b>0.003</b>
Absence of coronary artery disease	5.3	1.1–24.7	<b>0.03</b>
Increase in estimated glomerular filtration rate of 10 points	1.3	1.0–1.6	<b>0.02</b>

to patients who presented with non-VF arrest rhythms (i.e. asystole  $n = 13$ , 16%, or PEA  $n = 9$ , 11%). Survival to hospital discharge for VF, asystole, and PEA were found to be 67, 39, and 11% respectively. Our results are consistent with prior studies that also report a grim prognosis in patients presenting with non-VF rhythms at the time of cardiac arrest.<sup>16,17</sup> Although VF is engrained in clinicians' minds as a terminal rhythm, the ability to defibrillate and potentially reverse the underlying trigger is present whereas patients presenting with asystole or PEA, the underlying triggers are often difficult to identify, and when identified it is often too late to achieve favorable outcomes.

Preserved renal function was also an independent predictor of survival to hospital discharge, which to our knowledge has not been reported in prior studies of this patient population. We noted a 29% increase in survival for every 10-point increase in GFR. Chronic kidney disease is associated with increased risk of cardiovascular complications. A possible explanation for this finding is that diminished GFR often is a culmination of multiple chronic comorbidities such as hypertension, diabetes and vascular disease all of which are known risk factors for cardiovascular disease and associated with increased morbidity and mortality.

A shorter time from cardiac arrest to ROSC was another strong predictor to hospital discharge, which has been reported by others.<sup>15,16,18</sup> A shorter time from cardiac arrest to ROSC and brain perfusion decreases the often-irreversible ischemia induced processes responsible for cell death and organ failure including anoxic neuronal damage. Mechanisms of post-cardiac arrest brain injury which include release of excitatory neurotransmitters, free radical formation, activation of protease cascades and cell-death signaling pathways are induced by prolonged cerebral ischemia.<sup>9–11</sup> A shorter time from arrest to ROSC therefore decreases the likelihood of cerebral hypo perfusion, anoxia and the resulting insult from a prolonged post-resuscitation course.

Absence of coronary artery disease was an additional predictor of survival to hospital discharge. Patients with coronary disease are at a disadvantage at the time of a cardiac arrest for several reasons. First of all these patients are more likely to have myocardial scar creating an arrhythmogenic substrate for lethal arrhythmias. Secondly, patients with existing coronary artery disease likely have atheromatous changes in other vascular beds such as in the neurovascular system and therefore hypotension during cardiac arrest likely has a more profound and adverse affect on cerebral perfusion. Interestingly, the use of aspirin prior to cardiac arrest was also an independent predictor to hospital discharge likely due to its beneficial anti-platelet and antithrombotic properties particularly in patients with coronary artery disease and in those presenting with acute coronary syndromes.

Finally, Damian et al. suggested the combination of Coenzyme Q10 and mild hypothermia appeared to improve survival and neurological outcomes in survivors of cardiac arrest.<sup>19</sup> In our study, 62 (78%) patients received Coenzyme Q10 during therapeutic hypothermia and we found no added survival benefit with Coenzyme Q10 and alternatively no adverse events were noted with its use either. Further research into the use of Coenzyme Q10 during therapeutic hypothermia is needed.

Comparing our findings to historical controls from our medical center shows significant improvements in short and long term survival with therapeutic hypothermia. Fairbanks et al reported 539 patients who suffered an out of hospital cardiac arrest in our region between 1998 and 2001, during a period when therapeutic hypothermia was not available.<sup>20</sup> In their report, 107 patients had ROSC of whom 37 (35%) were alive at 30 days and 27 (25%) were alive at 1 year compared to 56 and 51% alive in our series at 30 days and 1 year, respectively.

Several limitations to our study are worth mentioning. Due to its retrospective design our study is limited by factors inherent in retrospective data gathering, analysis and interpretation. However, randomization of cardiac arrest survivors to a control group, i.e. normothermia group at this point in time would be unethical given the known benefits of therapeutic hypothermia. In addition, we did not collect long term follow-up neurologic function and recovery data on our patients and therefore we are unable to comment on the long-term effects of therapeutic hypothermia. Additionally, our cohort consisted of patients from a single medical center and so the results may be influenced by referral bias.

## 6. Conclusion

Therapeutic hypothermia is a useful option in the treatment of patients suffering a cardiac arrest. Several clinical factors may be helpful in predicting patients who are likely to survive to hospital discharge such as ROSC < 20 min, VF as presenting rhythm, absence of CAD, pre-arrest aspirin use, and preserved renal function. Validation of these clinical factors in a prospective manner is required. Wider availability of therapeutic hypothermia and the triage of patients to centers where therapeutic hypothermia is available will likely improve survival in cardiac arrest sufferers.

## Conflict of interest

All the authors declare no conflict of interest.

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