Original Article

Mortality and Neurological Outcomes in Out-of-Hospital Cardiac Arrest Patients With and Without Targeted Temperature Management in a Multiethnic Asian Population

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Abstract

Introduction: The use of targeted temperature management (TTM) is increasing although adoption is still variable. We describe our 6-year experience and compare the mortality and neurological outcomes of out-of-hospital cardiac arrest (OHCA) patients with and without the use of TTM in a multiethnic Asian population. **Materials and Methods:** We performed a retrospective observational study at a tertiary academic medical centre. OHCA survivors admitted to our hospital between April 2010–December 2016 were included. Outcomes of interest were 30-day mortality postresuscitation, Cerebral Performance Category (CPC) and Overall Performance Category (OPC) scores. **Results:** A total of 121 of 261 patients (46.3%) underwent TTM. TTM patients were younger (TTM 60.0 years old vs no TTM 63.7 years old, $P = 0.047$). There was no difference in the initial arrest rhythm of shockable origin between the 2 groups ($P = 0.289$). There was suggestion of lower 30-day mortality (TTM 24.3% vs no TTM 31.4%, $P = 0.214$), higher and good CPC/OPC scores (TTM 19.0% vs no TTM 15.7%, $P = 0.514$) with TTM although this did not reach statistical significance. On multivariable logistic regression analysis, TTM was not associated with 30-day mortality ($P = 0.07$). However, older age, initial non-shockable rhythm and increased duration from arrest to return of spontaneous circulation were associated with increased mortality. Malay ethnicity was associated with a poorer CPC/OPC score. **Conclusion:** Adoption and outcomes of TTM postresuscitation is variable and there is still a need to optimise management of the identified predictors of survival and good neurological outcomes while TTM is being used.

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Key words: Heart attack, Neurological function, Neuroprotection, Therapeutic hypothermia

Introduction

Targeted temperature management (TTM) is an established but evolving modality for treating out-of-hospital cardiac arrest (OHCA) patients. There have been significant advances in the management of OHCA patients and prevention of sudden cardiac death, but much is still unknown.^{1,2} Two landmark clinical studies performed in Europe and Australia demonstrated that the initiation of TTM improved mortality and neurological outcomes.^{3,4}

Since then, the International Liaison Committee on Resuscitation and the American Heart Association have recommended the use of TTM after cardiac arrest as soon as possible after return of spontaneous circulation (ROSC).⁵ They further released an advisory statement regarding TTM in 2015 recommending it for adults with OHCA who have an initial shockable or non-shockable rhythm but remain unresponsive after ROSC and TTM for at least 24 hours.⁶

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Almost 2 decades on and despite the recommendations, there are still areas of controversy. In many centres, adoption is still based on individual clinician and institutional discretion. There are unresolved issues of optimal targeted temperature, haemodynamic and neurological monitoring methods, and the treatment of fever among various other issues.⁷ Guidelines were developed based on studies of Caucasian populations, and the landmark studies recruited only patients with OHCA and ventricular fibrillation. In Asia, experience with the use of TTM is still developing and is variable.^{8,9} Most of the larger published Asian studies involved countries with ethnically homogenous populations (The Korea Hypothermia Network Registry from Korea¹⁰ and the J-PULSE-HYPO study registry from Japan).¹¹ In other parts of Asia, there are single-centre studies from Thailand^{12,13} and Taiwan,¹⁴ which again consist of ethnically homogenous populations. A pilot study from our own group in Singapore¹⁵ in 2014 showed that a therapeutic hypothermia protocol could be safely implemented, but consisted of a small sample size of TTM patients ($n = 25$). Furthermore, ethnic differences have also been shown to affect neurological outcomes in studies performed in the United States of America (USA). In particular, the non-White ethnic groups were demonstrated to have poorer neurological outcomes after cardiac arrest.^{16,17} A local study of a paediatric population with in-hospital cardiac arrests did not show any ethnic differences, although the sample size was small.¹⁸ Whether ethnicity is a factor affecting neurological outcomes in OHCA in our local context is not known.

As such, the primary aim of this study was to describe the use of TTM on OHCA patients admitted to a tertiary academic medical centre serving a multiethnic adult Asian population over a 6-year period. The outcomes of interest were 30-day mortality, good cerebral performance category (CPC) and overall performance category (OPC) scores. We aimed to identify predictors of improved 30-day mortality and CPC/OPC scores.

Materials and Methods

This was a retrospective observational study using Singapore data from the Pan-Asian Resuscitation Outcomes Study (PAROS)¹⁹ and our institution's electronic medical records. PAROS is a collaborative research network that collects data prospectively and aims to improve outcomes of prehospital and emergency care in the Asia-Pacific region.

Data was collected on all OHCA patients who presented to the Singapore General Hospital Emergency Department and survived to admission between April 2010–December 2016. The inclusion criteria for TTM were as follows (although discretion was given to the attending clinician as to whether to eventually initiate TTM): 1) OHCA

patients with all-presenting rhythms and sustained ROSC after cardiac arrest for >30 minutes, 2) patients who were comatose (with a Glasgow Coma Score of ≤ 8) or who were unresponsive postresuscitation, and 3) patients who were haemodynamically stable with systolic blood pressure (BP) >90 mmHg (with or without inotropic support). The exclusion criteria included OHCA patients deemed unsuitable for further active intervention, those who regained consciousness, patients with persistent hypotension despite fluid and/or vasopressor support, those with a positive pregnancy test in females <50 years old and trauma patients. Patient characteristics collected include demographics (age, gender, race and comorbidities), arrest details (location, time, witness, bystander cardiopulmonary resuscitation [CPR]), first presenting rhythm, time of ROSC, aetiology (cardiac vs non-cardiac) and post-ROSC interventions (percutaneous coronary intervention [PCI], coronary artery bypass graft, implantable cardioverter-defibrillator use). Prehospital data was obtained from the PAROS registry. The time of arrest was estimated and based on the time the patient was found unresponsive/unconscious with no pulse and no/abnormal breathing by relatives or a bystander. The time of ROSC was taken as the first ROSC confirmed by a palpable pulse and electrocardiogram in the emergency department. The main primary outcomes measured at 30 days postresuscitation were mortality, discharge status, CPC and OPC scores.²⁰ A good CPC score was defined as having a score of 1 or 2 according to the Glasgow-Pittsburg Outcome Categories. Neurological status was assessed by attending physician either upon discharge or at the 30 days postarrest. Mortality was assessed within 30 days of cardiac arrest. This would be documented in the inpatient discharge summary notes and extracted accordingly in the case record form by a clinical research coordinator.

Patients received standard intensive care as per the treating physician. Sedation was started with intravenous midazolam (0.02–0.08 mg/kg over 1–2 minutes, initially). Doses were uptitrated to achieve sedation as BP tolerated. Paralysis was induced with atracurium (0.4–0.5 mg/kg intravenous bolus, initially) and titrated as required. The target temperature was 34°C. The emergency department would initiate cooling with cold saline infusion and surface icepacks until the cooling device was commenced in the intensive care unit. Ice packs were subsequently replaced by a wearable cooling suit in July 2015 as standard-of-care treatment for eligible patients.²¹ Core temperature was monitored via rectal or oesophageal temperature probe. The target temperature of 34°C was maintained for 24 hours followed by passive rewarming to 36.5°C by setting the cooling unit accordingly. The aim was to increase temperature by 1°C every 4 hours and achieve rewarming over at least 12 hours. The patient would be warmed no

faster than 1°C in 4 hours over a period of 8 hours. A detailed protocol can be found in the Appendix.

Data management was carried out using the REDCap data entry platform.²² All data analyses were performed using SPSS version 23.0 (IBM Corp., Armonk, New York, USA). For categorical data, frequency tables, together with 95% confidence interval (CI) were reported. Continuous variables were reported using mean, and where appropriate the 95% CI and median with interquartile range were reported. Those with P values <0.2 were included for consideration to develop a multivariable logistic regression model. The significance level was set at 0.05.

The study protocol was approved by SingHealth Centralised Institutional Review Board with waiver of informed consent.

Results

There were 1171 OHCA patients who presented to our emergency department from April 2010–December 2016, and 262 survived to admission (Fig. 1). Of the 262, 1 was excluded due to incomplete documentation of relevant TTM variables. Out of 261 that were included in this study, 121 (46.4%) underwent TTM and 140 (53.6%) either did not undergo TTM or were ineligible for TTM.

Table 1 shows the baseline characteristics of OHCA patients, grouped by whether they underwent TTM. The mean age of those who underwent TTM was about 3 years younger than those who had not (60.0 years old vs 63.7 years old, $P = 0.047$). Significant differences between these 2 groups were age, race, incidence of stroke, year

of arrest, presence of witness to the arrest and the person who performed initial CPR. Among patients who did not undergo TTM, survival to discharge was 24.3%—compared to 31.4% in those who underwent TTM—although not statistically significant ($P = 0.200$). There was also no significant difference in good neurological outcome (CPC 1–2) between patients who underwent TTM and those without (19.0% vs 15.7%, $P = 0.514$). The 6-year trend of TTM use in our population is shown in Figure 2.

In the multivariable logistic regression analysis (Table 2), TTM was not associated with 30-day mortality ($P = 0.07$). However, 3 variables were found to be significantly associated. These were increased age (odds ratio [OR] 1.04, 95% CI 1.02–1.07), longer time between arrest and first ROSC (OR 1.06, 95% CI 1.04–1.09) and an initial non-shockable arrest rhythm (OR 6.62, 95% CI 3.16–14.54). Positive predictor of good neurological outcome was presence of prehospital defibrillation (OR 3.82, 95% CI 1.28–12.53). Negative predictors for good neurological outcome were age, duration between time of arrest and first ROSC, Malay ethnicity (with Chinese as the reference group, adjusted OR 0.10, 95% CI 0.01–0.65, $P = 0.0319$) and first CPR initiated by emergency medical services (EMS)/private ambulance (Table 3).

Discussion

The key findings from our paper are as follows: 1) patients who underwent TTM were younger and fewer had a past history of stroke, 2) while there was a suggestion of improved survival to discharge and better CPC/OPC scores in the TTM group, this did not reach statistical

Fig. 1. Flow chart of out-of-hospital cardiac arrest patients included in the study. ED: Emergency department; OHCA: Out-of-hospital cardiac arrest; TTM: Targeted temperature management

Table 1. Baseline Characteristics of Out-of-Hospital Cardiac Arrest Patients With and Without Targeted Temperature Management

Characteristic, n (%)	TTM (n = 121)	Non-TTM (n = 140)	P Value
Mean age in years (IQR)	60.0 (48 – 72)	63.7 (55 – 76)	0.047
Race			0.009
Chinese	92 (76.0)	88 (62.9)	
Malay	12 (9.9)	12 (8.6)	
Indian	11 (9.1)	16 (11.4)	
Eurasian	2 (1.7)	1 (0.7)	
Others	4 (3.3)	23 (16.4)	
Gender, male	92 (76.0)	96 (68.6)	0.214
Premorbidities			
No medical history	24 (19.8)	19 (13.6)	0.185
Unknown medical history	4 (3.3)	7 (5.0)	0.552
Heart disease	45 (37.2)	62 (44.3)	0.258
Diabetes	28 (23.1)	42 (30.0)	0.262
Cancer	8 (6.6)	11 (7.9)	0.813
Hypertension	61 (50.4)	66 (47.1)	0.621
Renal disease	13 (10.7)	20 (14.3)	0.457
Respiratory disease	24 (19.8)	21 (15.0)	0.327
Hyperlipidaemia	42 (34.7)	50 (35.7)	0.897
Stroke	7 (5.8)	19 (13.6)	0.040
Mean estimated time in minutes between cardiac arrest and first sustained ROSC (IQR)	48 (32 – 64)	46 (31 – 61)	0.656
Year of incidence			0.002
2010	5 (4.1)	20 (14.3)	
2011	13 (10.7)	24 (17.1)	
2012	12 (9.9)	23 (16.4)	
2013	15 (12.4)	16 (11.4)	
2014	32 (26.4)	21 (15.0)	
2015	15 (12.4)	19 (13.6)	
2016	19 (24.0)	17 (12.1)	
Arrest witnessed by			0.001
Not witnessed	17 (14.0)	43 (30.7)	
Emergency medical services/private ambulance	12 (9.9)	20 (14.3)	
Bystander	92 (76.0)	77 (55.0)	
Initial cardiopulmonary resuscitation performed by			0.029
Not performed	4 (3.3)	8 (5.7)	
Emergency medical services/private ambulance	54 (44.6)	79 (56.4)	
Bystander	59 (48.8)	53 (37.9)	
Hospital staff	4 (3.3)	0 (0)	
Cardiac cause of arrest	85 (70.2)	85 (60.7)	0.063
Initial rhythm			0.289
Shockable	34 (28.1)	48 (34.3)	
Non-shockable	87 (71.9)	92 (65.7)	

IQR: Interquartile range; ROSC: Return of spontaneous circulation; TTM: Targeted temperature management

Table 1. Baseline Characteristics of Out-of-Hospital Cardiac Arrest Patients With and Without Targeted Temperature Management (Cont'd)

Characteristic, n (%)	TTM (n = 121)	Non-TTM (n = 140)	P Value
Prehospital defibrillation	52 (43.0)	54 (38.6)	0.528
Emergency percutaneous coronary intervention/stent performed	34 (28.1)	29 (20.7)	0.192
Coronary artery bypass grafting performed	1 (0.8%)	0 (0)	0.464
Outcomes			
Survived to discharge	38 (31.4)	34 (24.3)	0.214
Mortality	83 (68.6)	106 (75.7)	0.214
Good Cerebral Performance Category score (1 – 2)	23 (19.0)	22 (15.7)	0.514

IQR: Interquartile range; ROSC: Return of spontaneous circulation; TTM: Targeted temperature management

Fig. 2. Trend of targeted temperature management (TTM) over the 6 years of the study.

Table 2. Multivariable Analysis of Predictors of Mortality

Variable	Number of Survivals	Number of Deaths	Odds Ratio (95% CI)	P Value
Mean age	61	178	1.04 (1.02 – 1.07)	0.0005
Time between arrest and ROSC (downtime)	61	178	1.06 (1.04 – 1.09)	<0.0001
First arrest rhythm				
Shockable	37	39	Reference	
Non-shockable	24	139	6.62 (3.16 – 14.54)	<0.0001

CI: Confidence interval; ROSC: Return of spontaneous circulation

significance, 3) an older age, a longer time from cardiac arrest to ROSC and presence of a non-shockable initial rhythm were predictors of mortality after adjustment, 4) a positive predictor of good neurological outcome was the use of prehospital defibrillation, and 5) Malay ethnicity as compared to Chinese ethnicity as the reference was associated with a poorer neurological outcome.

We compared the characteristics between our study population and previously published TTM populations

in developed Asia (South Korea and Japan), a centre in developing Asia and a registry based in the USA.^{10,11,13,23} The age across the populations was similar (about 60 years old) and there was a male predominance. Our TTM population had a higher proportion of patients who had witnessed arrest, but they were less likely to have an initial documented shockable rhythm. The difference in practices observed may be due to geographical size, provision of EMS services and individual hospital practices and would be of

Table 3. Multivariable Analysis of Neurological Outcome (CPC)

Variable	Poor CPC Score (3 – 4)	Good CPC Score (1 – 2)	Odds Ratio (95% CI)	P Value
Mean age	216	45	0.95 (0.92 – 0.98)	0.0049
Time between arrest and ROSC (downtime)	203	36	0.90 (0.86 – 0.93)	<0.0001
Race				
Chinese	150	30	Reference	
Malay	21	3	0.10 (0.01 – 0.65)	0.0319
Indian	24	3	-	0.9924
Others	21	9	1.89 (0.50 – 7.24)	0.3460
Who initiated CPR				
No CPR initiated	6	6	Reference	
Emergency medical services/private ambulance	120	13	0.07 (0.01 – 0.66)	0.0237
Bystander	87	25	0.19 (0.01 – 2.00)	0.1762
Hospital staff	3	1	0.13 (0.00 – 2.66)	0.2025
Any prehospital defibrillation				
No	140	15	Reference	
Yes	76	30	3.821 (1.28 – 12.53)	0.0196

CI: Confidence interval; CPC: Cerebral performance category; CPR: Cardiopulmonary resuscitation; ROSC: Return of spontaneous circulation

interest in further studies. This is because while guidelines are developed mainly from Caucasian populations,²⁴ these need to be suitably applied in an Asian⁷ or local context.

We identified predictors of mortality and good CPC/OPC scores in our population. Modifiable factors identified include time between arrest and ROSC, diabetes, hypertension, initial CPR performed by EMS/private ambulance, prehospital defibrillation and PCI/placement of stent. Better education of the public can reduce the incidence and severity of chronic diseases such as diabetes and hypertension. As prehospital defibrillation and CPR performed by EMS/private ambulance are of significance in reducing mortality, possible measures to increase these may be to educate lay people on where to find and use automated external defibrillators and to regularly ensure our paramedics are up-to-date with their CPR skills.²⁵ These findings as a whole strongly support a focus on basic life support measures through community and prehospital intervention to increase prompt and effective CPR and automated external defibrillator use, which have far greater effect on outcomes.^{25–27}

Although there was some suggestion that TTM improved mortality and CPC in our study population, there was insufficient power to demonstrate statistical significance. We postulate that TTM may not have been complete in many patients and complications may not have been accounted for. The next step in this study will be to analyse specific TTM factors such as duration of TTM, temperature used, presence of overcooling and complications from TTM which can theoretically cause TTM to be less effective than it should have been. This is especially so in light of

developments in TTM, such as a randomised-controlled trial (RCT) in 2013 by Nielsen et al showing that there were similar favourable outcomes in patients who underwent regimens of TTM set to 33°C and 36°C.²⁸ Another example is also evidence that time to target temperature plays a role in outcomes.²⁹ Precautions must be taken because TTM can be associated with complications such as sepsis and renal failure.³⁰ Clinicians taking care of such patients need to be well versed in managing patients with medical complexity beyond the cardiac issue itself. This parallels the trend of subspecialty training in cardiac intensive care.³¹ It can be postulated that benefits of TTM are realised in non-trial populations. As the finer technical details of TTM are investigated,³² clinician familiarity in treating TTM patients improves and more refined patient selection is achieved. As such, ongoing registries will continue to play an important role in informing care of OHCA patients.^{19,33} Having knowledge of these factors can thus aid us to utilise TTM to greatly benefit our patients.

Ethnicity has previously been reported to be a factor in affecting outcomes of patients undergoing TTM. A study by Jacobs et al in a single tertiary care hospital in the USA demonstrated that despite a strict TTM protocol, non-white patients were associated with poorer outcomes as compared to white patients, despite adjusting for possible confounders.³⁴ This echoes a previous study performed by Agarwal et al which demonstrated that Hispanic ethnicity was associated with a poorer 1-year neurological outcome.³⁵ Chen et al studied an in-hospital cardiac arrest population and found that black survivors had a lower absolute rate of long-term survival after discharge from hospital, although

they could not rule out effects of postdischarge care.¹⁶ Ethnic differences in our local context have been shown to affect disease outcomes, such as in diabetes control.¹⁷ Our study consisted of a multiethnic Asian population. Based on the above studies, we would possibly have expected a difference in neurological outcomes. In our study (with Chinese as the reference group), Malays were less likely to have a good neurological outcome on multivariable analysis (adjusted OR 0.10, 95% CI 0.01–0.65, $P=0.0319$) although this was not observed in Indians and other ethnicities. This finding deserves further investigation in future studies to understand whether it is an ethnic-specific or systems-specific factor that is resulting in this observed disparity.

A final discussion point would be that the protocols used in our study—in comparison to the 2 TTM trials mentioned—were different. In our study, TTM was initiated in the emergency department via external cooling and then initiation of internal cooling within 30 minutes. In the trial by the Hypothermia after Cardiac Arrest Study Group, temperature management was performed via an external cooling blanket³ and temperature was maintained between 32–34°C for 24 hours before rewarming. In the study by Bernard et al, cooling was initiated prehospital by paramedics via applying cold packs externally and continued in the emergency department.⁴ The total cooling period was 12 hours at 33°C in this study and thereafter they were rewarmed. In our study, our patients did not have prehospital cooling and instead of using external cooling alone, internal cooling was also performed. The target temperature in our study was also 34°C. As there was heterogeneity in the initiation of cooling, the methods used to cool, the target temperature, the duration of cooling and the study population characteristics, it is therefore not surprising that we observed a non-significant neurological benefit although there was a trend towards this. Our paramedics are currently not trained to initiate TTM in the field, although this could be for further discussion with the relevant authorities to improve prehospital care.^{36,37} We believe that further RCTs, with a standardised protocol, would highlight further the external validity of the trials in different populations and health systems.

Strengths and Limitations

To the best of our knowledge, this study is the largest reported population of OHCA patients in a multiethnic Asian population. We were able to collect mortality and neurological outcome data over a 6-year period with a high percentage of data available for analysis (99.6%, 261/262). However, we do acknowledge that this was a single-centre study that may limit generalisation. As this was a retrospective study, and because PAROS did not capture the reasons why patients were not included for TTM, we cannot conclusively describe why certain patients who met

the inclusion criteria were not started on TTM. We did not have information on time of TTM induction, duration of TTM, target temperature achieved, cooling methods for each group or complications experienced. Also, we could only demonstrate association and not causation in this observational study. Multicentre collaborative efforts to study TTM and well designed RCTs can be the focus of future efforts.

Conclusion

Adoption and outcomes of TTM postresuscitation varies and there is still a need to optimise management of the identified predictors of survival and good neurological outcomes while TTM is being used. Further longitudinal studies on TTM use in Asian populations are warranted.

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Conflict of Interest

Marcus EH Ong has a licensing agreement and patent filing (Application no: 13/047,348) with Zoll Medical Corporation for a study titled 'Method of predicting acute cardiopulmonary events and survivability of a patient'. He is also a Scientific Advisor for Global Healthcare SG, a commercial entity that manufactures cooling devices.

REFERENCES

1. Chua MT, Chan GW, Kuan WS. Reversible causes in cardiovascular collapse at the emergency department using ultrasonography (REVIVE-US). *Ann Acad Med Singapore* 2017;46:310–6.
2. Oh YZ, Lee CT, Lim AT, Tong KL. Sports-related sudden cardiac deaths in Singapore – an eleven-year review. *Ann Acad Med Singapore* 2019;48:156–60.
3. Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med* 2002;346:549–56.

4. Bernard SA, Gray TW, Buist MD, Jones BM, Silvester W, Gutteridge G, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med* 2002;346:557–63.
5. Nolan JP, Morley PT, Vanden Hoek TL, Hickey RW, Kloeck WG, Billi J, et al. Therapeutic hypothermia after cardiac arrest: an advisory statement by the advanced life support task force of the International Liaison Committee on Resuscitation. *Circulation* 2003;108:118–21.
6. Donnino MW, Andersen LW, Berg KM, Reynolds JC, Nolan JP, Morley PT, et al. Temperature management after cardiac arrest. *Circulation* 2015;132:2448–56.
7. Aibiki M, Chiang MC, Muengtawepong S, Pothiwala S, Huang CH. Asian Targeted Temperature Management Task Panel Report. *Ther Hypothermia Temp Manag* 2017;7:16–23.
8. Ong ME, Shin SD, De Souza NN, Tanaka H, Nishiuchi T, Song KJ, et al. Outcomes for out-of-hospital cardiac arrests across 7 countries in Asia: the Pan Asian Resuscitation Outcomes Study (PAROS). *Resuscitation* 2015;96:100–8.
9. Tan TXZ, Hao Y, Ho AFW, Shahidah N, Yap S, Ng YY, et al. Inter-hospital variations in resuscitation processes and outcomes of out-of-hospital cardiac arrests in Singapore. *J Emerg Crit Care Med* 2019;3:21.
10. Lee BK, Park KN, Kang GH, Kim KH, Kim G, Kim WY, et al. Outcome and current status of therapeutic hypothermia after out-of-hospital cardiac arrest in Korea using data from the Korea Hypothermia Network registry. *Clin Exp Emerg Med* 2014;1:19–27.
11. Yokoyama H, Nagao K, Hase M, Tahara Y, Hazui H, Arimoto H, et al. Impact of therapeutic hypothermia in the treatment of patients with out-of-hospital cardiac arrest from the J-PULSE-HYPO study registry. *Circ J* 2011;75:1063–70.
12. Vattanavanit V, Bhurayanontachai R. Clinical outcomes of 3-year experience of targeted temperature management in patients with out-of-hospital cardiac arrest at Songklanagarind Hospital in Southern Thailand: an analysis of the MICU-TTM registry. *Open Access Emerg Med* 2016;8:67–72.
13. Srivilaithon W, Muengtawepong S. The outcomes of targeted temperature management after cardiac arrest at emergency department: a real-world experience in a developing country. *Ther Hypothermia Temp Manag* 2017;7:24–9.
14. Hung SW, Chen CC, Shih HC, Huang CF, Chen KC, Chong CF, et al. Are new resuscitation guidelines better? Experience of an Asian metropolitan hospital. *Ann Acad Med Singapore* 2010;39:569–75.
15. Ng M, Wong ASL, Chew HC, Shahidah N, Pek PP, Poh J, et al. Pilot prospective study of therapeutic hypothermia for treatment of post-cardiac arrest patients. *Int J Cardiol* 2014;173:612–3.
16. Chen LM, Nallamotheu BK, Spertus JA, Tang Y, Chan PS. Racial differences in long-term outcomes among older survivors of in-hospital cardiac arrest. *Circulation* 2018;138:1643–50.
17. Hong CY, Chia KS, Hughes K, Ling SL. Ethnic differences among Chinese, Malay and Indian patients with type 2 diabetes mellitus in Singapore. *Singapore Med J* 2004;45:154–60.
18. Mok YH, Loke AP, Loh TF, Lee JH. Characteristics and risk factors for mortality in paediatric in-hospital cardiac events in Singapore: retrospective single centre experience. *Ann Acad Med Singapore* 2016;45:534–41.
19. Ong ME, Shin SD, Tanaka H, Ma MH, Khruengkarnchana P, Hisamuddin N, et al. Pan-Asian Resuscitation Outcomes Study (PAROS): rationale, methodology, and implementation. *Acad Emerg Med* 2011;18:890–7.
20. Safar P. Cerebral resuscitation after cardiac arrest: summaries and suggestions. *Am J Emerg Med* 1983;1:198–214.
21. Yap LG, Shahidah N, Pothiwala S, Tan KBK, Wong ASL, Sewa DW, et al. Novel wearable cooling device for early initiation of targeted temperature management in the emergency department. *J Emerg Crit Care Med* 2020. Available at: <http://jcccm.amegroups.com/article/view/5598>. Accessed on 14 February 2020.
22. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap) – a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009;42:377–81.
23. Mader TJ, Nathanson BH, Soares WE 3rd, Coute RA, McNally BF. Comparative effectiveness of therapeutic hypothermia after out-of-hospital cardiac arrest: insight from a large data registry. *Ther Hypothermia Temp Manag* 2014;4:21–31.
24. Callaway CW, Donnino MW, Fink EL, Geocadin RG, Golan E, Kern KB, et al. Part 8: Post-Cardiac Arrest Care: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* 2015;132:S465–82.
25. Ho AFW, Hao Y, Pek PP, Shahidah N, Yap S, Ng YY, et al. Outcomes and modifiable resuscitative characteristics amongst pan-Asian out-of-hospital cardiac arrest occurring at night. *Medicine (Baltimore)* 2019;98:e14611.
26. Cummins RO, Ornato JP, Thies WH, Pepe PE. Improving survival from sudden cardiac arrest: the “chain of survival” concept. A statement for health professionals from the Advanced Cardiac Life Support Subcommittee and the Emergency Cardiac Care Committee, American Heart Association. *Circulation* 1991;83:1832–47.
27. Tanaka H, Ong MEH, Siddiqui FJ, Ma MHM, Kaneko H, Lee KW, et al. Modifiable factors associated with survival after out-of-hospital cardiac arrest in the Pan-Asian Resuscitation Outcomes Study. *Ann Emerg Med* 2018;71:608–17.e15.
28. Nielsen N, Wetterslev J, Cronberg T, Erlinge D, Gasche Y, Hassager C, et al. Targeted temperature management at 33°C versus 36°C after cardiac arrest. *N Engl J Med* 2013;369:2197–206.
29. Haugk M, Testori C, Sterz F, Uranitsch M, Holzer M, Behringer W, et al. Relationship between time to target temperature and outcome in patients treated with therapeutic hypothermia after cardiac arrest. *Crit Care* 2011;15:R101.
30. Soleimanpour H, Rahmani F, Goltzari SE, Safari S. Main complications of mild induced hypothermia after cardiac arrest: a review article. *J Cardiovasc Thorac Res* 2014;6:1–8.
31. Fuster V. The (r)evolution of the CICU. Better for the patient, better for education. *J Am Coll Cardiol* 2018;72:2269–71.
32. Look X, Li H, Ng M, Lim ETS, Pothiwala S, Tan KBK, et al. Randomized controlled trial of internal and external targeted temperature management methods in post-cardiac arrest patients. *Am J Emerg Med* 2018;36:66–72.
33. Tan AT, Emmanuel SC, Tan BY, Teo WS, Chua TS, Tan BH. Myocardial infarction in Singapore: a nationwide 10-year study of multiethnic differences in incidence and mortality. *Ann Acad Med Singapore* 2002;31:479–86.
34. Jacobs CS, Beers L, Park S, Scirica B, Henderson GV, Hsu L, et al. Racial and ethnic disparities in postcardiac arrest targeted temperature management outcomes. *Crit Care Med* 2020;48:56–63.
35. Agarwal S, Presciutti A, Roth W, Matthews E, Rodriguez A, Roh DJ, et al. Determinants of long-term neurological recovery patterns relative to hospital discharge among cardiac arrest survivors. *Crit Care Med* 2018;46:e141–50.
36. Doctor NE, Yap S, Gan HN, Leong BSH, Goh ES, Chia MYC, et al. Recognition and treatment of out-of-hospital cardiac arrests by non-emergency ambulance services in Singapore. *Ann Acad Med Singapore* 2013;42:445–50.
37. Goh ES, Liang B, Fook-Chong S, Shahidah N, Soon SS, Yap S, et al. Effect of location of out-of-hospital cardiac arrest on survival outcomes. *Ann Acad Med Singapore* 2013;42:437–44.

Appendix

TTM Protocol

Induction Phase:

- The Emergency Department will initiate cooling with cold saline infusion 2 L over 2 hours and ice packs on patient's axilla and groin until the cooling device is started in the CCU/MICU.
- Reach target temperature rapidly.
- Insert a temperature sensing foley catheter or rectal temperature probe or oesophageal temperature probe to monitor core temp.
- Record temp every 30 min until rewarming is complete (temperature data should be downloaded if possible or at least every 15 minutes during induction phase).
- Obtain a Glasgow Coma Score prior to giving paralytics.
- Sedate and paralyse to avoid shivering.
- Time to reach target temperature.
- The lowest temperature ever reached.

Sedation Protocol:

- IV Midazolam initial dose 0.02-0.08 mg/kg over 1-2 min, then 0.04 mg/kg/hr titrate up to 0.2 mg/kg/hr to achieve sedation, and if blood pressure tolerates.

Paralytic Protocol:

- Atracurium 0.4-0.5 mg/kg I.V. bolus then 5-10 mg/kg/min and titrate as needed
- CCU/MICU to place patient on Heat, Moisture, Exchange (HME) unit during cooling rather than heated wire circuit (ventilator).
- Initiate cooling device according to manufacturers' protocol.
- Set the target temperature on the cooling unit to 34°C.
- Ice packs to axilla and groin can be removed at this point.
- Once patient temperature of 34°C is achieved (will take about 3-8 hrs), keep target temperature at 34°C.

Maintenance Phase:

- Target MAP >80 mmHg to maintain cerebral perfusion.
- Administer vasopressors through central venous access; as per physician's discretion.
- If hypertensive, short acting vasodilators such as Nitroglycerine may be used.
- Keep CVP 10-15 mmHg or PCOP >12 mmHg using Normal Saline or Lactated Ringers (CVP or PCOP monitoring not mandatory) per doctor's order.
- Use Low Molecular Weight heparin (LMWH), *Enoxaparine* at a dose of 40 mg once daily, if no contraindications.
- Lacrilube to both eyes quarter hour while receiving paralytics.
- Skin care to avoid cold-related injury.

- Frequent suctioning and pulmonary toilet.
- Nursing interventions to avoid complications of immobility (DVT, UTI, skin breakdown).
- Follow mixed venous saturation (SvO₂) when available per doctor's orders rather than cardiac index since the O₂ extraction ratio will be very low due to a markedly decreased metabolic demand from hypothermia and paralytics. Avoid dobutamine or other arrhythmogenic inotropes if SvO₂ is close to 70%.
- Stress Ulcer Prophylaxis: Famotidine 20 mg IV q 12 hr, or Famotidine 20 mg NGT q 12 hr per doctor's order.
- EEG monitoring is recommended to detect seizures in the paralysed patient.
- Manage status epilepticus with antiepileptic medication according to standard procedure.
- Any cardiac arrhythmias should be treated with standard anti-arrhythmia protocols.
- Potential laboratory abnormalities associated with hypothermia:

Potential Lab Abnormalities Treatment

Increased amylase → No intervention unless persistent after rewarming.

Increased LFT's → No intervention unless persistent after rewarming.

Increased serum glucose → Follow insulin protocol.

Decreased K⁺, Mg, Phosp, Ca → Correct as needed.

Increased lactate → Optimise oxygen delivery.

Metabolic acidosis → Optimise oxygen delivery.

Thrombocytopenia → Correct if <30k, or to >50k if active bleeding.

Leukopenia → No intervention unless persistent after rewarming.

• If the patient needs to go for cardiac catheterisation, the cooling device should accompany the patient. The patient may be unplugged from the device enroute, but cooling should be reinstituted on arrival at the catheterisation lab.

• In the event of cardiac arrest requiring defibrillation or cardioversion, it is suggested that the lower energy setting be initially employed, with escalating energy settings as necessary.

Rewarming Phase:

• After 24 hours at 34°C, rewarm passively to 36.5°C by setting the cooling unit accordingly.

Aim to increase temperature by 1°C every 4 hours, and achieve rewarming over at least 12 h.

Warm no faster than 1°C in 4 hours.

• If experiencing difficulty rewarming as above, use heated ventilator air to provide core rewarming.

• Discontinue all potassium in IVF during rewarming per doctor's order. Cases of severe hyperkalemia have been reported on rewarming. Represents a transcellular shift rather than true K⁺ depletion.

Documentation

• Temperature every 1 hour or more frequently.

• V/S every 1 hour or more frequently.

• Glasgow Coma scores on initiation and every 4 hours.

• Skin evaluation and care given every 2 hours or more frequent.

• Time of initiation and completion of cooling and reaching target temperature.

• Patient's response to procedure.

• All completed data will then be collected and sent to the research team for data management.

• At the end of rewarming, after target warm temperature achieved, to inform trial coordinator to perform data download from the machine data log.

• Temperature variation.

• Other cooling or warming methods used to reach and/or maintain target.