

## Analysis of complications after out-of-hospital cardiac arrest of target temperature management

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### Abstract

**Objective:** To analyse the prevalence of complications related to out-of-hospital cardiac arrest patients achieving target temperature management within 360 minutes compared to those taking more than 360 minutes.

**Method:** The retrospective study was conducted at a medical centre in Taiwan, and comprised data from January 1, 2014, to December 31, 2020. Data was retrieved using the International Classification of Diseases version 10 codes I46.2, I46.8 and I46.9 related to adult patients of either gender presenting to the Emergency Medicine department with out-of-hospital cardiac arrest. Data included gender, age, medical history, body mass index, acute physiology and chronic health evaluation II score, blood glucose levels, electrocardiogram results, and complications occurring within the target temperature management timeframe. Data was divided into group A having patients who achieved target temperature management within 360 minutes, and group B having patients with delayed TTM of more than 360 minutes. Data was analysed using SPSS 22.

**Results:** Of the 127 patients, 76(59%) were males, 51(41%) were females, 47(37%) were aged >75 years, and 13(10.3%) were aged <50 years. Of the total, 65(51.2%) patients were in group A, and 62(48.8%) were in group B. Pneumonia, urinary tract infection, septic shock and gastrointestinal bleeding had lower incidence rates in group A than group B ( $p<0.05$ ). The odds of death were 2.879 times higher in group B patients than group A (95% confidence interval: 1.908-8.916).

**Conclusions:** Hypothermia treatment should be started as soon as possible to achieve target temperature management within 360 minutes to reduce the risk of complications and mortality.

**Keywords:** Out-of-hospital cardiac arrest, Target temperature management, Risk of death. (JPMA 74: 1094; 2024)

DOI: <https://doi.org/10.47391/JPMA.10129>

### Introduction

Out-of-hospital cardiac arrest (OHCA) is an emergency indicating a race against time. It is a significant disease threatening human health and is the third leading cause of death worldwide.<sup>1</sup> The World Health Organisation (WHO) has also designated it as one of the leading causes of human death.<sup>2</sup> Based on the statistics on heart and stroke released by the American Heart Association in 2019, there were more than 350,000 patients with OHCA in the United States annually, and there was no downward trend.<sup>3</sup> Statistics showed 55 cases of OHCA per 100,000 adults per year globally.<sup>4</sup> However, OHCA's prognosis is very poor, with significant mortality after resuscitation, and the nervous system-caused disability is mainly due to multiple system dysfunction caused by prolonged systemic ischaemia.<sup>5,6</sup> Globally, <10% of OHCA patients can survive

until discharge.<sup>7</sup> However, a study in Australia showed an increasing trend in OHCA survival, with 30-day survival increasing from 4.2% in 2001 to 16.4% in 2018.<sup>8</sup> However, Taiwan has reported 9,815 OHCA cases annually, with a survival rate of 9.8%.<sup>9</sup>

A large-scale generational study in the US, conducted from 2009 to 2016, gathered approximately 26,000 cases of OHCA receiving target temperature management (TTM) treatment. The analysis focussed on favourable neurological outcomes, categorised as Cerebral Performance Category (CPC) 1 and 2. The results confirmed that the TTM group exhibited significantly better neurological prognosis compared to the non-TTM group.<sup>10</sup> Numerous clinical studies have further validated the ability of TTM to improve neurological outcomes after the return of spontaneous circulation (ROSC) and reduce mortality in OHCA patients.<sup>11</sup> This underscores the importance of establishing specialised technical guidelines for post-TTM recovery in critical care medicine. In the Taiwan region, the Ministry of Health and Welfare announced on December 1, 2015, that therapeutic hypothermia had been included in the National Health Insurance coverage.<sup>12</sup> The eligible conditions encompass neonatal hypoxic-ischaemic encephalopathy and adult patients who experience

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**Submission complete:** 08-08-2023

**Review began:** 06-09-2023

**Acceptance:** 06-03-2024

**Review end:** 07-02-2024

sudden cardiac arrest, recover their heartbeat after emergency measures, but remain unconscious.

TTM controls the body temperature of OHCA patients and is also known as therapeutic hypothermia (TH).<sup>13</sup> TTM is a complex intervention clinically used primarily in OHCA patients post-ROSC to minimise post-hypoxic damage and improve neurological outcomes after cardiac arrest. The equipment and protocols used to achieve cooling vary widely and include induction, target temperature, maintenance, rewarming, sedation and fever management after TTM.<sup>14</sup> TTM is primarily performed post-ROSC; within 360 minutes of preparation for prime time, an ice blanket is used to maintain the core body temperature from 32°C to 36°C and lasts for 24 hours.<sup>15</sup> Integrated analysis pointed out that using TTM intervention in OHCA patients can reduce mortality and improve the possibility of an excellent neurological prognosis.<sup>16</sup> However, many patients after emergency department (ED) resuscitation received TTM, but the survival rate was reduced, and the neurological prognosis was poor because of comorbidities.<sup>17</sup>

The current study was planned to analyse the prevalence of complications related to OHCA patients achieving TTM within 360 minutes compared to those taking >360 minutes.

## Patients and Methods

The retrospective study was conducted at a medical centre in Taiwan, and comprised data from January 1, 2014, to December 31, 2020. After approval from the institutional ethics review committee, data was retrieved from the hospital information system using the International Classification of Diseases version 10 (ICD-10) codes I46.2, I46.8 and I46.9 related to adult patients of either gender presenting to ED with OHCA. The sample was raised using consecutive sampling technique.<sup>18</sup>

Those included were patients with non-traumatic ventricular fibrillation, with stopped heartbeat caused by pulseless ventricular tachycardia, and patients who were unconscious after ED resuscitation with Glasgow Coma Scale (GCS) score <8. Data was excluded for patients with systolic blood pressure (SBP) <90mmHg, in whom coma was not caused by psychogenic causes (such as drug overdose), were pregnant, terminally ill, had psychogenic shock, ear temperature <30°C, were unconscious before the heartbeat stopped, and had central nervous system (CNS) depression caused by drugs. Data was divided into group A having patients who achieved TTM within 360 minutes, and

group B having patients with delayed TTM of >360 minutes.

Data of each patient was reviewed individually, and variables noted down included gender, age, medical history, body mass index (BMI), acute physiology and chronic health evaluation II (APACHE II) score, blood glucose levels, electrocardiogram (ECG) findings, and complications occurring within the TTM timeframe. Additionally, variables related to complications arising from delayed attainment of the target temperature during TTM for OHCA were also noted. CPC scale was used, as appropriate, and the scores ranged 1-5, with higher scores indicating more significant disability.<sup>19</sup>

Data was analysed using SPSS 22.1. Independent samples t-test, Pearson chi-square test and Fisher's exact test were used, as appropriate. Variables showing statistical significance  $p < 0.05$  were included in logistic regression analysis for intergroup comparisons. Odds ratios (ORs) were calculated with 95% confidence interval (CI).

## Results

Of the 127 patients, 76(59%) were males, 51(41%) were females, 47(37%) were aged >75 years, and 13(10.3%) were aged <50 years. There were 65(51.2%) patients in group A and 62(48.8%) in group B. Mean APACHE II score for group A was lower than group B ( $p < 0.01$ ) (Table 1).

Pneumonia, urinary tract infection (UTI), septic shock (SS) and gastrointestinal (GI) bleeding had lower incidence rates in group A than in group B (Table 2).

There were significant differences in blood glucose and potassium levels as well as heartbeat rate at the time of ED presentation compared to TTM days 1 and 2 (Table 3).

**Table-1:** Baseline characteristics.

	Total (n=127)		TTM within	TTM in more than	p-value
	Min/max		360 minutes (n=65)	360 minutes (n=62)	
	n (%)		n (%)	n (%)	
<b>Gender</b>					0.294
Male	76 (59)		36 (56)	40 (64)	
Female	51 (41)		29 (44)	22 (36)	
<b>Age (years)</b>					0.137
<50	13 (10.3)		10 (16)	3 (4.8)	
50-64	39 (30.7)		22 (33)	17 (27.4)	
65-74	28 (22)		13 (20)	15 (24.3)	
>75	47 (37)		20 (31)	27 (43.5)	
<b>Mean BMI (kg/m<sup>2</sup>)</b>	14/41	25.38	24.72±5.19	25.78±5.92	0.719
<b>Mean Elixhauser</b>	-3/29	6.12	4.4±5.20	8.03±7.44	0.715
<b>Mean APACHE II</b>	12/32	24.0	23.22±2.98	25.74±3.81	0.01
<b>Mean Blood Glucose (mg/dl)</b>	27/578	302.0	213.28±113.59	246±135.8	0.483
<b>Mean K<sup>+</sup> (mmol/L)</b>	2.3/10.1	3.96	3.8±0.62	4.07±1.1	0.228
<b>Mean Heartbeat (bpm)</b>	44/206	108.2	111.83±27.52	103.67±34.36	0.275

TTM: Target temperature management; BMI: Body mass index; APACHE: Acute physiology and chronic health evaluation; K<sup>+</sup>: Potassium.

Mortality rate and CPC scores were significantly better in group A compared to group B (Table 4).

The odds of death were higher in group B patients than group A (OR: 2.879; 95% CI: 1.908-8.916) (Table 5).

**Table-2:** Comparison of complications between the groups.

	<b>Total (n=127)</b> n (%)	<b>TTM within 360 minutes (n=65)</b> n (%)	<b>TTM in more than 360 minutes (n=62)</b> n (%)	<b>t-test</b>	<b>p-value</b>
Pneumonia	49(39)	9(13)	40(64)	0.000	0.001
UTI	10(8)	3(5)	7(11)	0.084	0.001
SS	52(40)	11(16)	41(66)	0.000	0.006
GB	48(40)	11(18)	37(61)	0.000	0.028

UTI: Urinary tract infections; SS: Septic shock; GB: Gastrointestinal bleeding; TTM: Target temperature management.

**Table-3:** TTM-associated complications between the groups.

	<b>TTM within 360 minutes</b>	<b>TTM in more than 360 minutes</b>	<b>Mean difference [95% CI]</b>	<b>p-value</b>
<b>Mean Blood Glucose (mg/dl)</b>				
Emergency	190.16±116.32	237.19±106.45	-2.30 [-87.7~-6.67]	0.023
TTM day1	132.44±65.36	162.76±90.96	-2.12 [-58.8~-59]	0.038
TTM day 2	105.72±50.09	131.56±70.38	-2.32 [-47.8~-3.81]	0.022
Re-warm	130.64±53.31	149.71±56.22	-1.90 [-38.87~0.73]	0.059
<b>Mean K<sup>+</sup> (mmol/L)</b>				
Emergency	3.85±0.68	4.07±1.09	-1.334 [-.551~0.107]	0.185
TTM day1	3.46±0.51	3.55±0.53	-1.00 [-0.283~0.093]	0.319
TTM day 2	3.29±0.36	3.39±0.57	-1.13 [-.274~0.075]	0.261
Re-warm	3.59±0.33	3.7±0.56	-1.261 [-0.275~0.06]	0.021
<b>Mean Heartbeat (bpm)</b>				
Emergency	111.26±27.65	105.12±32.61	1.114 [-4.77~17.06]	0.267
TTM day1	75.9±17.2	74.69±18.99	0.365 [-5.34~7.75]	0.716
TTM day 2	66.41±15.4	63.12±16.12	0.311 [-4.99~-6.92]	0.66
Re-warm	84.08±16.67	93.56±82.58	0.878 [-30.84~11.89]	0.382

CI: Confidence interval; K<sup>+</sup>: Potassium; TTM: Target temperature management.

**Table-4:** TTM-associated complications between the groups.

	<b>TTM Within 360 minutes (n=65)</b> n (%)	<b>TTM in more than 360 minutes (n=62)</b> n (%)	<b>p-value</b>
<b>Discharge</b>			
Survival	41 (63)	23 (37)	0.001
Death	24 (37)	39 (63)	
<b>CPC score</b>			
Good recovery	16 (25)	4 (6)	0.001
Moderate disability	7 (10)	8 (13)	
Severe disability	13 (21)	11 (18)	
Vegetative	6 (10)	10 (16)	
Death	23 (34)	29 (47)	

CPC: Cerebral Performance Category, TTM: Target temperature management.

**Table-5:** Odds ratio of survival rate between the groups.

	<b>TTM within 360 minutes (n=65)</b> n (%)	<b>TTM in more than 360 minutes (n=62)</b> n (%)	<b>OR (95% CI)</b>
Survive	41(63)	23(37)	1
Death	24(37)	39(63)	2.897 (1.908 to 8.916)

OR: Odds ratio; CI: Confidence interval.

## Discussion

The current study had male patients accounting for >60% of the sample, which was in line with literature.<sup>20,21</sup>

The current study showed that group B had a significantly higher APACHE II score than group A, which was consistent with the increased risk of OHCA caused by comorbidities.<sup>22</sup> No significant difference was found in blood glucose level and BMI between the groups, but the average values of blood glucose and BMI were higher than normal. In addition, higher blood sugar and BMI were associated with longer cooling time and a higher risk of OHCA, which was consistent with earlier findings.<sup>23,24</sup>

The current group B showed higher incidence of pneumonia, UTI, SS and GI bleeding compared to group A. Hypothermia reduces the secretion of pro-inflammatory cytokines, inhibits the migration and phagocytosis of white blood cells (WBCs), and increases the risk of infection.<sup>25</sup> In addition, during hypothermia, continuous hypothermia will cause insulin resistance (IR), which can cause hyperglycaemia and a higher risk of infection.<sup>26</sup>

Teng et al. in 2022 noted that low temperatures could inhibit leukocyte migration and phagocytosis, thereby increasing the risk of infection.<sup>27</sup> Furthermore,

Bjertnæs et al. in 2022 pointed out that longer cooling periods were associated with an increased risk of bleeding, thereby leading to a higher probability of GI bleeding.<sup>28</sup>

The current group B experienced high blood glucose levels during TTM on days 1 and 2. This may be related to the higher severity of the disease at the time ED presentation after OHCA and concurrent infection and SS. In cases of infection and SS, the immune system and brain initiate a protective response that induces hyperglycaemia through endothelial dysfunction, and increases free radical production and inflammatory response.<sup>29</sup>

The current study confirmed that a good CPC score within 360 minutes could achieve a better neurological prognosis and reduce mortality. A study found that within 48 hours of OHCA occurrence, the body temperature is higher than the threshold of 37°C, which is related to adverse neurological results, and every degree of increase will increase the risk of death.<sup>30</sup> Early initiation of TTM was significantly related to improving mortality and reducing

nerve damage.<sup>31</sup>

The current study has limitations as it was conducted at a single centre with a small sample size. Also, treatment selection bias among the cases may have affected the results. Comprehensive, large-scale, multi-centre, prospective studies are recommended.

## Conclusion

TTM within 360 minutes showed significantly better results than TTM >360 minutes. Hypothermia treatment should be started as soon as possible to achieve TTM within 360 minutes to reduce the risk of complications and mortality.

**Disclaimer:** None.

**Conflict of Interest:** None.

**Source of Funding:** None.

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**Author Contribution:**

SJ: Data acquisition, analysis, drafting, final approval, accountable for all aspects of the work.

SA, SAA: Concept, design, Revision, final approval, accountable for all aspects of the work.

AKK, AN, SI: Data interpretation, drafting, final approval, accountable for all aspects of the work.