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Prognostic factors for neurological outcomes in Korean targeted temperature management recipients with return of spontaneous circulation after out-of-hospital cardiac arrests

A nationwide observational study

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Abstract

Targeted temperature management (TTM) is recommended for comatose patients after out-of-hospital cardiac arrests (OHCAs). Even after successful TTM, several factors could influence the neuroprotective effect of TTM. The aim of this study is to identify prognostic factors associated with good neurological outcomes in TTM recipients.

This study used nationwide data during 2012 to 2016 to investigate prognostic factors associated with good neurological outcomes in patients who received TTM after the return of spontaneous circulation (ROSC). Multivariate logistic regression analysis was conducted to analyse the factors that may affect the neurological outcomes in the TTM recipients.

The study included 1578 eligible patients, comprising 767 with good and 811 with poor neurological outcomes. Multivariable analyses showed that OHCA in public places (OR, 1.599; 95% CI, 1.100–2.323, $P = .014$), initial shockable rhythms (OR, 1.721; 95% CI, 1.191–2.486, $P = .004$), pre-hospital ROSCs (OR, 6.748; 95% CI, 4.703–9.682, $P < .001$), bystander cardiopulmonary resuscitation (CPR) (OR, 1.715; 95% CI, 1.200–2.450, $P = .003$), and primary coronary interventions (PCIs) (OR, 2.488; 95% CI, 1.639–3.778, $P < .001$) were statistically significantly associated with good neurological outcomes. Whereas, increase of age (OR, 0.962; 95% CI, 0.950–0.974, $P < .001$) and conventional cooling (OR, 0.478; 95% CI, 0.255–0.895, $P = .021$) were statistically significantly associated with poor neurological outcome.

This study suggests that being younger, experiencing OHCA in public places, having initial shockable rhythm, pre-hospital ROSC, and bystander CPR, implementing PCIs and applying intravascular or surface cooling devices compared to conventional cooling method could predict good neurological outcomes in post-cardiac arrest patients who received TTM.

Abbreviations: CI = confidence interval, CPC = cerebral performance category, CPR = cardiopulmonary resuscitation, ECMO = extracorporeal membrane oxygenation, EMS = emergency medical service, KCDC = Korean Centres for Disease Control and Prevention, OHCA = out-of-hospital cardiac arrest, OHCAS = Out-of-Hospital Cardiac Arrest Surveillance, OR = odds ratio, PCI = percutaneous coronary intervention, ROSC = return of spontaneous circulation, TTM = targeted temperature management, VF = ventricular fibrillation, VT = ventricular tachycardia.

Keywords: Nationwide observation study, neurological outcomes, out-of-hospital cardiac arrest, prognosis, targeted temperature management

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JGK and HS contributed equally to this work.

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1. Introduction

Severe neurological injury is the most common cause of death among patients who experience out-of-hospital cardiac arrests (OHCAs).[1] A minority of OHCA patients are successfully resuscitated and survive with good neurological outcomes.

Targeted temperature management (TTM) is widely recommended during the critical care of patients who are comatose post-cardiac arrest.[2–4] TTM as a neuroprotective treatment improves outcomes in post-resuscitation care,[4,5] and it minimizes neuronal loss and brain damage.[6] The potential mechanisms of TTM that improve neurologic outcomes are as follows: a lower cerebral metabolic rate for oxygen, suppression of the chemical reaction associated with reperfusion injury, or activation of anti-apoptotic mechanisms via cooling or control.[7,8] Since several factors, including advanced life support, access to emergent coronary angiography, optimising support for cerebral and organ perfusion, and preventing hyperglycemia and infections,[5,9–13] influence the neuroprotective effects of TTM, few patients achieve good neurological outcomes post-cardiac arrest, even after successful cardiopulmonary resuscitation (CPR) and TTM.

Many studies of several prognostic factors have evaluated their associations with neurological outcomes after the implementation of TTM.[14,15] However, predicting neurological outcomes is difficult, even if TTM is successful. In this study, we analysed data from a nationwide cohort of patients who experienced OHCAs to identify prognostic factors associated with good neurological outcomes in TTM recipients.

2. Methods

2.1. Study design and settings

This was a retrospective observational study that evaluated the prognostic factors associated with good neurological outcomes in patients who underwent TTM from January 2012 to December 2016, using nationwide data from the Out-of-Hospital Cardiac Arrest Surveillance (OHCAS) database that is managed by the Korean Centers for Disease Control and Prevention (KCDC) (https://cdc.go.kr). OHCAS is undertaken in 17 provinces within South Korea, which has a population of 50 million people, and the database contains information describing the timing of the patients' cardiac arrests and the patients' outcomes at hospital discharge. The local ethics committee approved this study (Kangnam Sacred Heart Hospital's Institutional Review Board No. 2018-07-025-001), and the need for informed consent was waived because of the retrospective nature of the study and the use of anonymous clinical data for the analysis. The KCDC approved the use of the data for this study.

The application of and the types of TTM methods used were decided by physicians in accordance with the hospitals' protocols. This study's methodology fulfilled the criteria in the Strengthening the Reporting of Observational Studies in Epidemiology checklist.[16]

2.2. Data source

The OHCAS database comprises a population-based, EMS-assessed OHCA registry and a retrospective patient cohort. The data from patients who had experienced OHCAs were extracted from the EMS registry; these data are collected by emergency medical technicians using EMS run sheets (patient records), and they are input by EMS providers immediately after the transportation of OHCA patients. The data describing the OHCA patients' hospital care and outcomes at hospital discharge were provided by the KCDC's medical record reviewers who visit all of the emergency departments (EDs) and hospitals to which OHCA patients are referred, and they review the medical records in relation to the patients' treatment and outcomes.

The OHCAS database contains information that describes individuals and settings, EMSs, ED care, hospital procedures, and the outcomes at discharge, including mortality and the neurological outcomes, using a customised survey form. The registry form was developed based on the Utstein-style guidelines[17] and the Resuscitation Outcome Consortium Project.[18]

2.3. Study population

A total of 142,905 patients had experienced OHCAs and were registered in the OHCAS database between January 2012 and December 2016, and, of these, patients aged ≥18 years who experienced OHCAs and received TTM in hospital settings after ROSC as a result of CPR were included in the study. We excluded patients whose OHCAs were a consequence of trauma, patients aged <18 years, any patients whose data describing their neurological status were invalid.

2.4. Variables

Information was collected that described the patients' ages and sexes, the places where the cardiac arrests occurred (public vs non-public), the aetiological factors (cardiac vs non-cardiac), the initially monitored rhythm (shockable vs non-shockable), witnessed cardiac arrests, bystander CPR, TTM-related factors, including the cooling method, pre-induction time, and induction time, PCIs, extracorporeal membrane oxygenation (ECMO), and mechanical CPR. Regarding the places where the cardiac arrests occurred, public places were defined as any places that are generally accessible to people, including roads, public buildings, parks, and beaches. An initial shockable rhythm was defined as initially monitored ventricular fibrillation (VF) or ventricular tachycardia (VT). ROSC was defined for all rhythms as the restoration of a spontaneous rhythm that was sustained for >20 min. The cardiac origins of the OHCAs, including ischemic heart disease, arrhythmias, and cardiac tamponade, were identified from reviews of the medical records. A cardiac arrest was presumed to have had a non-cardiac origin if it was caused by trauma, drowning, poisoning, burns, asphyxia, hanging, or any other non-cardiac factor.

PCI included ballooning and primary stenting. Regarding initiation time of TTM, the pre-induction time was defined as the interval between the cardiac arrest and TTM initiation, and the induction time was defined as the interval between TTM initiation and the achievement of the target temperature.

The external temperature management systems used comprised external pads that were applied to the body surface to reduce the body temperature, and they included the Arctic Sun system (Medivance Inc, Louisville, CO), Gaymar products (Gaymar Industries Inc, Orchard Park, NY), the Blanketrol III system (Cincinnati Sub-Zero Products, Cincinnati, OH), and the Emcools Flex.Pad device (Emcools Medical Cooling Systems GmbH, Traiskirchen, Austria). The intravascular cooling devices used comprised intravascular catheters inserted into large vessels to reduce body temperature, and they included the Coolgard

3000 Thermal Regulation System (Alsius Medical Corporation, Irvine, CA). Conventional cooling methods were defined as basic external cooling devices that included fans and ice packs that were placed on the main vascular access points, or basic internal cooling methods, including stomach irrigation with cool saline administered through a Levin tube, urinary bladder irrigation using cold saline administered through a Foley catheter, and cold saline intravenous infusions.

Target temperature and maintenance time for TTM were not provided from the raw data of OHCAS in this study. However, all TTM protocol in the South Korea has been adhering to the international 2010 to 2015 American Heart Association guidelines (target temperature: 32 to 36°C, maintenance time: 12 to 24 h).[19,20]

Patients with invalid or missing data on neurological outcome were excluded from the study population.

2.5. Outcome measures

The study's outcome was the neurological outcome at hospital discharge, which was assessed using the cerebral performance category (CPC) scoring system. CPC scores of 1 and 2 were considered good neurological outcomes, and CPC scores of 3, 4, and 5 were considered poor neurological outcomes. The neurological outcomes were determined according to the discharge summaries in the patients' medical records.

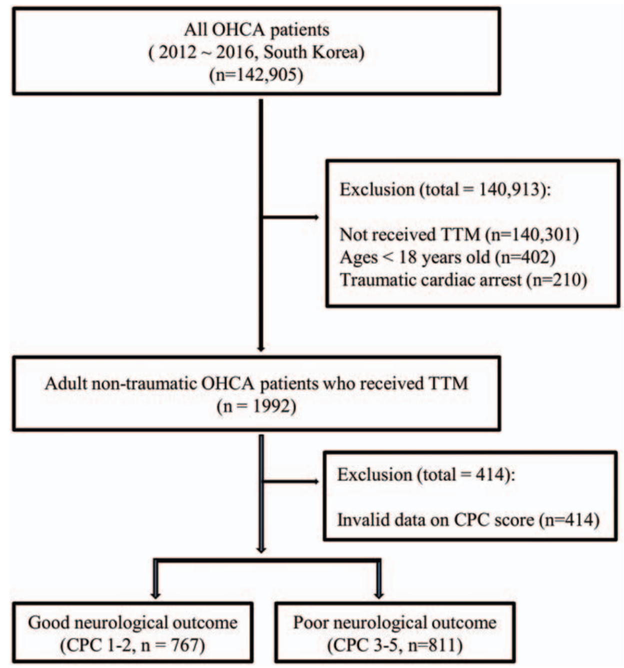

Figure 1. Study's flow diagram. CPC = cerebral performance category, OHCA = out-of-hospital cardiac arrest, TTM = target temperature management.

2.6. Statistical analyses

The continuous data are presented as the medians and interquartile ranges, and the categorical data are presented as numbers and percentages. The Kolmogorov–Smirnov test was used to assess the normality of the data. The continuous variables were analysed using the independent sample *t* test for the parametric data and the Mann–Whitney *U* test for the nonparametric data. Pearson's chi-square test and Fisher's exact test were used to analyse the categorical variables. Multivariate logistic regression analysis, which used a backward likelihood ratio model, was conducted to analyse the factors that may affect the neurological outcomes in the TTM recipients. Any variables with P values <.05 in the univariate analyses were included in the multivariate regression analysis. All of the statistical analyses were conducted using IBMSPSS software, version 24.0 (IBM Corporation, Armonk, NY) and R, version 3.3.2 (The R Foundation for Statistical Computing, Vienna, Austria). A value of $P<.05$ was considered statistically significant.

3. Results

3.1. Characteristics of the study subjects

Of the 142,905 patients who had experienced OHCAs and were registered during the study period, we excluded patients who did not receive TTM (n = 140,301), patients aged <18 years or those who had experienced traumatic OHCAs (n = 612), and patients whose CPC scores were unknown at hospital discharge (n = 414). The remaining 1578 patients were enrolled to participate in this study, and, of these, 767 (48.6%) comprised the good neurological outcome group, and 811 (51.4%) comprised the poor neurological outcome group (Fig. 1).

Table 1 summarizes the clinical characteristics of the patients in the two groups. The median age of the patients in the good neurological outcome group was significantly lower than that of the patients in the poor neurological outcome group ($P<.001$). The numbers of male patients ($P=.003$), OHCAs in public places ($P<.001$), pre-hospital ROSCs ($P<.001$), witnessed cardiac arrests ($P<.001$), patients who underwent bystander CPR ($P<.001$), initial shockable rhythms ($P<.001$), OHCAs of cardiac origin ($P<.001$), and percutaneous coronary interventions (PCI) ($P<.001$) were significantly higher in the good neurological outcome group than those in the poor neurological outcomes group. The rate of mechanical CPR was significantly lower in the good neurological outcome group than that in the poor neurological outcome group ($P=.004$). The induction time was significantly longer in the good neurological outcome than that in the poor neurological outcome group ($P<.001$), and the TTM cooling methods differed significantly between the groups ($P<.001$).

3.2. Analysis of prognostic factors associated with neurological outcomes

We performed multivariate logistic regression analyses to identify factors associated with good neurological outcomes. The variables included in the analyses were age, sex, OHCA in a public place, pre-hospital ROSC, witnessed cardiac arrest, bystander CPR, initial shockable rhythm, cause of cardiac arrest, mechanical CPR, TTM cooling method and initiation time, PCI, and ECMO. Among these variables, OHCA in a public places (odds ratio [OR]: 1.599; 95% confidence interval [CI]: 1.100–2.323; $P=.014$), initial shockable rhythm (OR: 1.721; 95% CI: 1.191–2.486; $P=.004$), pre-hospital ROSC (OR: 6.748; 95% CI: 4.703–9.682; $P<.001$), bystander CPR (OR: 1.715; 95% CI: 1.200–2.450; $P=.003$), and PCI (OR: 2.489; 95% CI: 1.639–3.778; $P<.001$) were statistically significantly associated with good neurological outcomes (Table 2). Whereas, older age (OR: 0.962; 95% CI: 0.950–0.974; $P<.001$) and conventional cooling

Table 1

Patients' demographic characteristics according to the neurological outcomes.

Variables	Good neurologic outcome (CPC1-2, n=767)	Poor neurologic outcome (CPC3–5, n=811)	*P*
Pre and intra-cardiac arrest factors			
Age (years)	51 (40–59)	63 (52–73)	<.001
Sex (male, %)	604 (74.5%)	619 (80.7%)	.003
OHCA in public places	266 (34.7%)	209 (25.8%)	<.001
Pre-hospital ROSC	516 (67.3%)	129 (15.9%)	<.001
Witnessed cardiac arrest	636 (82.9%)	572 (70.5%)	<.001
Bystander CPR	365 (47.6%)	211 (26.0%)	<.001
Initial monitored rhythm			<.001
Shockable	547 (71.3%)	231 (28.5%)	
Non-shockable	220 (28.7)	580 (71.5%)	
Cause of cardiac arrest			
Cardiac origin	757 (98.7%)	770 (94.9%)	<.001
Non-cardiac origin	10 (1.3%)	41 (5.1%)	
Mechanical CPR	13 (1.7%)	34 (4.2%)	.004
Post-cardiac arrest care			
Target temperature management			
Cooling devices			<.001
Intravascular cooling devices	91 (11.9%)	70 (8.6%)	
External cooling devices	503 (65.6%)	495 (61.0%)	
Conventional cooling methods	173 (22.5%)	246 (30.4%)	
Initiation time (hours)			
Pre-induction time (hours)*	3.0 (2.00–4.25)	2.9 (1.91–4.21)	.425
Induction time (hours)†	4.1 (2.40–7.00)	2.4 (1.16–4.83)	<.001
PCI	205 (26.7%)	94 (11.6)	<.001
ECMO	33 (4.3%)	25 (3.1%)	.229

CPC=cerebral performance category, CPR=cardiopulmonary resuscitation, ECMO=extracorporeal membrane oxygenation, OHCA=out of hospital cardiac arrest, PCI=primary coronary intervention, ROSC=return of spontaneous circulation.

* The pre-induction time was the interval between cardiac arrest and the initiation of target temperature management.

† The induction time was the interval from the initiation of target temperature management to the achievement of the target temperature.

Table 2

Multivariate logistic regression of good neurological outcomes in recipients of target temperature management.

Variables	OR(95%CI)	*P*
Pre and intra-arrest factors		
Age (years)	0.962 (0.950–0.974)	<.001
OHCA in public places	1.599 (1.100–2.323)	.014
Initial shockable rhythm	1.721 (1.191–2.486)	.004
Pre-hospital ROSC	6.748 (4.703–9.682)	<.001
Witnessed cardiac arrest	1.522 (0.999–2.319)	.051
Bystander CPR	1.715 (1.200–2.450)	.003
Post-cardiac arrest cares		
PCI	2.488 (1.639–3.778)	<.001
TTM cooling methods		
Intravascular cooling devices	–	Reference
External cooling devices	0.720 (0.417–1.244)	.239
Conventional cooling methods*	0.478 (0.255–0.895)	.021

The backward likelihood ratio model was used for the multivariate logistic regression analysis.
CI=confidence interval, CPR=cardiopulmonary resuscitation, OHCA=out of hospital cardiac arrest, OR=odds ratio, PCI=primary coronary intervention, ROSC=return of spontaneous circulation, TTM=targeted temperature management.

* Conventional cooling methods were defined as basic cooling that included fans, ice packs, and stomach or urinary bladder irrigation with cold saline.

methods (OR: 0.478; 95% CI: 0.255–0.895; $P=.021$) were statistically significantly associated with poor neurological outcomes (Table 2; Fig. 2). A witnessed cardiac arrest was not a prognostic factor for the neurological outcomes (OR: 1.522; 95% CI: 0.999–2.319, $P<.239$). There was no statistically significantly difference between intravascular and external cooling devices in relation to the neurological outcomes (OR: 0.720; 95% CI: 0.417–1.244; $P<.239$) (Table 2).

4. Discussion

We analysed nationwide data to identify prognostic factors associated with good neurological outcomes in adult OHCA patients who received TTM. OHCAs in public places, initial shockable rhythms, pre-hospital ROSC, bystander CPR, and PCI were associated with good neurological outcomes in TTM recipients after OHCA. Whereas older age and the use of conventional cooling methods were adversely associated with good neurological outcomes.

TTM has neuroprotective effect in patient with cardiac arrest.[6,21] However, the neurological outcomes could additionally be influenced by the degree of hypoxic brain injury during CPR and post-cardiac arrest management. An absence of cerebral blood flow for >5 min is associated with a poor recovery of cerebral function,[22] and beyond this time point, varying degrees of brain tissue damage occur.[23] Cerebral blood flow could also be influenced by the hemodynamic instability caused by myocardial dysfunction after ROSC and the adverse effects of TTM.[21,22,24] Accordingly, the neurological outcomes after TTM could be impacted by several factors that affect cerebral blood flow before and after TTM, including the interval between the collapse and the first CPR, the attainment of ROSC, and PCIs.[25–27]

Our analysis showed that an OHCA in a public place was a prognostic factor for good neurological outcomes. The American Heart Association (AHA) guidelines describe early access, early CPR, and early defibrillation as the first three 'links in the chain of survival', which are highly dependent on public engagement for most cardiac arrest events.[28] The likelihood of basic life support being provided, including mobilising the delivery of emergency care, administering CPR, and using automated external defibrillators (AEDs), is higher in public places than that in non-public places.[29] OHCAs are more likely to be witnessed by laypeople in public places, and the survival rates associated with OHCAs are higher in public places than those in non-public places.[29–32] Murakami et al[29] reported that the presence of publicly accessible defibrillation facilities and the use of AEDs by the public improved OHCA patients' outcomes. While the patients' exact mental statuses after ROSC were not determined in this study, the brain of a patient whose OHCA occurred in a public place might be less injured before TTM began; hence, patients who receive TTM after OHCAs in public places might have better neurological outcomes than those who experience OHCAs in non-public places.

This study's findings also showed that TTM recipients with initial shockable rhythms namely, VF and pulseless VT, had good neurological outcomes. While TTM could benefit patients with non-shockable rhythms, patients with shockable rhythms have better outcomes than patients with non-shockable rhythms.[33–35] It was because that patients who experience cardiac arrests with non-shockable rhythms do not tend to benefit from defibrillation, and the conditions of the brains of these patients

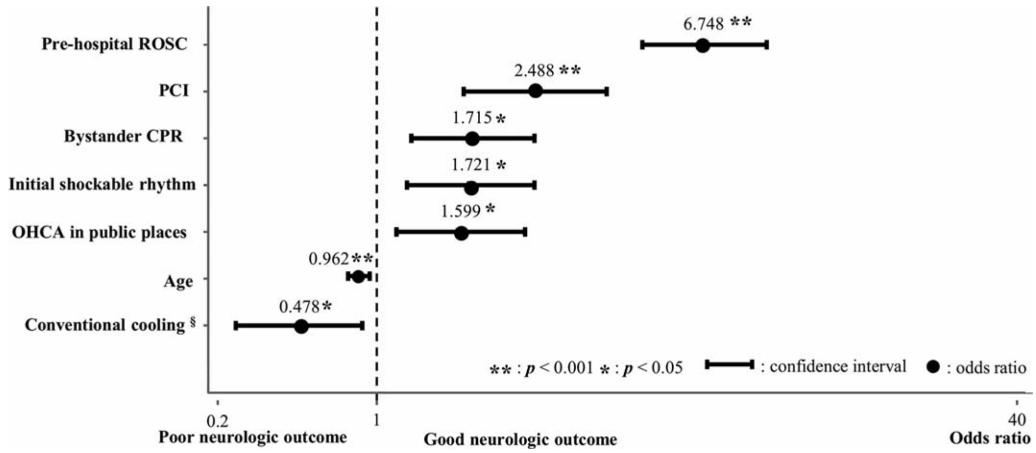

Figure 2. Independent predictors of good neurological outcomes in recipients of target temperature management following out-of-hospital cardiac arrest. CPR = cardiopulmonary resuscitation, OHCA = out of hospital cardiac arrest, PCI = primary coronary intervention, ROSC = return of spontaneous circulation.

who are less likely to undergo ROSCs and who experience longer periods of CPR before the ROSC, could worsen before TTM.

A pre-hospital ROSC was a prognostic factor for good neurological outcomes associated with TTM in our analysis. Chest compressions only generate 25% to 30% of the normal cardiac output when they are performed under optimal conditions. Hence, prolonged CPR is related to cerebral damage and a low likelihood of a ROSC.[36] Consequently, a pre-hospital ROSC could contribute to good neurological outcomes in TTM recipients by reducing levels of brain damage before TTM.

Bystander CPR was identified as a prognostic factor for good neurological outcomes associated with TTM in this study. Cerebral blood flow is extremely low during closed-chest CPR following a prolonged cardiac arrest.[37–39] Low cerebral blood flow is deleterious during cerebral resuscitation.[40] The AHA and European guidelines stress the importance of early CPR as part of the chain of survival.[41] Kragholm et al[42] reported that compared with no bystander resuscitation, bystander CPR significantly reduced the brain damage and nursing home admission rates. If bystander CPR is implemented properly, it could yield better cerebral blood flows, and, therefore, contribute improved neurological outcomes after TTM.[43]

In post-cardiac arrest management, PCI was identified as a prognostic factor for good neurological outcomes in the TTM recipients who had experienced OHCAs in this study. The 2015 AHA guidelines recommend emergency coronary angiography for adult patients who are comatose after OHCAs with suspected cardiac origins.[3] Given that TTM could worsen cardiac dysfunction and hemodynamic imbalances and that coronary artery disease is a major cause of adult OHCA, PCI could contribute to good neurological outcomes in TTM recipients by removing the presumed cause of the OHCA and supporting the hemodynamic status during post-resuscitation care.[21,35,44] Previous studies' findings have also shown that PCI in addition to TTM could positively influence the neurological outcomes in TTM recipients.[45–48]

Regarding cooling methods, this study's findings showed that compared with intravascular cooling systems, the neurological outcomes were adversely associated with conventional cooling methods, and that there were no differences between intravascular and external cooling devices. Conventional cooling methods, for example, crushed ice or ice bags, are the easiest ways to apply TTM,[49] but they are associated with high rates of unintentional overcooling below the target temperature, which could have deleterious effects, including atrial or ventricular arrhythmias, coagulopathy, and increased risks of infection.[50–53] Furthermore, compared with external or intravascular cooling devices, conventional cooling methods are less effective at maintaining temperatures,[54] and these disadvantages could weaken the neuroprotective effect of TTM and adversely affect the neurological outcomes after TTM.[55]

We found an adverse association between older age and the neurological outcomes after TTM. Oh et al[56] reported that age was a negative prognostic factor for neurological outcomes (OR: 0.94; 95% CI: 0.93–0.96; $P < .001$). Winther–Jensen et al[57] reported that older age was associated with increased rates of unfavourable neurological outcomes. As people age, comorbidity, and disability rates increase,[58] and neurological function and neuronal plasticity decline[58,59]; hence, older patients may respond poorly to TTM.

5. Limitation

Our study has several limitations. First, since this was a retrospective observational study, it may have been subject to selection bias relating to the type of TTM method used and the post-cardiac arrest management procedure implemented such as PCI. Therefore, result of this study should be interpreted with caution.

Second, we could not assess the patients' neurological outcomes beyond hospital discharge, because the neurological outcomes were measured using data from the patients' medical records at hospital discharge. Early CPC scores measured at hospital discharge can change until 6 months post-discharge[60,61]; therefore, prognostic factors in this study could be different compared with prognostic factors for long-term neurological outcome of TTM recipients.

Third, our retrospective registry did not contain data that described potential confounders, for example, the patients' underlying diseases, hemodynamic statuses, mental statuses before TTM, the laboratory findings, and descriptions of the cardiac arrest durations. These factors could affect patient survival and the patients' neurological outcomes. Thus, more studies that include more variables related to the patients' statuses and TTM are required to corroborate our results.

Fourth, target temperature and maintenance time for TTM were not provided from the raw data of OHCAS in this study. However, all TTM protocol in the South Korea has been adhering to the international 2010 to 2015 American Heart Association guidelines (target temperature: 32–36°C, maintenance time: 12–24 h).[19,20] Therefore, the TTM guideline change from 2010 to 2015 might affect the outcomes of patients.

Finally, whether our study's findings can be generalised to other countries with different medical systems is uncertain. The study was performed in the context of South Korea's emergency medical service (EMS), which does not permit the provision of advanced cardiac life support to patients. Hence, the findings from this study should be interpreted with caution regarding their generalisability to other countries' medical systems that provide advanced cardiac life support to patients. To generate more generalizable data, studies involving other races and countries are required.

6. Conclusion

Good neurological outcomes could be expected among TTM recipients if patients are younger, experience OHCAs in public places, have initial shockable rhythms, and have prehospital ROSCs, and bystander CPR is performed. In post-cardiac arrest care, the implementation of PCIs, and intravascular or surface cooling rather than conventional cooling methods could improve patients' neurological outcomes after TTM.

Author contributions

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