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Effectiveness of Targeted Temperature Management in Post-Cardiac Arrest Patients on Neurological Outcomes: A Literature Review

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Abstrak

Targeted temperature management (TTM) merupakan intervensi terapeutik yang memberikan efek neuroprotektif yang dapat memberikan efek *delayed awakening* dengan mengurangi derajat cedera otak secara permanen. Tujuan penelitian ini adalah untuk mengetahui efektivitas TTM pada pasien pasca henti jantung terhadap hasil neurologi. Desain penelitian ini menggunakan *literature review* yang berdiskusi tentang efektivitas targeted temperature management pada pasien pasca henti jantung terhadap hasil neurologi pasien (*cerebral performance category*). Penelusuran literature dilakukan melalui database Pubmed, ScienceDirect, and Google Scholar. *Literature review* dilakukan berdasarkan studi yang terdapat pada database yang dipublikasikan dari tahun Januari 2014 sampai dengan Agustus 2023 dan artikel dalam bentuk bahasa inggris yang diambil. Hasil penelitian menunjukkan bahwa implementasi dari TTM memiliki pengaruh terhadap status neurologi pada pasien pasca henti jantung yang mengalami *return of spontaneous circulation* (ROSC) baik pada pasien dengan *in-hospital cardiac arrest* (IHCA) maupun *out-hospital cardiac arrest* (OHCA). Hasil penelitian menunjukkan bahwa TTM pada pasien *cardiac arrest* berpengaruh pada *favorable neurogical outconmes* atau *good neurological outcomes* (CPC skor 1-2). *Targeted temperature management* yang diberikan pada pasien pasca henti jantung yang mengalami ROSC baik pada pasien IHCA atau OHCA secara signifikan memiliki efek pada neurological outcome atau cerebral performan category (CPC) pada kategori favorable neurogical outcomes atau good neurological outcome (CPC skor 1-2) yang diukur pada saat hospital discharge).
Kata Kunci: *Targeted Temperature Management, Henti Jantung, Hasil Neurologi, ROSC*

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Abstract

Targeted temperature management (TTM) is a therapeutic intervention that provides a neuroprotective effect to provide a delayed awakening effect so that it can reduce the degree of brain injury permanently. This study aimed to determine the effectiveness of TTM on neurological outcomes in patients after cardiac arrest. This research design used a literature review of research results discussing the effectiveness of targeted temperature management on patient neurological outcomes (cerebral performance category) in patients after cardiac arrest. Literature searches were carried out by searching through the Pubmed, ScienceDirect, and Google Scholar databases. A literature review was carried out based on research studies contained in the database and published from January 2014 to August 2023 and articles published in English and found 11 articles that met the inclusion criteria. The results of the study showed that TTM influenced the neurological status of post-cardiac arrest patients who experienced the return of spontaneous circulation (ROSC), both in patients with in-hospital cardiac arrest (IHCA) and out-hospital cardiac arrest (OHCA). The research results also showed that TTM in cardiac arrest patients affected favorable neurological outcomes or good neurological outcomes (CPC score 1-2). Targeted temperature management given to post-cardiac arrest patients who experience ROSC, whether in IHCA or OHCA patients, has a significant effect on the neurological outcome or cerebral performance category (CPC) in the favorable neurological outcomes or good neurological outcome (CPC score 1-2) category. measured at hospital discharge.

Keywords: *Targeted Temperature Management, Cardiac Arrest, Neurology Outcomes, ROSC*

INTRODUCTION

Emergency conditions such as heart attacks are conditions that cannot be predicted. Cardiac arrest is a life-threatening emergency condition and if not treated immediately it will result in death. If cardiac arrest occurs, blood flow to both the brain and the rest of the body cannot be distributed throughout the body. This will cause brain damage within 4-6 minutes and become irreversible within 8-10 minutes. Death due to cardiac arrest can be prevented by providing basic life support per the 6 steps of the chain of survival, both in-hospital chain of survival (IHCA) and out-hospital chain of survival (Goodarzi et al., 2022; Ngurah & Putra, 2019).

Nearly 500,000 deaths each year in the United States and Europe are cardiac arrests. In cases of cardiac arrest, the survival of OHCA patients is <15%, while the survival of IHCA patients is around 22%. Based on the results of research on 1000 cases of cardiac arrest, it was found that 22% of patients had ROSC (return of spontaneous circulation) more than 30 minutes after resuscitation measures. There is a significant risk of neurological disability in patients with ROSC (both IHCA and OHCA). High mortality during the post-resuscitation phase may be attributed to a combination of whole-body ischemia, reperfusion-mediated

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damage, and the underlying pathological process of cardiac arrest. Optimal strategies in post-cardiac arrest care can improve the quality of life of post-ROSC patients (Goodarzi et al., 2022; Saigal et al., 2015).

Management of patients after cardiac arrest generally focuses on the triggering factors, respiratory & hemodynamic support, and neurological care. The patient's condition before and during cardiac arrest determines the severity of post-cardiac arrest syndrome and requires several interventions. The pathophysiological course of patients after experiencing cardiac arrest consists of 4 components, including hypoxic brain injury, systemic ischemia-reperfusion injury, myocardial dysfunction, and the underlying etiology of cardiac arrest. One form of post-cardiac arrest syndrome is brain injury which develops over hours or even days after ischemia due to cardiac arrest. Some management that can be given to these patients is optimizing cerebral perfusion, oxygenation, ventilation, neuroprotective pharmacological agents, and controlling seizures. One additional intervention that can be given is targeted temperature management (Madder & Reynolds, 2018).

The research results of Nishikimi et al (2021), show that the administration of TTM (33-34°C) significantly impacts good neurological outcomes (p-value 0.022; $\alpha<0.05$). TTM is a complex therapeutic intervention designed to induce body temperature to mild hypothermia over a certain period. TTM can provide a neuroprotective effect by providing a delayed awakening effect by permanently reducing the degree of brain injury (Irisawa et al., 2017). This study aimed to determine the effectiveness of TTM on neurological outcomes in patients after cardiac arrest.

RESEARCH METHOD

The study design was a literature review discussing the effectiveness of targeted temperature management in post-cardiac arrest patients on the patient's neurological status (cerebral performance category). The literature was searched through Pubmed, ScienceDirect, and Google Scholar databases. A literature review was conducted by a report published from January 2014 until August 2023 and English language articles were included. Keywords have been adjusted to Medical Subject Heading (MeSH), namely: Targeted Temperature Management OR Targeted Temperature Management, Post Cardiac Arrest Syndrome OR Return of Spontaneous Circulation OR Unassisted Return of Spontaneous Circulation, and Neurologic Outcome OR Cerebral Performance Category.

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Table 1 Research Problems based on PICOS

Criteria	Inclusion	Exclusion
Population	Cardiac arrest patients experiencing ROSC	There are no exclusions
Intervention	*Targeted Temperature Management (induction phase temperature: 32-34C)*	outside the temperature range of 32-34C
Comparison	Standard Operating Procedures or standards of care	
Outcomes	*Neurologic Outcome: good neurologic* atau *favorable neurological outcomes* (CPC 1-2)	
Study Design and Publication Type	*Research article*	There are no exclusions
Publication Years	2014 s.d 2023	
Language	English	There are no exclusions

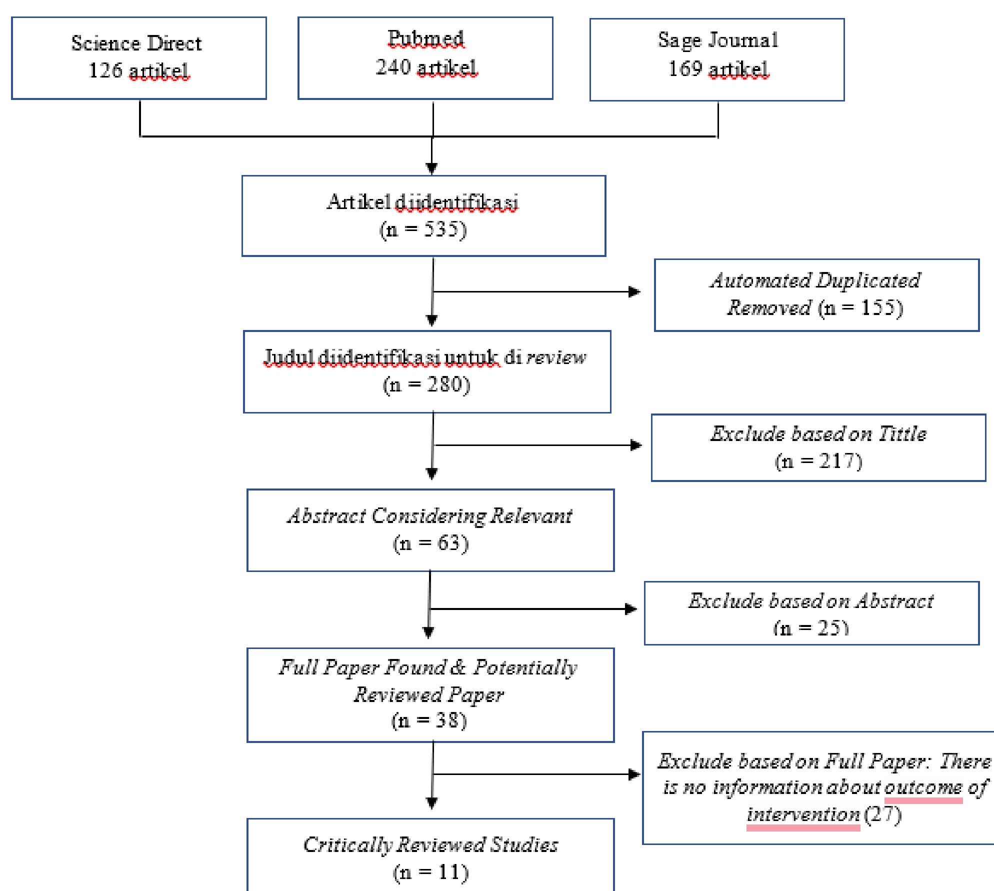

Figure 1 Prisma Flow

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RESULT AND DISCUSSION

Table 2 *Article Review*

Authors (Tahun)	Objective	Method	Result
Hsu et al., (2014)	To evaluate the effectiveness of TTM on cerebral performance categories in post-arrest patients in hospital	Design *Retrospective chart review* Sample: The total sample was 2,417 cardiac arrest patients who experienced ROSC at 2 Academic Medical Centers from May 2005 to December 2012. TTM was given with an external cooling device with a target temperature of 33-34C. A total of 582 (24.1%) patients survived until hospital discharge and 140 patients (24.1%) were given TTM. Outcomes: The CPC score was measured when the patient was discharged from the hospital	The research results showed that the majority of respondents who were given TTM had a CPC score of 1 when they left the hospital of 42.9%, while the prevalence of other respondents had a CPC score of 2 of 27.1%, a CPC score of 3 of 18.65, a CPC score of 4 of 11.4% The highest long-term survival was found in respondents who had a CPC score of 1 followed by a CPC score of 2 and CPC 3 respectively, while respondents who had a CPC score of 4 had the lowest long-term survival (p-value <0.001, log-rank test).
Frydland et al (2015)	To evaluate the effectiveness of TTM on cerebral performance categories in patients with non-shockable rhythm after cardiac arrest.	Design: *A multi-center randomized* Sample: The total sample was 950 patients who were given TTM and 43 patients dropped out. Inclusion criteria: 1) Age ≥18 years; 2) Coma (GCS <8) in post-cardiac arrest patients; 3) Patients with ROSC >20 minutes. Exclusion criteria: 1) Patients with ROSC >240 minutes; 2) Cardiac arrest with unknown initial rhythm; 3) Patients with refractory shock. Intervention:	*Primary outcomes:* *The results showed that 84% of patients died in the TTM 33C and TTM 36C groups.* *Secondary outcomes:* *The results showed that the group of respondents with TTM 33C had good neurological function by 30% and the TTM 36C group had good neurological function by 15%.*

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		Giving TTM with a target temperature of 33C and 36C. Outcomes: Primary outcomes: Mortality can be followed up up to 180 days. Secondary outcomes: Neurological status is assessed using the cerebral performance category (CPC) which is categorized into 2, namely poor neurological function (CPC 3-4) and good neurological function (CPS 1-2).	
Kim et al., (2015)	To determine the relationship between side effects and neurological status at hospital discharge in out-of-hospital cardiac arrest (OHCA) patients with TTM.	Design: A multicenter retrospective study Sample: The total sample was 930 OHCA patients in 24 hospitals. Inclusion criteria were age ≥18 years after ROSC. Exclusion criteria were traumatic cardiac arrest. Intervention: Interventions include: 1) TTM at 33C; 2) 24 hour maintenance; 3) normothermia is administered after 72 hours of ROSC. Outcomes: Primary outcomes: neurological outcome by looking at the CPC score 3-5 when the patient goes home for treatment.	The results showed that 32.4% of respondents had good neurological function at discharge, namely 27.4% CPC 1 and 4.9% CPC 2. The prevalence of respondents with poor neurological function was 67.6%, namely 7.1% CPC 3, 30.4% CPC 4, and 30.1% CPC 5 in OHCA patients treated with an average of 14-15 days of hospital stay. The results of multivariate analysis showed that there were factors associated with poor neurological function in OHCA patients, namely CRRT, non-shockable initial rhythm, non-cardiac causes of cardiac arrest, unfavorable medical history, time from cardiac arrest to ROSC, age, initial GCS ≥5 , first pupillary reflex, and coronary angiography (p-value <0.05; α <0.05).
Perman et al., (2015)	To evaluate the impact of early administration of TTM on neurological status and	Design: A multicenter retrospective study Sample: The total sample was 321 patients from level-1 trauma centers and academic	The research results showed that respondents who were given TTM had a good neurologic outcome (CPC 1-2) of 30.8%.

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	neurological disorders	community affiliates with The Penn Alliance for Therapeutic Hypothermia (PATH) Registry. Inclusion criteria: 1) Age ≥18 years; 2) IHCA or OHCA patients with any cardiac arrest rhythm; 3) The patient experiences ROSC; 4) The patient has no pulse <60 minutes; 5) Patients with GCS <6 after ROSC. Exclusion criteria: Patients with intracranial hemorrhage. Intervention: The intervention was given at a temperature of 33C.	The median TTM induction time in the good neurologic group was 180 minutes (min-max: 100-276 minutes), while the mean in the poor neurologic group was 236.5 minutes (min-max: 142-361 minutes). The results of further analysis showed that there was a difference in the mean TTM induction time between the good neurologic group and the poor neurologic group (p-value = 0.004; α <0.05).
Kirkegaard et al (2017)	To find out the difference between TTM at 33C for 48 hours and TTM at 24 hours according to standards	Desain: *A randomized clinical superiority trial* Sample: The sample size was 355 ROSC patients in the ICU from 10 university hospitals in 6 European countries. Intervention: The first group was given TTM (33±10C) for 48 hours (n=176). The second group was given TTM (33±10C) for 24 hours (n=179). Outcomes: Primary outcomes: CPC score 1-2 measured in the sixth month. Secondary outcomes: mortality within 6 months including time to death, incidence of side effects, use of ICU.	*Primary outcomes:* The results showed that the prevalence of respondents with CPC 1-2 for 6 months in the 48-hour group was 69% and in the 24-hour group was 64%. The results of further analysis showed that there was no significant difference between the 48-hour group and the 24-hour group (p-value = 0.33; α < 0.05). *Secondary outcomes:* The results showed that there was no significant difference between mortality in the 48-hour group and the 24-hour group, p-value = 0.19; α < 0.05). There was a significant difference in the incidence of side effects between the 48-hour group and the 24-hour group (p-value = 0.03; α < 0.05).
Boulé-Laghzali et al (2019)	To evaluate the effectiveness of TTM on the incidence of mortality and neurological	Design: A Retrospective Observational Study Sample: The number of samples was 147 patients after cardiac arrest. Inclusion	The results showed that most of the prevalence of mortality incidents and CPC scores ≥3 was 54.5%. The results of the analysis showed that the factors that significantly

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	outcomes in comatose patients after cardiac arrest.	criteria: 1) Coma (GCS >8); 2) Witnessed cardiac arrest; 3) ROSC in 60 minutes; 4) There is hope of life. Exclusion criteria: 1) Non-cardiac causes of cardiac arrest; 2) Severe hemodynamic instability; 3) Severe coagulopathy; 4) Bleeding. Intervention: TTM was given at a temperature of 32-34C modified to 35-36C and is given for 24 hours using an external cooling system. Outcomes: The cerebral performance category was measured when the patient was discharged from treatment.	influenced poor neurological function (CPC ≥3) in post-cardiac arrest patients who were given TTM were lactate, creatinine, and time during ROCS (p-value <0.05; α <0.05).
Lascarrou et al (2019)	To determine the difference in CPC at TTM temperature 33C and TTM temperature 36C in patients with non-shockable rhythm.	Design: A randomized controlled trial Sample: The total sample was 584 ROSC patients with non-shockable rhythm from 25 ICUs. Inclusion criteria: 1) Age ≥18 years in OHCA and IHCA patients with non-shockable rhythm; 2) Comatose patients with GCS ≤8; 3) Patients with lower scores when entering the ICU. Exclusion criteria: 1) No-flow time (initiation of CPR from cardiac arrest) >10 minutes; 2) Lo-flow time (ROSC initiation) >60 minutes; 3) Hemodynamic instability; 4) Time from cardiac arrest to screening >300 minutes; 5) Moribund condition; 6) Severe liver cirrhosis; 7) Pregnancy or breastfeeding; 8) The patient is a prisoner. Intervention:	The research results showed that most of the group of respondents who had a favorable neurological outcome (CPC score 1-2) were the group of respondents with a TTM temperature of 33C, 29 respondents (10.2%), while in the normothermic group, there were 17 respondents (5.7%). The results of further analysis showed that there was a significant difference in the prevalence of favorable neurological outcomes (CPC score 1-2) in the 33C TTM group and the 37C TTM group (p-value = 0.04; α <0.05).

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		Intervention group (n=284): Administration of TTM at 330C for the first 24 hours Control group (n=297): Administration of TTM with a normothermic temperature of 370C Outcomes: Favorable neurology is assessed with a CPC score of 1-2	
Johnson et al., (2020)	To determine the differences in neurological function in OHCA patients given TTM at 33C and TTM at 36C.	Design: A retrospective cohort study Sample: The total sample was 453 OHCA patients who experienced ROSC from January 1 2010 to April 30 2017. Inclusion criteria were age ≥18 years in non-traumatic OHCA patients. Intervention: TTM was given at temperatures of 33C and 36C. Outcomes: Primary outcomes: Neurological status when the patient is discharged from treatment. Secondary outcomes: Mortality and care processes.	*Primary outcomes*: The results showed that the majority of respondents had good neurological status (CPC 1-2) in the group with TTM 33C, 40%, while in the 36C group it was 30%. The results of further analysis showed that there was a significant relationship between neurological status in both the TTM 33C group and the TTM 36C group (p-value <0.05; $\alpha <0.05$). *Secondary outcomes:* There was no significant difference in mortality between the TTM 33C group and the TTM 36C group (p-value $= 0.08$; $\alpha < 0.05$).
Lee et al (2020)	To evaluate the impact of cardiac arrest time on neurology in OHCA patients	Design: Cross-sectional study Sample: The total sample was 1,963 OHCA patients using a hospital-based nationwide registry in Korea in 2012-2016. Inclusion criteria: 1) Patients who witnessed OHCA; 2) Age ≥15 years and given TTM. Exclusion criteria: 1) Patients without ROSC; 2) The patient is	The research results showed that overall respondents who had favorable neurologic (CPC 1-2) were 30.5%, there was a significant difference in OHCA patients who were given TTM in terms of cardiac arrest time at 10 minute intervals (p-value <0.001; $\alpha <0.05$).

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		declared dead in the emergency room; 3) Unwitnessed cardiac arrest. Outcomes: The patient's neurological status at hospital discharge: 1) Favorable neurologic (CPC 1-2); 2) Poor neurology (CPC 3-5)	
Kocayigit et al (2021)	To determine the effectiveness of TTM on neurological status in ROSC patients with GCS <8	Desain: *Retrospective cohort study* *Sample:* *The number of samples was 58 ROSC patients with GCS <8. Inclusion criteria: 1) Age 18-70 years with GCS <8; 2) Patients who experience ROSC after cardiac arrest; 3) Patients who enter the emergency room or coronary care unit. Exclusion criteria: 1) Patients with cardiac arrest with causes other than myocardial infarction; 2) CPR waiting time data does not exist; 3) The patient died before the TTM administration ended.* *Intervention:* *Intervention group (n=27 respondents): 1) Rapid cooling with a temperature of 33-35C for 1-3 hours; 2) The maintenance temperature is given at 33-35C within 24 hours; 3) Re-warming 0.2-0.33C per hour until it reaches a temperature of 36.5-37.5C. Control group (n=31 respondents): Respondents without TTM (normothermia).* *Outcomes:* *Neurological status at the time the patient was discharged from the hospital.*	The results showed that the prevalence of respondents in the intervention group who had good neurologic (CPC 1-2) was 40.7%, while in the control group, it was 6.5%. The results of further analysis showed that there was a difference in the prevalence of good neurology (CPC 1-2) between the intervention group and the control group (p-value = 0.002; α <0.05).

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Blanc et al., (2022)	To determine the effectiveness of TTM 33C on neurological status in IHCA with non-shockable rhythm compared with normothermic patients	Design: A randomized controlled trial Sample: The total sample was 159 IHCA patients with non-shockable rhythms. Intervention: Intervention group (n = 73 respondents): Given TTM intervention with a temperature of 33C for 24 hours. Control group (n= 86 respondents): Given TTM intervention with a temperature of 37C. Outcomes: Neurological status: good neurological outcome (CPC score 1-2) within 90 days.	The results showed that the prevalence of good neurological outcome (CPC score 1-2) on day 90 in the intervention group was 16.4%, while the control group was 5.8%. The results of further analysis showed that there was a difference in good neurological outcome (CPC score 1-2) on the 90th day between the control group and the intervention group (p-value = 0.002; α <0.05).

Based on Table 2, the results showed that the implementation of targeted temperature management (TTM) influences the neurological status of post-cardiac arrest patients who experience the return of spontaneous circulation, both in patients with in-hospital cardiac arrest and out-hospital cardiac arrest. The research results showed that TTM in cardiac arrest patients affected favorable neurological outcomes or good neurological outcomes (CPC score 1-2).

Discussion

Targeted temperature management (TTM) is a complex therapeutic intervention designed to induce body temperature to mild hypothermia over a certain period. Controlling body temperature is part of treatment that has the potential to prevent secondary brain damage. TTM provides neuroprotective effects by various mechanisms, namely 1) Reducing brain metabolism; 2) Weakens the formation of reactive oxygen; 3) Weakens the immune response during reperfusion; 4) Blockage of apoptosis. The hypothermia temperature given is 32-34 C in the first 24 hours. This is done to reduce mortality rates and improve neurological function (Chien et al., 2021; Johnsson et al., 2020).

TTM can be divided into 3 phases, namely induction, maintenance, and rewarming. The goal of the induction phase is to reach the target body temperature (32-340C) as quickly

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as possible. The target temperature is controlled at a set level during the maintenance phase for 24-48 hours. At the end of the maintenance phase, the patient's temperature is increased gradually at a rate of 0.25-0.50C per hour. The initiation to start administering TTM according to European Resuscitation guidelines is to begin as soon as possible after the return of spontaneous circulation (Tripathy & Mahapatra, 2015).

Research conducted by Perman et al., (2015), showed that respondents who were given TTM had a good neurologic outcome (CPC 1-2) of 30.8%. Other research also shows that 32.4% of respondents had a good neurological function at discharge, namely 27.4% CPC 1 and 4.9% CPC (Kim et al., 2015). The American Heart Association and the International Liaison Committee on Resuscitation recommend TTM as an intervention that can improve outcomes in comatose patients who have out-hospital cardiac arrest (OHCA), namely neuroprotective (which protects the nerves). There is evidence that a decrease in brain temperature can reduce blood flow to the brain and brain oxygen consumption. The neuroprotective effect may cause delayed awakening by permanently reducing the degree of brain injury (Irisawa et al., 2017).

The hypothalamus and brain stem are responsible for controlling thermoregulation. Hypothermia affects pathways that cause excitotoxicity, inflammation, apoptosis, and free radical production such as blood flow, blood-brain barrier integrity, and cerebral metabolism. Hypothermia also affects the processes of neurogenesis, angiogenesis, and gliogenesis. Perman et al., (2015), The results of further analysis showed that there was a difference in the mean TTM induction time between the good neurologic group and the poor neurologic group (p-value = 0.004; $\alpha < 0.05$).

The relationship between induction time and good neurological outcomes in ROSC patients given TTM is related to age, initial shockable rhythm, and duration of downtime which are predictors related to neurological outcomes. The results of the study also showed that there was an increase in good neurological outcomes by 86% with increasingly advanced induction times and prolonged induction times correlated with improved neurological outcomes. Longer induction times may also cause patients who experience ROSC after cardiac arrest to experience greater neurologic injury and the possibility of experiencing more extensive ischemic injury. (Perman et al., 2015).

CONCLUSION

Targeted temperature management is given to post-cardiac arrest patients who experience ROSC, whether in IHCA or OHCA patients and has a significant effect on the

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neurological outcome or cerebral performance category (CPC) in the favorable neurological outcomes or good neurological outcome (CPC score 1-2) category. measured at hospital discharge).

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