RESEARCH ARTICLE

Assessing the Impact of Temperature Management Interventions on Survival Outcomes in Adult Out-of-Hospital Cardiac Arrest: A Comprehensive Review of Randomized Controlled Trials

Ahmed M. Asiri[1*], Salman A. Alzahrani[2], Afrah Y. Saddeek[3], Faisal A. Ghazwani[4], Abdulhakeem Alotaibi[5], Shahalil Alqani[6]

[1]*Department of Emergency Medical Services, Prince Sultan Military College of Health Sciences, Kingdom of Saudi Arabia.*
[2]*Saudi red crescent, Kingdom of Saudi Arabia.*
[3]*Directorate of Health Affairs, Albaha region, Kingdom of Saudi Arabia.*
[4]*Department of Emergency Medical Services, Prince Sultan Military College of Health Sciences, Kingdom of Saudi Arabia.*
[5]*Department of Emergency Medical Services and Disasters-KSMC, Kingdom of Saudi Arabia.*
[6]*HDU/SDU unit manager, Ministry of Health, Kingdom of Saudi Arabia.*

Received: 26th June, 2023; Revised: 09th July, 2023; Accepted: 06th August, 2023; Available Online: 25th September, 2023

ABSTRACT

A cardiac arrest patient who has recovered outside the hospital, managing body temperature is beneficial. There is still uncertainty as to what specific circumstances should be met in order for such interventions to be initiated. Researchers have used different methods to study OHCA TTM interventions due to the uncertainty surrounding their outcomes. The study's main objective is to determine if temperature management affects survival outcomes in adult cardiac arrests occurring outside of the hospital. Several online databases were examined to collect data, including Web of Science, PubMed Central, Medline, Embase and Cochrane. Our study examined several randomized controlled trials, including randomized clinical trials and randomized controlled trials that involved TTM interventions in adult OHCA patients. An analysis was conducted based on the search criteria for screening, collecting, and extracting data. Based primarily on qualitative analysis, a synthesis was conducted. There were 21 studies with a total of 11435 participants, with a median sample of 355, and none of them demonstrated sufficient qualitative and quantitative evidence indicating that TTM interventional variants were safe, feasible, efficient, and effective on neurological and mortality outcomes in OHCA patients.

Keywords: Targeted temperature management, Cardiac arrest patients, OHCA TTM, Clinical trials.

International Journal of Pharmaceutical Quality Assurance (2023); DOI: 10.25258/ijpqa.14.3.09

How to cite this article: Asiri AM, Alzahrani SA, Saddeek AY, Ghazwani FA, Alotaibi A, Alqani S. Assessing the Impact of Temperature Management Interventions on Survival Outcomes in Adult Out-of-Hospital Cardiac Arrest: A Comprehensive Review of Randomized Controlled Trials. International Journal of Pharmaceutical Quality Assurance. 2023;14(3):514-522.

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

Patients following cardiac arrest under out-of-hospital conditions can benefit from temperature management (also known as "therapeutic hypothermia" or "cooling"), although its benefits are not yet fully understood where and where should this intervention be initiated under certain conditions. Approximately 10% to 13% of patients discharged from hospitals suffering cardiac arrest survive, while 12% of patients discharged from hospitals suffering cardiac arrest survive was 25%. Out-of-hospital cardiac arrest (OHCA) targeted temperature management (TTM) interventions have attracted the attention of various methodological research methods. While these findings are important and valuable, there are uncertainties in TTM intervention programs with clear target temperature levels. Continued investigation of TTM interventions in OHCA patients is needed because the severity of the outcome may be a factor that impedes the effectiveness of the intervention.

There are long- and short-term outcomes associated with OHCASA due to its difficulty in detection and the uncertainty surrounding its diagnosis.[1,2]

The condition is particularly challenging because of its prognosis uncertainty, high mortality rate, and neurological dysfunction. In this case, when blood circulation is stopped, brain cells are directly destroyed under the influence of hypoxia and an molecule is created when adenosine triphosphate (ATP)

**Author for Correspondence: aalasiri@psmchs.edu.sa*

is split into two. Despite restoring blood circulation, brain cells are still damaged even after restoring blood flow by various pathophysiological phenomena such as microcirculatory disorders and nerve cell necrosis and apoptosis caused by other factors such as fever etc. The patient needs resuscitation.

Following resuscitation and hospital admission, post-resuscitation care aims to minimize secondary cardiac arrest-related damage during blood flow restoration.[1,3]

Several guidelines recommend cooling comatose patients who have survived out-of-hospital ventricular fibrillation cardiac arrest to a target temperature of 32 to 36°C.[4,5] In addition to ice packs, cooling pads, cold-air mattresses, etc., medical professionals have access to a variety of surface cooling methods that can be used to target the body and cool it effectively. There may, however, not be a practical or feasible way of implementing all of the methods in every case or at all times.

These two channels and their underlying mechanisms are restricted by hypothermic temperature management.[3] In order to have effective intervention, it is also necessary to control the duration of TTM. Hence, studies have focused on comparing the standard duration of TTM with durations of up to 72 hours, mainly in new-borns, controlling for the duration of the TTM intervention.[6,7]Additionally, the effects of prolonged cooling or TTM have been shown in various *in-vitro* studies.[8,9]

According to some research, there has been substantial evidence showing that TTM and its variants are important and clinically beneficial. However, there have been a few studies suggesting the opposite. As a result, there are questions concerning the efficacy of TTM interventions and their variants, such as the timing, onset, duration, and additions intended to enhance outcomes, etc. A broad range of hypothermic interventions based on control of cooling, its onset and duration, as well as any additional therapies can be administered under randomized comparative trial designs in out-of-hospital adult cardiac arrest patients to assess the effect of target temperature management on neurological and survival outcomes.

MATERIALS AND METHODS

Study Type

In this comprehensive review, we encompass a diverse range of study designs, incorporating both randomized comparative trials and randomized quasi-controlled trials. Specifically, our analysis encompasses randomized controlled trials, randomized clinical trials, and post-hoc analyses derived from randomized clinical trials. Moreover, we extend our purview to trials lacking a conventional or explicitly defined control group. These trials, while devoid of a traditional control, meticulously compare multiple treatment groups amongst themselves. Central to these investigations is the evaluation of TTM as a pivotal intervention for patients experiencing OHCA.

The deliberate incorporation of quasi-controlled trials serves to encompass a range of interventions. These trials adhere to a controlled framework where There are only a few mechanisms which can be controlled, such as odd/even days. This, in turn, enables the study to offer a more enriched and nuanced panorama of the existing literature on this subject. Additionally, the integration of retrospective or post-hoc studies based on registry trials stems from a similar rationale. Such studies, in alignment with established research precedents, contribute to a comprehensive exploration of TTM's efficacy.

Inclusion criteria

The review encompassed studies that satisfied specific criteria: participants aged above 18 years, a diverse array of randomized comparative trial formats, including randomized controlled trials, randomized clinical trials, and other types like post hoc or retrospective analyses sourced from comprehensive trial registries. Furthermore, the study selection was confined to publications spanning the period from 2010 to 2021.

Exclusion criteria

The review's scope was explicitly delimited by exclusion criteria, which encompassed the following considerations: firstly, studies focusing exclusively on pediatric subjects were omitted from consideration. Secondly, papers not presented in the English language were excluded. Moreover, studies lacking a coherent and explicit delineation of patient outcomes were also ineligible for inclusion. Lastly, the review exclusively incorporated studies for which complete full-text copies were accessible, ensuring a comprehensive analysis of the research landscape.

Study Selection

The study selection process was intricately interwoven with the systematic search approach. Broadly speaking, the initial screening of studies involved an assessment of their titles and abstracts to ascertain the presence of relevant keywords or their synonymous counterparts in alignment with our research objectives. A randomized comparative trial, accompanied by optimal temperature management, out-of-hospital cardiac arrests, adults, neurological outcomes, survival outcomes, and randomized comparative trials, comprised the core search terms, were explored in both their literal and colloquial interpretations. This preliminary evaluation, guided by the outlined criteria, facilitated a rapid and comprehensive initial assessment. Records meeting these initial screening benchmarks were meticulously cataloged in Zotero. Subsequently, a comprehensive examination of the textual content of these shortlisted papers ensued, leading to the meticulous curation of a final compilation of studies eligible for comprehensive review. This multifaceted approach ensured a rigorous and systematic selection process, enhancing the robustness and reliability of the study's findings.

Type of Participants

The study encompassed adult participants who had encountered OHCA and subsequently underwent post-resuscitation TTM.

Types of Interventions

Within the scope of this study, a comparative analysis was conducted involving diverse variants of TTM. These variants were explored across varying durations, encompassing

comparisons between routine and novel or proposed protocols, as well as contrasting TTM against established standards with specific proposed target temperatures. Moreover, the study extended its purview to encompass scenarios where TTM was coupled with additional interventional therapies, as relevant to the context of OHCA patients.

Types of Control or Randomization

The selection of studies for inclusion was meticulously tailored to facilitate comparisons between the proposed intervention-based groups and either placebo or conventional forms of TTM variants. These comparisons encompassed various dimensions, including but not limited to time, duration, onset, prevalence, or efficacy, often in conjunction with specific additional therapies relevant to the context of OHCA patients. To achieve this, the selected studies adhered to a randomized allocation strategy, often employing a 1:1 ratio or equivalent distribution, effectively assigning participants to the two comparative groups.

Types of Outcomes

Primary outcomes

The included studies assessed post-intervention neurologic, survival, and various other outcomes at different time points. Although some studies prioritized different outcomes as primary or secondary, our review concentrated on neurologic and survival outcomes, regardless of their categorization in the original studies, aligning with our study objectives.

Secondary outcomes

It encompassed adverse events (reported or study-author delineated, binary/categorical data), hospital/ICU stay (continuous data), and diverse outcomes from studies, even if straying from targets, yet adhering to participant and intervention criteria.

Data Collection and Analysis

Extraction of data and its management

A methodical data collection process was undertaken using a dedicated data extraction form (Appendix 1) specifically designed for this purpose. The collected data was meticulously organized and stored within an MS Excel record. The data extraction form encompassed an extensive range of more than 20 data fields, thoughtfully aligned with the research goals and objectives. These fields spanned across six comprehensive areas within the research publications: The details of the bibliography and metadata, the research objectives, themes, and focus, the methodology and design, the analysis of quality and risk of bias, the presentation of results, findings, and limitations, and the prospects for future exploration (Figure 1). This comprehensive approach to data extraction ensured a thorough and systematic capture of relevant information, thereby enhancing the depth and breadth of the study's analysis.

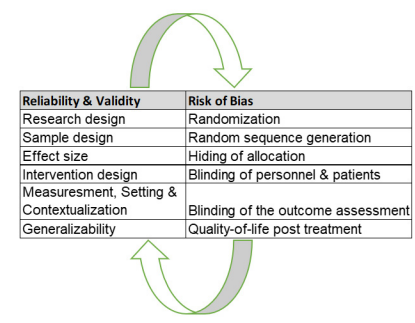


Figure 1: Bias risk and reliability are key measures of research quality

Studies are assessed for their reliability, validity, and risk bias

The assessment of study validity, reliability, and bias risks were primarily centered on reported randomization, blinding, and control measures in each study. Domain-specific evaluation weighed the level of control and randomization against respective requirements and feasibility. Key In addition to generating random sequences and concealing allocations, blinding was also evaluated of outcome assessment, and post-intervention quality of life. Addressing incomplete reporting selectively on outcomes, or unexplained participant exclusions factored into research quality and bias assessment. Given OHCA patient characteristics and retrospective registry-based designs, blinding was often unfeasible, linking reliability, validity, and bias. Reported levels were categorized as low, moderate, high, or unclear for reliability and validity, and low, moderate, or high for bias risk.

Data synthesis

This review undertakes an encompassing process of integration, interpretation, and thematic delineation, guided by the methodology outlined.[10]Although the subject area under scrutiny, namely TTM, is not novel, the initial search strategy yielded insufficient results. Consequently, the review embraces a diverse range of methodological and thematic variants to comprehensively explore TTM's impact on neurologic and survival outcomes in OHCA patients. This approach necessitates a meticulous qualitative evaluation, data synthesis, and integration. Quantitative synthesis will be judiciously employed, contingent upon the availability of comparable data across the study outcomes. Specifically, the review contemplates calculating combined hazard ratios with corresponding 95% confidence intervals for dichotomous variables. Likewise, mean or standardized mean differences will be computed for continuous variables. This quantitative synthesis will be employed judiciously, ensuring its application aligns with data comparability and relevance, augmenting the robustness of the review's findings.

RESULTS

Study Description

The systematic exploration across designated databases, as well as Google Scholar and Search, spanning the interval from 2010 to 2021, yielded an initial pool of 1,477 findings after meticulous deduplication (Figure 2). Subsequent phases of assessment involved the meticulous evaluation of titles,

abstracts, and swift perusal to sift through the literature. Papers eliminated during this phase often lacked substantive alignment with research objectives, even though they frequently intersected with our focus on treatment of cardiac arrest patients outside the hospital with TTM. Notably, certain potentially relevant papers were hampered by limitations in full-text availability due to database constraints. Consequently, the screening process led to the exclusion of 1,312 records, narrowing down the pool to 165 papers eligible for further scrutiny. Upon a rigorous full-text examination, following defined criteria and accounting for duplicates, a selection of 21 studies emerged for synthesis. This assortment included 20 completed investigations alongside three ongoing studies. The rationale behind including these ongoing studies rests upon their adherence to all inclusion criteria and their satisfactory progress in ongoing research endeavors.

Design

All encompassed studies adopted randomized comparative trial formats, comprising a mix of prospective, retrospective trials, and registry-based standalone prospective designs. More specifically, the review incorporated 11 studies (equating to 52%) based on randomized controlled trial (RCT) methodologies, along with 10 studies (amounting to 48%) derived from RCT-based post-hoc/retrospective approaches (Figure 3). As expounded in the methodology segment, the latter category offers nuanced insights, augmenting the body of research and literature pertaining to TTM or TTM-based interventions for OHCA patients. These studies, while shedding light on neurologic and survival outcomes, contribute to a comprehensive understanding of TTM's efficacy and its broader therapeutic implications for adult OHCA patients.

Size of the Sample

The studies reviewed exhibited a considerable range in sample sizes. The smallest sample comprised 25 participants[11], while the largest encompassed 1,900 individuals.[12] Among the total of 21 studies, 5 (23.8%) fell into the category of small studies, 11 (52.4%) were classified as medium-sized, and 5 (23.8%) were characterized as large-scale investigations (Figure 3). The collective mean sample size emerged at 544.52, while the median size stood at 355, revealing a positively skewed distribution across all studies. To accommodate potential variations in sample sizes influenced by diverse study design variants within the review, summary statistics were computed for both RCT studies and RCT-based post-hoc studies. This analysis unveiled a similar trend across individual study categories, with slightly greater variability in sample sizes observed among RCT studies in comparison to RCT-based post-hoc studies.

Study's Participants

Although the participant pool uniformly consisted of adult OHCA patients, the inclusion criteria exhibited heterogeneity. Notably, several studies differentiated participants based on variations in the patient's condition or demographic characteristics (Figure 4). Among the included studies,

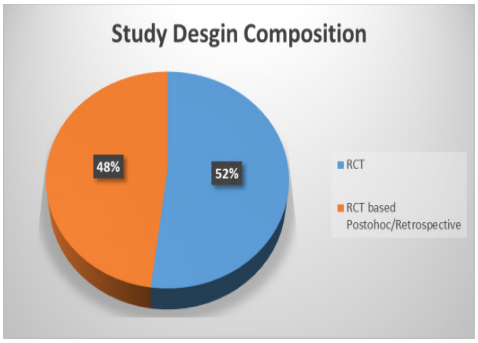


Figure 2: Study design composition

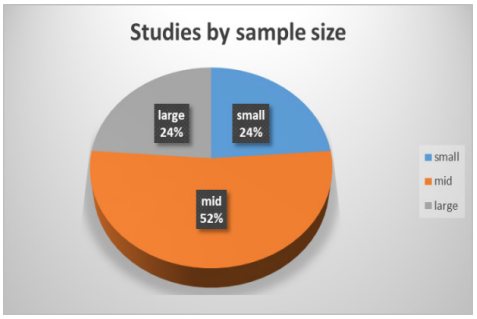


Figure: 3 Sample size

four explicitly included patients who had undergone cardiopulmonary resuscitation (CPR), while at least two included patients who had not. Three studies enrolled comatose patients after initial resuscitation, which indicates that patient conditions changed after initial resuscitation. Throughout all studies, cardiac arrest (CA) was commonly attributed to a cardiac origin, with the majority stating that cardiac arrest is the cause of cardiac arrest. While the study population was consistently study participants were aged 18 to 64 in two studies.[13] OHCA participants aged 65.5 years on average were included in their study, albeit exclusively male. Further intricacies surfaced as six studies incorporated A survivor of an OHCA who suffers from a specific condition, like hypertension or non-traumatic cardiac arrest, delineating the diversity within the participant cohort.

Study Interventions

All 21 included studies revolved around interventions centered on TTM. Table 1 illustrates the spectrum of TTM interventions vis-à-vis corresponding controls in each study. The table underscores the nuanced variations often interwoven into TTM versus control scenarios, encompassing factors like cooling methodologies. For instance,[14] probed the impact of TTM with two distinct rewarming rates 0.25°C/hour versus 0.15°C/hour showcasing an intervention variant that diverges within TTM itself. Thus, the control group often transcended a mere placebo, encompassing standard care or its derivatives, in contrast to the TTM intervention or its variations.

Table 2 offers a comparative summation of the intervention variants deployed across the reviewed studies' intervention-control pairs, encapsulating the frequency of specific intervention types. Notably, 24% (5 out of 21) studies utilized

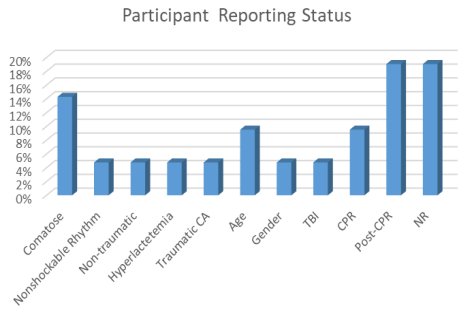


Figure 4: Reporting status overview of participants in all studies

a controls and plain TTM interventions are compared using placebos or standard care. Instances encompassed mild TTM. The use of mild therapeutic hypothermia compared with fever control[15] as well as TTM versus normothermia[16] is supported by research studies scenarios.[11,12,17] This category witnessed a spectrum of cooling methods, including intravascular and surface cooling in tandem with TTM intervention. Three studies aligned under temperature variation as an intervention, comprising mild TTM and room temperature,[18] and TTM at 32–34 and 35–36°C to evaluate OHCA outcomes.[19] Significantly, three studies juxtaposed TTM with additional therapies or medications, probing their effects on OHCA patients relative to plain TTM intervention.

In aggregate, the studies explored TTM's impact, incorporating diverse variables such as There are three factors that are important for treating this condition: time, temperature, and delayed onset or early onset outcomes. Figure 5 offers a graphical representation of these intervention types' comparative distribution. Notably, the presence of placebos, diverse standard treatments, augmented TTM interventions, and cooling method variations has generated an intricate tapestry within the TTM intervention review. These insights can be deciphered through hierarchical or clustered analyses, unravelling a treasure trove of patterns within these clusters and paving the way for a deeper comprehension of the nuanced intervention landscape.

Outcome Measures

Several pivotal outcomes emerged from the review of studies domains, with a pronounced emphasis on feasibility, safety, efficacy, and effectiveness within the context of TTM interventions. Feasibility emerged as a predominant primary outcome domain across most investigations (Figure 6), whereas safety emerged as the most frequently addressed secondary outcome domain (Figure 7). For instance,[20] centered their inquiry on the hydrogen intake efficacy combined with TTM for patients grappling with post-cardiac arrest syndrome stemming from OHCA. In this study, the primary focus rested on evaluating the effectiveness of the HI-augmented TTM intervention in comparison to the control group. Concurrently, A secondary intervention was explored by the researcher's focal point. Likewise,[13] delved into the effects of continuous infusion of a neuromuscular blocker in comatose OHCA patients undergoing TTM. In this context, the primary outcome domain centered on assessing NMB infusion: a feasibility study during TTM, while the secondary emphasis lay on ensuring the intervention's safety for patients. In essence, the reviewed studies uniformly converged on pivotal outcome areas encompassing feasibility, safety, efficacy, and effectiveness within the realm of TTM interventions, reflecting a comprehensive exploration of diverse dimensions associated with this therapeutic approach.

Reliability and Validity of Included Studies

Figure 8 illustrates noteworthy distinctions between the concepts of reliability, validity, and risk of bias, serving as a foundation for assessing the quality and bias risk of studies within this review. This assessment hinges on the divergent applications of these concepts. The review's reliability and validity hinge on factors such as study design, outcomes, and context, in contrast to bias risk assessment, which primarily centers on randomization and blinding. Notably, the majority of studies (Figure 8 and Table 3) demonstrated high reliability and validity, while instances of low reliability and validity were relatively scarce. The exemplar of robust reliability and validity can be drawn,[20] characterized by stringent adherence to standardized protocols throughout the research phases. Comparing risk of bias profiles with validity outcomes reveals an interesting divergence, underscoring that the composition of the study set within the review is influenced differently by these two distinct measures of study quality. These measures form the bedrock of the evaluation process, contributing distinct facets to the comprehensive evaluation of study quality and potential sources of bias.

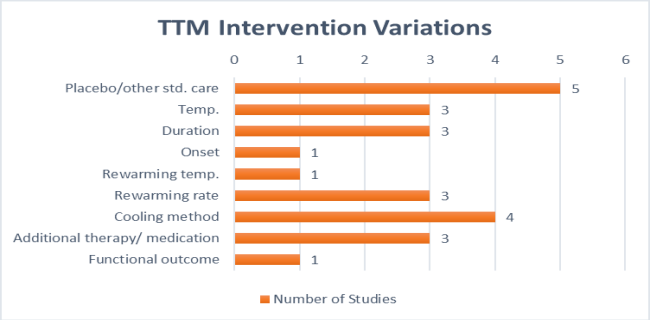


Figure 5: Study differences in intervention types examined in a comparative study

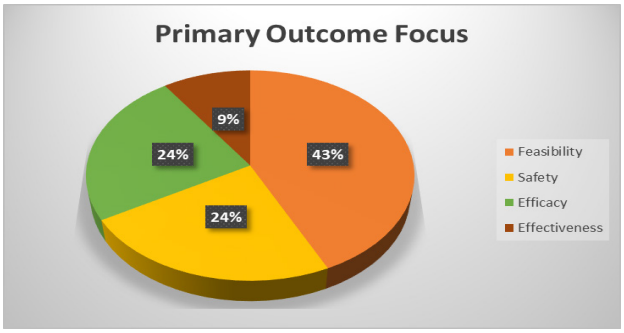


Figure 6: A breakdown of the studies according to their primary outcomes

Table 1: Observations in reviews of interventions

SI No.	*Author (s)*	*TTM intervention/ control*	*Note*
1	Kirkegaard *et al.,* (2017)	48/24 hours	Patients were randomized to TTM (33±1°C) for 48 hours (n=176) or 24 hours (n=179), followed by gradual rewarming of 0.5°C per hour until reaching 37°C
2	Lascarrow *et al.,* (2019)	Mild TTM/ Normothermia	Patients were randomized to moderate therapeutic hypothermia (TTM at 33+/- 5°C)durng the first 24 hours followed by slow rewarming to 36.5 to 37.5° Calso for 24 hours. This was the treatment group the control group condidted of patients assigned to normothermia group whose body temperatue was maintained ar 36.5 to 37.5°C for 48 hours according to the standard protocol in each ICU
3	Tamura *et al.,* (2017)	TTM with hydrogen intake (HI)/TTM with non-HI	Patients were randomized 1:1 to either the Hi group (hydrogen intake with 2% hydrogen and 24 to 50% oxygen inhalation) with TTM for 18 hours after admission via mechanical ventillation
4	Tahara *et al.,* (2021)	12/24 hours	-
5	Stanger *et al.,* (2019)	Early /delayed door to TTM initiation	-
6	Okazaki *et al.,* (2019)	TTM at 32-34/35-36°C	-
7	Oh *et al.,* (2015)	Surfave/endovascular cooling method	-

Table 2: A comparison of interventions and controls with variations

TTM intervention/ control	*Placebo/other std.care*	*Temp.*	*Duration onset*	*Rewarming temp*	*Rewarming rate*	*Cooling method*	*Additional therapy/ medication*	*Funvtional outcome*
48/24 hours			√					
Mild TTM/ Normaothermia		√		√	√			
TTM with hydrogen intake (Hi)/ TTM with non -Hi					√		√	
12/24 hours		√						
early /deayed Door to TTM initiation			√					
TTm at 32-34/35-36 deg C								
Surfave/ endoveasular cooling method	√					√		
Mild TTM/ No TTM								
TTM-NMB to TTM-place bo	√							
TTM ICD/TTM-SCD						√		
MTH/fever control								
TTM with fav functional outcome/TTM with unfav functional outcome								
TTM with SFC/TTM with IF C								
TTM with rewarming @ 025 deg/hr/TTM wuth rewarming @.15°/hour					√			
Theapwutic Hypothemia for 48 h/ normothermia after 72 hours	√							
Tocllizumab administration with TTM/Placebo with TTM								
Mild TTm (@33°C)/targeted normothermia	√							
Mild TTM fo 48/24 hours			√					
TTM at 32/36°C		√						

TTM through rapid indusion of 2ML cold saline / standard care	√							
Endovascular vs surface TTM								
Number of studies 96								
Number of students	5	3	3	1	1	3	3	1
%	24	14	14	5	5	14	14	5

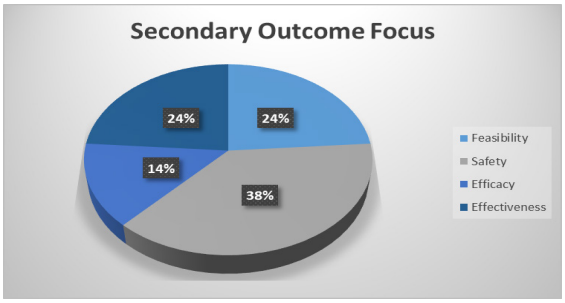


Figure 7: Secondary outcome focus in study composition

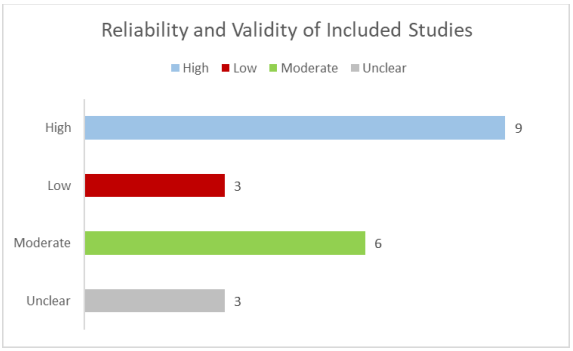
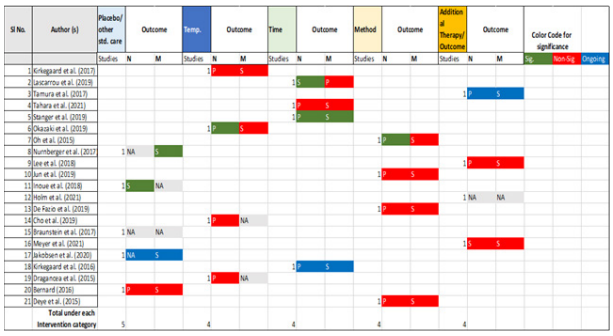


Figure 8: Composition of included studies by reliability and validity



N=Neurological; M=Mortality; P=Primary; S=Secondary; NA=Not Applicable

Figure 9: Results and outcomes of included studies are depicted in the following infographic

Table 3: Reliability and validity appraisal of some included studies

Study NO.	*Author (S)*	*High*	*Low*	*Moderate*	*Unclear*
1	Kirkegaard *et al.* (2017)	√			
2	Lascarrou *et al.* (2019)				√
3	Tamura *et al.* (2017)	√			
4	Tahara *et al,* (2021)		√		
5	Stanger *et al.* (2019)		√		
6	Okazaki *et al.* (2019)				√
7	Oh *et al.* (2019)				√
8	Nurnberger *et al.* (2017)			√	
9	Lee *et al.* (2018)			√	
10	Jun *et al.* (2019)			√	

Intervention Effects

As elucidated in the methods section, the evaluation process entails a comprehensive synthesis encompassing integration, interpretation, and thematic elucidation of intervention variables. Within the context of intervention outcomes, the survey initially undergoes categorization based on intervention variables, as depicted in Figure 5. However, this classification is subsequently refined, yielding five distinct categories: placebo/std care, temperature, time, (cooling) methods, and therapy intervention types of TTM. This nuanced grouping enhances precision. Following this classification, each study is subjected to an evaluative process, culminating in the graphical integration of neurological and interventional findings. Figure 9 serves as a visual representation of the synthesis and evaluation outcomes. Notably, the depicted pattern underscores that neurological outcomes predominantly occupy the primary outcome slot across most studies, with mortality rates constituting secondary outcomes. A secondary outcome is mortality in all three studies, whereas a primary outcome is neurological outcome in two of them. While a significant proportion of studies reflect non-significant outcomes, those that do exhibit significance frequently emanate from the time-based intervention variants of TTM. Within this subset, interventions concerning duration, onset, or cooling rate bear prominence. A distinctive instance emerges in the realm of mild TTM versus normothermia intervention, revealing a noteworthy finding on the survival rate at 90 days is at least 10%, which is a favorable and significant outcome. It's noteworthy, however, that this distinction didn't manifest between the hypothermia and non-hypothermia groups. Notably, within the placebo or standard therapy studies, two investigations, underscored significant secondary outcomes. The variance in evidence strength for placebo interventions is likely attributed to the risk of bias or comparatively lower study power. Conversely, weaker evidence for other interventions aligns more closely with the interventions' actual efficacy and performance, rather than methodological limitations. This comprehensive evaluation and synthesis framework offers a holistic understanding of intervention outcomes, their significance, and the contributing factors shaping these findings.

DISCUSSION

This systematic literature review synthesizes key findings categorized by intervention type, focusing on safety, feasibility, efficacy, efficiency, time, temperature, methods, and other treatment-based aspects in the context of TTM for major neurological disorders and mortality or survival endpoints in OHCA patients. Encompassing[21] studies with a total of 11,435 participants, the review underscores that while TTM intervention variants showcase relative safety, feasibility, efficiency, and efficacy for OHCA patients, the quantitative and qualitative evidence remains insufficient to definitively establish mortality outcomes. Notably, the median sample size was 355, with original RCTs demonstrating slightly larger samples compared to RCT-based post hoc studies. A predominant proportion of studies (48%) were rated as due to factors such as a lack of blinding, this study has moderate bias and deficiencies in randomization. Selection bias and measurement bias were frequently reported, often linked to deviations in result measurement due to suboptimal intervention indicator assessment. While most studies exhibited high validity (9 out of 21 studies), challenges in reliability were often attributed to small sample sizes and low study power. The presence of ongoing studies further contributes to the nuanced confidence levels regarding outcomes within this review.

CONCLUSION

Although the existing evidence and reliability exhibit limitations, a notable trend within many studies points towards future research endeavours employing the same interventional variants but with substantially larger sample sizes. This strategic approach aims to enhance the capacity to discern significant effects in neurological, survival, and additional outcome domains, thereby mitigating the risk of type I errors. Importantly, researchers are advised not to prematurely dismiss the potential of the interventions examined in this study. Instead, they are encouraged to persevere by delving into further exploration and research, strategically addressing and surmounting the reported limitations.

Study Implications

Presently, upon a qualitative synthesis and appraisal of quantitative evidence, the comprehensive evidence regarding the impact of TTM intervention variants exhibits significant limitations in terms of outcomes, barring the realm of time-based variants. Collectively, there exists a lack of conclusive evidence delineating distinct advantages or disadvantages associated with varied intervention variants concerning aspects such as safety, reliability, and efficiency. Notably, the discernment of TTM's value in contrast to placebos or supplementary treatments remains unresolved. Consequently, healthcare practitioners are recommended to duly consider these findings as they make informed decisions moving forward.

ACKNOWLEDGEMENTS

For the strength and blessing to write this dissertation, I am indebted to Allah, the most gracious and merciful. The King of Saudi Arabia's support and motivation made this master's degree possible, and this would not have been possible without their support and motivation throughout my study abroad experience. I received a great deal of information and learning from Queen Mary University of London.

REFERENCE

1. Arrich J, Holzer M, Havel C, Müllner M, Herkner H. Hypothermia for neuroprotection in adults after cardiopulmonary resuscitation. Cochrane Database Syst Rev. 2016 Feb 15;2(2):CD004128.
2. Kirkegaard H, Søreide E, de Haas I, Pettilä V, Taccone FS, Arus U, Storm C, Hassager C, Nielsen JF, Sørensen CA, Ilkjær S, Jeppesen AN, Grejs AM, Duez CHV, Hjort J, Larsen AI, Toome V, Tiainen M, Hästbacka J, Laitio T, Skrifvars MB. Targeted Temperature Management for 48 vs 24 Hours and Neurologic Outcome After Out-of-Hospital Cardiac Arrest: A Randomized Clinical Trial. JAMA. 2017 Jul 25;318(4):341-350.
3. Holzer M. Targeted temperature management for comatose survivors of cardiac arrest. N Engl J Med. 2010 Sep 23;363(13):1256-64.
4. Callaway CW, Donnino MW, Fink EL, Geocadin RG, Golan E, Kern KB, Leary M, Meurer WJ, Peberdy MA, Thompson TM, Zimmerman JL. Part 8: Post-Cardiac Arrest Care: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2015 Nov 3;132 (18 Suppl 2): S465-82.
5. Soar J, Nolan JP, Böttiger BW, Perkins GD, Lott C, Carli P, Pellis T, Sandroni C, Skrifvars MB, Smith GB, Sunde K, Deakin CD; Adult advanced life support section Collaborators. European Resuscitation Council Guidelines for Resuscitation 2015: Section 3. Adult advanced life support. Resuscitation. 2015 Oct; 95:100-47.
6. Hifumi T, Sakai A, Kondo Y, Yamamoto A, Morine N, Ato M, Shibayama K, Umezawa K, Kiriu N, Kato H, Koido Y, Inoue J, Kawakita K, Kuroda Y. Venomous snake bites: clinical diagnosis and treatment. J Intensive Care. 2015 Apr 1;3(1):16.
7. Nagao A, Mituyama T, Huang H, Chen D, Siomi MC, Siomi H. Biogenesis pathways of piRNAs loaded onto AGO3 in the Drosophila testis. RNA. 2010 Dec;16(12):2503-15.
8. Vivian Bih Che, Karen Fontijn, Gerald G.J. Ernst, Matthieu Kervyn, Marlina Elburg, Eric Van Ranst, Cheo Emmanuel Suh. Evaluating the degree of weathering in landslide-prone soils in the humid tropics: The case of Limbe, SW Cameroon. 2012; 170: 378–389,
9. Suh J, Eigsti IM, Naigles L, Barton M, Kelley E, Fein D. Narrative performance of optimal outcome children and adolescents with a history of an Autism Spectrum Disorder (ASD). J Autism Dev Disord. 2014 Jul;44(7):1681-94.
10. Okoli, Chitu. "A Guide to Conducting a Standalone Systematic Literature Review," Communications of the Association for Information Systems. 2015; Vol. 37, Article 43.
11. Braunstein LM, Gross JJ, Ochsner KN. Explicit and implicit emotion regulation: a multi-level framework. Soc Cogn Affect Neurosci. 2017 Oct 1;12(10):1545-1557.
12. Jakobsen, I.S., Madsen, L.M.R., Mau, M. *et al.* The relationship between resilience and loneliness elucidated by a Danish version of the resilience scale for adults. BMC Psychol. 2020; 8: 131.
13. Lee, J.J., Wedow, R., Okbay, A. *et al.* Gene discovery and polygenic prediction from a genome-wide association study of educational attainment in 1.1 million individuals. Nat Genet.

2018; 50: 1112–1121.
14. Cho NH, Shaw JE, Karuranga S, Huang Y, da Rocha Fernandes JD, Ohlrogge AW, Malanda B. IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. Diabetes Res Clin Pract. 2018 Apr; 138:271-281.
15. Gust AA, Pruitt R, Nürnberger T. Sensing Danger: Key to Activating Plant Immunity. Trends Plant Sci. 2017 Sep;22(9):779-791.
16. Inoue Y, Qin B, Poti J, Sokol R, Gordon-Larsen P. Epidemiology of Obesity in Adults: Latest Trends. Curr Obes Rep. 2018 Dec;7(4):276-288.
17. Deye N, Cariou A, Girardie P, Pichon N, Megarbane B, Midez P, Tonnelier JM, Boulain T, Outin H, Delahaye A, Cravoisy A, Mercat A, Blanc P, Santré C, Quintard H, Brivet F, Charpentier J, Garrigue D, Francois B, Quenot JP, Vincent F, Gueugniaud PY, Mira JP, Carli P, Vicaut E, Baud FJ; Clinical and Economical Impact of Endovascular Cooling in the Management of Cardiac Arrest (ICEREA) Study Group. Endovascular Versus External Targeted Temperature Management for Patients With Out-of-Hospital Cardiac Arrest: A Randomized, Controlled Study. Circulation. 2015 Jul 21;132(3):182-93.
18. Lascarrou JB, Merdji H, Le Gouge A, Colin G, Grillet G, Girardie P, Coupez E, Dequin PF, Cariou A, Boulain T, Brule N, Frat JP, Asfar P, Pichon N, Landais M, Plantefeve G, Quenot JP, Chakarian JC, Sirodot M, Legriel S, Letheulle J, Thevenin D, Desachy A, Delahaye A, Botoc V, Vimeux S, Martino F, Giraudeau B, Reignier J; CRICS-TRIGGERSEP Group. Targeted Temperature Management for Cardiac Arrest with Nonshockable Rhythm. N Engl J Med. 2019 Dec 12;381(24):2327-2337.
19. Okazaki, Ki., Wöhlert, D., Warnau, J. *et al.* Mechanism of the electroneutral sodium/proton antiporter PaNhaP from transition-path shooting. Nat Commun. 2019; 10: 1742.
20. Tamura M, Sakurai H, Mizumoto M, Kamizawa S, Murayama S, Yamashita H, Takao S, Suzuki R, Shirato H, Ito YM. Lifetime attributable risk of radiation-induced secondary cancer from proton beam therapy compared with that of intensity-modulated X-ray therapy in randomly sampled pediatric cancer patients. J Radiat Res. 2017 May 1;58(3):363-371