Target Temperature Management Following Pediatric Cardiac Arrest: A Systematic Review and Network Meta-Analysis to Compare the Effectiveness of the Length of Therapeutic Hypothermia

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Abstract

We aimed to compare the efficacy of therapeutic hypothermia for 24, 48, and 72 h, and normothermia following pediatric cardiac arrest. We searched the Cochrane Central Register of Controlled Trials, MEDLINE via Ovid, World Health Organization International Clinical Trials Platform Search Portal, and ClinicalTrials.gov, from their inception to December 2021. We included randomized controlled trials and observational studies evaluating target temperature management (TTM) in children aged <18 years with the return of spontaneous circulation (ROSC) after cardiac arrest. We compared four intervention groups (normothermia, therapeutic hypothermia for 24 h (TTM 24h), therapeutic hypothermia for 48 h (TTM 48h), and therapeutic hypothermia for 72 h (TTM 72h)) using network meta-analysis. The outcomes were survival and favorable neurological outcome at 6 months or more. Seven studies involving 1088 patients and four studies involving 684 patients were included in the quantitative synthesis of survival and neurological outcome, respectively. TTM for 72 h was associated with a higher survival rate, compared to normothermia (RR 1.75 (95% CI 1.27–2.40)) (very low certainty), and TTM 24h (RR 1.53 (95% CI 1.06–2.19)) (low certainty), TTM 48h (RR 1.54 (95% CI 1.06–2.22)) (very low certainty). TTM for 72 h was also associated with favorable neurological outcomes compared with normothermia (RR 9.36 (95% CI 2.04–42.91)), or TTM 48h (RR 8.15 (95% CI 1.6–40.59)) (all very low certainty). TTM for 24 h was associated with favorable neurological outcome, compared with normothermia (RR 8.02 (95% CI 1.28-50.50)) (very low certainty). In the ranking analysis, the hierarchies for efficacy for survival and favorable neurological outcome were TTM 72h > TTM 48h > TTM 24h > normothermia. Although prolonged therapeutic hypothermia might be effective in pediatric patients with ROSC after cardiac arrest, the evidence to support this result is only weak to very weak. There is no conclusive evidence regarding the effectiveness and length of therapeutic hypothermia and high-quality RCTs comparing long-length therapeutic hypothermia to short-length hypothermia and normothermia are needed.

Introduction And Background

Cardiac arrest often results in death or poor neurological outcome in survivors and is, thus, a significant health burden worldwide. Although cardiac arrest is uncommon in children, their public health burden is high given the potential years of life lost and the length of time that a child may survive with sequelae [1,2]. Hypoxic-ischemic brain injury is the major cause of poor neurological outcomes in survivors of cardiac arrest [3]. As a brain-protective therapy for patients with return of sustained circulation (ROSC), target temperature management (TTM), such as therapeutic normothermia or hypothermia, may be used. TTM is thought to reduce hypoxic-ischemic brain injury by decreasing the cerebral metabolic rate, mitigating reperfusion injury, and inhibiting pathways that lead to neuronal death [4]. The guidelines for post-resuscitation care from the European Resuscitation Council and the American Heart Association recommend TTM for comatose adults after ROSC [5-8]. Therapeutic hypothermia has also been shown to be effective in newborns with birth anoxia [9]. However, it is difficult to directly apply evidence on TTM from newborns with birth anoxia and adults to children after cardiac arrest.

Several observational studies have demonstrated the safety of TTM in children. Randomized controlled trials (RCTs) on the use of TTM in children after cardiac arrest have been published in 2015 and 2017 [10,11]. However, these studies did not demonstrate the efficacy of therapeutic hypothermia in children after a cardiac arrest. A systematic review/meta-analysis published in 2019 did not find any results that supported...
or rejected the use of hypothermia [12]. Although the duration of therapeutic hypothermia is considered important, previous studies have shown that therapeutic hypothermia is conducted for various durations, including 24 h, 48 h, and 72 h [10,11,13-24]. While current guidelines recommend TTM, there is no mention of the appropriate temperature or length of the treatment [7,8]. Therefore, the comparative effectiveness of different TTM durations in improving survival and neurological outcomes remains unclear.

To compare the efficacy of therapeutic hypothermia of different durations and therapeutic normothermia, we conducted a systematic review and network meta-analysis of observational studies and RCTs to evaluate the relative efficacy of four post-resuscitation target temperatures in comatose patients following cardiac arrest, namely, TTM with normothermia (more than 35.1°C), TTM with induced hypothermia (32-35°C) for 24 h, TTM with induced hypothermia (32-35°C) for 48 h, and TTM with induced hypothermia (32-35°C) for 72 h.

**Review**

**Materials and methods**

**Protocol and Registration**

This systematic review was designed based on the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) extension statements for reporting systematic reviews that incorporate network meta-analysis [25]. The review protocol was registered in PROSPERO (CRD42021258215).

**Studies, Participants, Interventions/Comparators, and Outcomes**

We included RCTs and prospective and retrospective non-randomized studies with a comparator group (non-randomized controlled trials, interrupted time series, controlled before-and-after studies, and cohort studies) in all languages. Cluster randomized trials, crossover trials, case reports or case series, review articles, editorials, and comments were excluded. This meta-analysis included pediatric patients < 18 years of age with ROSC after in-hospital and out-of-hospital cardiac arrest who are in a comatose state. Studies on neonates with perinatal asphyxia were excluded. We included studies that compared at least two of the following four TTM parameters: (1) TTM with normothermia (more than 35.1°C); (2) TTM with induced hypothermia (32-35°C) for 24 h (TTM 24h); (3) TTM with induced hypothermia (32-35°C) for 48 h (TTM 48h); and (4) TTM with induced hypothermia (32-35°C) for 72 h (TTM 72h). We divided the patients into the four intervention groups according to body temperature and TTM length and compared the four groups using a network meta-analysis. Studies with no specifically identified TTM but which reported body temperature were included in the normothermia group thus allowing us to confirm a normal body temperature in patients. Studies that did not report body temperatures and studies with varying TTM times were not included in the quantitative analysis, and qualitative evaluations were conducted.

The primary outcome was the survival rate at discharge or at the longest timepoint described in the studies. The secondary outcome was the rate of a favorable neurological outcome (defined as a Pediatric Cerebral Performance Category 1-5, Cerebral Performance Category 1-2, Glasgow Outcome Scale 4-5, VABS-II score ≥70) at the longest timepoint ≥6 months, as described in the studies [26-28].

**Data Sources and Search Details**

The Cochrane Central Register of Controlled Trials (CENTRAL) and MEDLINE via Ovid were searched for eligible published trials. The World Health Organization International Clinical Trials Platform Search Portal (ICTRP) and ClinicalTrials.gov trial registries were also searched for ongoing trials. If data were missing, we attempted to contact the authors of the study. The search was performed on December 1, 2021. Details of the search strategy and the performed searches are presented in Appendix: Table 10.

**Study Selection, Data Collection Process, and Data items**

Citations were documented and duplicates were removed using EndNote software (Thomson Reuters, Toronto, Ontario, Canada). Rayyan software was used for the systematic review. The titles and/or summaries of studies retrieved using the search strategy as well as summaries of studies from additional sources were individually screened by two authors (OT and SK) to determine whether they met the selection criteria described above. The full texts of potentially eligible studies were retrieved and independently assessed for eligibility by two review team members (OT and SK). Any disagreements regarding study eligibility were resolved through discussion with a third reviewer (SA). A standardized pre-pilot form was used to extract data from the included studies and to assess the quality of the studies and synthesis of the evidence. The following information was extracted for analysis: baseline characteristics of the study population and participants, details of the intervention and control conditions, study methodology, outcomes and timepoints of measurement, and information to assess the risk of bias. Two review authors (OT and SK) independently extracted the data, and discrepancies were identified and resolved through discussion with a third author (SA), as necessary.
Risk of Bias Assessment Within Individual Studies

We evaluated the risk of bias in RCTs using the Cochrane Risk of Bias tool 2.0 including bias arising from the randomization process, bias due to deviations from the intended interventions, bias due to missing outcome data, bias in the measurement of the outcomes, and bias in the selection of the reported results [29]. We then classified each study as having low risk, some concerns, or high risk of bias for each of these risk of bias categories. Discrepancies between the two authors were resolved through discussions that included the third author.

We evaluated the risk of bias of non-RCTs using the ROBINS-I tools for non-RCT risk of bias assessment (observational studies) in various domains, namely, bias due to confounding factors, bias in the selection of the study participants, bias in the classification of interventions, bias due to deviations from the intended interventions, bias due to missing data, bias in the measurement of outcomes, and bias in the selection of the reported results [30]. We then classified each study as having low, moderate, serious, or critical risk, or having no information on bias for each item. Discrepancies between the two authors were resolved through a discussion that included the third author.

Statistical Analysis

A network plot was constructed to determine the number of studies and patients included in the meta-analysis. Network meta-analysis (NMA) was performed with the "netmeta 2.0-1" R package (version 4.1.2) using a frequency-based approach with multivariate random effects meta-analysis, and the effect sizes were expressed as RR (95% CI). The certainty of the evidence of the network effect estimate was evaluated based on the following factors using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) working-group approach of the NMA.

The underlying transitivity assumptions of the NMA were assessed by comparing the distributions of clinical and methodological variables that may serve as effect modifiers across treatment comparisons. The assessment of the risk of bias between studies followed the considerations of pairwise meta-analyses. The conditions associated with ‘suspicious’ and ‘undetected’ bias across studies were determined by the presence of publication bias, as indicated by direct comparisons. The indirectness of each study included in the network was assessed according to its relevance to the research question, consisting of the study population, intervention, outcome, and study setting, and was categorized as low, medium, or high. Study-level judgments could be combined into a contribution matrix. The approach for imprecision involved comparing the range of treatment effects included in the 95% CI with the range of equivalence. The heterogeneity of the treatment effect for clinically important risk ratios (<0.8 or > 1.25) in the CI was assessed. To assess the amount of heterogeneity, we compared the posterior distribution of the estimated heterogeneity variance with its predicted distribution [31]. The CI-based assessment and agreement between the prediction intervals were used to assess the importance of heterogeneity with or without capturing heterogeneity. The heterogeneity of the treatment effect was assessed when the clinically important risk ratio was <0.8 or >1.25 in the prediction interval. Inconsistencies in the network model were estimated from the inconsistency factors and their uncertainty, and consistency was statistically assessed using a design-by-design interaction test [32]. For comparisons informed only by direct evidence, there were no inconsistencies between sources of evidence, and thus "no concern" of inconsistency. When only indirect evidence was included, there was always "some concern." "Major concern" was considered when the p-value of the interaction test per treatment was <0.01.

As a ranking analysis, the P-score was calculated from the point estimate of the network and the standard error. A treatment’s P-score can be interpreted as the average degree of confidence that the treatment is superior to others.

Results

Study Selection

We identified 1499 articles in the search and screened 1344 articles following the removal of duplicates (Figure 1). Of these, 80 articles were retained for a full-text review. We contacted the investigators of an unpublished study registered on ClinicalTrials.gov. but did not receive an answer. After review, 14 studies [10,11,13-24] were included in the qualitative analysis and 7 studies [10,11,13-17] in the quantitative synthesis (NMA). The reasons for not including 7 studies [18-24] in the quantitative analysis are given in Table 2.
**FIGURE 1: Flowchart of included studies**
| Study               | Survival | Neurological outcome | Narrative summary                                                                 | Reasons for exclusion from quantitative synthesis |
|--------------------|----------|----------------------|-------------------------------------------------------------------------------------|---------------------------------------------------|
| Fink et al., 2010  | Hospital discharge | PCPC at hospital discharge | TTM was not significantly associated with survival and favorable neurological outcome. | NA                                                |
| Lin et al., 2013   | Hospital discharge | PCPC at hospital discharge | TTM was significantly associated with survival and not significantly associated with favorable neurological outcome. | NA                                                |
| Scholefield et al., 2015 | Hospital discharge | NA | TTM was not significantly associated with survival. Point estimate was TTM-dominant. | NA                                                |
| Moler et al., 2015 | 12 months | VABS-II score at 12 months | TTM was not significantly associated with survival and favorable neurological outcome. Point estimate was TTM-dominant. | NA                                                |
| Moler et al., 2017 | 12 months | VABS-II score at 12 months | TTM was not significantly associated with survival and favorable neurological outcome. | NA                                                |
| Lin et al., 2018   | 6 months | PCPC at 6 months | TTM was significantly associated with survival and favorable neurological outcome. | NA                                                |
| Fink et al., 2018  | 6 months | PCPC at 6 months | TTM 72h was not significantly associated with survival and favorable neurological outcome. Point estimate for survival was TTM 72h-dominant. | NA                                                |
| Studies not included in quantitative synthesis but included in qualitative analysis | | | | |
| Doherty et al., 2009 | 6 months | PCPC at 6 months | TTM was not significantly associated with survival and favorable neurological outcome. | Length of therapeutic hypothermia varied. |
| Buttram et al., 2010 | Hospital discharge | PCPC at hospital discharge | TTM was not significantly associated with survival and favorable neurological outcome. Point estimate was TTM dominant. | Length of therapeutic hypothermia not reported. |
| van Zelem et al., 2015 | Hospital discharge | NA | TTM was not significantly associated with survival. | Body temperature of no TTM group was not reported. |
| Chang et al., 2016  | Hospital discharge | CPC at hospital discharge | TTM was not significantly associated with survival and favorable neurological outcome. | Length of therapeutic hypothermia varied. |
| Cheng et al., 2018  | Hospital discharge | NA | TTM was not significantly associated with survival. | Body temperature of no TTM group was low (mean 34.7°C). |
| Matsui et al., 2021 | 1 month | PCPC at 1 month | TTM was not significantly associated with survival and good neurological outcome. | Length of therapeutic hypothermia varied. |
| Magee et al., 2021  | NA | Health-related quality of life at 3.8 years (median) | TTM was significantly associated with good neurological outcome. | Length of therapeutic hypothermia varied. |

**TABLE 1: Study characteristics-1**

The characteristics of the included studies are shown in Tables 1, 2, and 3. Of the 7 studies included in the NMA, 3 were RCTs and 4 were observational studies. The 7 studies included only in the qualitative analyses were observational.
| Study                          | Years of recruitment | Country of recruitment | Study type     | Therapeutic hypothermia | Length | Comparator | Number of patients Treatment/Comparator |
|-------------------------------|----------------------|------------------------|----------------|--------------------------|--------|------------|----------------------------------------|
| Fink et al., 2010 [13]        | 2000–2006            | US                     | Observational study | 33–35°C                      | 24h    | No TTM: 35.4 (33.5–36.3)                   | 40/141                              |
| Lin et al., 2013 [14]         | 2010–2012            | Taiwan                 | Observational study | 32–34°C                      | 72h    | Normothermia                                  | 14/28                               |
| Scholefield et al., 2015 [15] | 2004–2010            | UK                     | Observational study | 32–34°C                      | 24h    | TTM<38°C                                     | 38/35                               |
| Moler et al., 2015 [10]       | 2009–2012            | US                     | RCT             | 32–34°C                      | 48h    | TTM 36–37.5°C                               | 151/136                             |
| Moler et al., 2017 [11]       | 2009–2015            | US                     | RCT             | 32–34°C                      | 48h    | TTM 36–37.5°C                               | 166/161                             |
| Lin et al., 2018 [16]         | 2010–2017            | Taiwan                 | Observational study | 32–34°C                      | 72h    | TTM 35.5–37.5°C                             | 25/39                               |
| Fink et al., 2018 [17]        | 2009–2013            | US                     | RCT             | 32–34°C                      | 24h    | TTM 72h                                     | 17/17                               |
| Doherty et al., 2009 [19]     | 2001–2003            | Canada and UK          | Observational study | <35°C                        | Variable | No TTM                                    | 29/50                               |
| Buttram et al., 2010 [20]     | 2007–2009            | US                     | Observational study | NA                          | NA     | No TTM                                     | 33/13                               |
| van Zellem et al., 2015 [18]  | 2002–2011            | Netherlands            | Observational study | 32–34°C                      | 24h    | No TTM                                     | 63/137                              |
| Chang et al., 2016 [21]       | 2008–2014            | Korea                  | Observational study | 32–34°C                      | Variable | No TTM                                   | 81/562                              |
| Cheng et al., 2018 [22]       | 2012–2015            | US                     | Observational study | 32–34°C                      | 48h (≥1y), 72h (<1y) | No TTM                                    | 26/49                               |
| Matsui et al., 2021 [23]      | 2014–2017            | Japan                  | Observational study | 33–36°C                      | Variable | No TTM                                   | 47/120                              |
| Magee et al., 2021 [24]       | 2012–2017            | Australia              | Observational study | 33–34°C                      | Variable | No TTM                                   | 50/78                               |

**TABLE 2: Study characteristics-2**
### TABLE 3: Study characteristics-3

A total of 1008 patients were included in the NMA. The studies were published between 2010 and 2018, with patient recruitment conducted from 2000 to 2017. Three studies exclusively included patients with out-of-hospital cardiac arrest, one exclusively included patients with in-hospital cardiac arrest, and the remaining three studies included mixed populations, regardless of the location where the cardiac arrest occurred. Three different durations of TTM and normothermia were evaluated: 24h (n = 95, 9.4%), 48h (n = 317, 31.4%), 72h (n = 56, 5.6%), and normothermia (n = 540, 53.6%).

**Risk of Bias Within Individual Studies**

The risk of bias within the included studies is shown in Table 4-7. The risk of bias of 2 RCTs was low in all domains [10,11] and the risk of bias in 1 small RCT was classified as having "some concern" [17]. Among the 5 observational studies, the risk of bias in 3 studies was determined to be "serious", due to bias in the classification of interventions [13,14,16], with the risk of bias in the other 1 study was determined to be "moderate" [15].

| Study | Intervention | Number of patients | Age (years) (median, IQR) | Gender, male (%) | Cardiac history | Presumed cardiac cause of arrest | Presumed asphyxia cause of arrest | In-hospital cardiac arrest | Initial shockable rhythms | Witnessed arrest | Bystander CPR | Duration of CPR |
|-------|--------------|-------------------|---------------------------|------------------|----------------|-------------------------------|-----------------------------|------------------------|------------------|---------------|---------------|----------------|
| Fink et al., 2010 [10] | TTM 24h | 40 | 2.4 (0.4-11.8) | NA | 24 | 5 | NA | 16 | 24 | 3 | 25 | NA | 15 (10-26) |
| No TTM | 141 | 2.9 (1.1-11.1) | NA | 82 | 9 | NA | 78 | 63 | 16 | 111 | NA | 8 (3-15) |
| Lin et al., 2013 [14] | TTM 72h | 14 | NA | 10 | 2 | 1 | 14 | 6 | 9 | 1 | NA | NA | mean 20.56±6.35 |
| No TTM | 30 | NA | 18 | 0 | 0 | 28 | 8 | 20 | 0 | NA | NA | mean 24.83±22.2 |
| Scholefield et al., 2015 [15] | TTM 24h | 38 | 1.5 (0-5.8) | NA | 17 | 1 | 4 | NA | 0 | 26 | 5 | 23 | 30 | 16 (26-56) |
| Normothermia | 35 | 1.0 (0-4.0) | NA | 8 | 3 | 1 | NA | 0 | 35 | 1 | 22 | 15 | 29 (21-46) |
| Moler et al., 2015 [10] | TTM 48h | 151 | 2.1 (0-10.1) | 132 | 14 | 14 | 111 | 0 | 155 | 14 | 58 | 101 | 23 (15-35) |
| Normothermia | 136 | 1.6 (0-7.0) | 94 | 21 | 18 | 102 | 0 | 140 | 9 | 51 | 85 | 28 (19-45) |
| Moler et al., 2017 [11] | TTM 48h | 166 | 1.4 (0-5.7) | 97 | 163 | 89 | 45 | 168 | 0 | 17 | NA | 186 | 23 (7-42) |
| Normothermia | 161 | 0.6 (0-2.4) | 89 | 146 | 74 | 55 | 163 | 0 | 17 | NA | 163 | 22 (7-61) |
| Lin et al., 2018 [16] | TTM 72h | 25 | NA | 21 | NA | 0 | 25 | 0 | 25 | 0 | 12 | 4 | mean 25.5±15.48 |
| Normothermia | 39 | NA | 28 | NA | 0 | 39 | 0 | 39 | 0 | 25 | 8 | mean 26.0±16.77 |
| Fink et al., 2018 [17] | TTM 72h | 17 | 4.6 (3-3.0) | 9 | NA | 1 | 16 | 3 | 14 | 0 | 5 | 13 | 17 (10-27.5) |
| TTM 24h | 17 | 5.7 (3-12.7) | 5 | NA | 3 | 14 | 3 | 14 | 1 | 7 | 14 | 25.5 (17.5-30) |
| Study                  | Randomization process | Deviations from intended interventions | Missing outcome data | Measurement of the outcome | Selection of the reported result | Overall bias |
|-----------------------|-----------------------|----------------------------------------|---------------------|---------------------------|---------------------------------|--------------|
| Moler et al., 2015    | Low                   | Low                                    | Low                 | Low                       | Low                             | Low          |
| Moler et al., 2017    | Low                   | Low                                    | Low                 | Low                       | Low                             | Low          |
| Fink et al., 2018     | Low                   | Some concern                           | Low                 | Low                       | Low                             | Some concern |

**TABLE 4: Risk of bias for survival of randomized controlled trials**

| Study                  | Bias due to confounding | Bias due to selection participants | Bias in classification interventions | Bias due to deviations from intended interventions | Bias due to missing date | Bias in measurement of outcomes | Bias in selection of the reported result | Overall bias |
|-----------------------|-------------------------|------------------------------------|--------------------------------------|--------------------------------------------------|------------------------|----------------------------------|------------------------------------------|--------------|
| Fink et al., 2010     | Moderate                | Moderate                            | Serious                              | Moderate                                         | Low                    | Low                              | Low                                      | Serious       |
| Lin et al., 2013      | Serious                 | Moderate                            | Serious                              | Moderate                                         | Low                    | Low                              | Low                                      | Serious       |
| Scholefield et al., 2015 | Moderate              | Low                                 | Moderate                             | Low                                              | Low                    | Low                              | Low                                      | Moderate      |
| Lin et al., 2018      | Moderate                | Moderate                            | Serious                              | Moderate                                         | Low                    | Low                              | Low                                      | Serious       |

**TABLE 5: Risk of bias for the neurological outcome of randomized controlled trials**

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**TABLE 6: Risk of bias for survival of observational studies**
Study | Bias due to confounding | Bias due to selection participants | Bias in classification interventions | Bias due to deviations from intended interventions | Bias due to missing date | Bias in measurement of outcomes | Bias in selection of the reported result | Overall bias
---|---|---|---|---|---|---|---|---
Lin et al., 2018 [16] | Moderate | Moderate | Serious | Moderate | Low | Moderate | Low | Serious

### TABLE 7: Risk of bias for neurological outcome of observational studies

**Survival at Discharge or the Longest Timepoint Described in the Studies**

Survival was reported in 7 studies, which included 1008 patients, with the network plot for survival shown in Figure 2. Pairwise comparisons are shown in Figure 3. Pairwise comparison from a small observational study showed that 72h TTM was associated with a significantly higher rate of survival than normothermia, with network estimates shown in Table 8 and Figure 4. TTM 72h was associated with a higher survival rate, compared with normothermia (RR 1.75 (95% CI 1.27-2.40)), TTM 24h (RR 1.53 (95% CI 1.06-2.19)), or TTM 48h (RR 1.54 (95% CI 1.06-2.22)). We did not find any association in the other comparisons. A summary of the confidence in the network estimates is shown in Table 9. The certainty in the network estimates was moderate for TTM 48h vs normothermia, low for TTM 72h vs TTM 24h; very low for TTM 24h vs normothermia, TTM 72h vs normothermia, TTM 48h vs TTM 24h, and TTM 72h vs TTM 48h. The P-scores for survival are shown in Table 10. The hierarchy for efficacy in survival was TTM 72h (P-score 0.99) > TTM 48h (P-score 0.47) > TTM 24h (P-score 0.44) > normothermia (P-score 0.10).

![Network plot for A: survival and B: Favorable neurological outcome](image)

**FIGURE 2: Network plot for A: survival and B: Favorable neurological outcome**

The node size corresponds to the number of patients who received the intervention. The thickness of the line corresponds to the number of studies that compared the two linked interventions.
[a] Survival at RCTs

(a-1) TTM 48h vs Normothermia

| Comparison | Direct estimate RR (95% CI) | Indirect estimate RR (95% CI) | Network estimate RR (95% CI) | Certainty of evidence for NMA |
|------------|-----------------------------|------------------------------|------------------------------|-----------------------------|
| TTM 48h vs Normothermia | 1.12 (0.82–1.34) | 1.24 (0.66–2.35) | 1.14 (0.84–1.55) | Very low |
| TTM 48h vs Normothermia | 1.14 (0.94–1.37) | NA | 1.14 (0.94–1.37) | Moderate |
| TTM 72h vs Normothermia | 1.80 (1.24–2.60) | 1.61 (0.86–3.00) | 1.75 (1.27–2.40) | Very low |
| TTM 48h vs TTM 24h | NA | 0.99 (0.70–1.42) | 0.99 (0.70–1.42) | Very low |
| TTM 72h vs TTM 24h | 1.45 (0.86–2.43) | 1.61 (0.97–2.67) | 1.53 (1.06–2.19) | Low |
| TTM 72h vs TTM 48h | NA | 1.54 (1.06–2.22) | 1.54 (1.06–2.22) | Very low |

(b-1) TTM 48h vs Normothermia

(b-2) TTM 72h vs Normothermia

(b-3) TTM 72h vs Normothermia

(b-4) TTM 72h vs Normothermia

[FIGURE 3: Forest plots for the pairwise comparison of survival]

TTM 72h was associated with a higher survival rate compared to normothermia. We did not find any association in the other comparisons.

TABLE 8: Network estimates for survival

| Comparison | Direct estimate RR (95% CI) | Indirect estimate RR (95% CI) | Network estimate RR (95% CI) | Certainty of evidence for NMA |
|------------|-----------------------------|------------------------------|------------------------------|-----------------------------|
| TTM 48h vs Normothermia | 1.12 (0.82–1.34) | 1.24 (0.66–2.35) | 1.14 (0.84–1.55) | Very low |
| TTM 48h vs Normothermia | 1.14 (0.94–1.37) | NA | 1.14 (0.94–1.37) | Moderate |
| TTM 72h vs Normothermia | 1.80 (1.24–2.60) | 1.61 (0.86–3.00) | 1.75 (1.27–2.40) | Very low |
| TTM 48h vs TTM 24h | NA | 0.99 (0.70–1.42) | 0.99 (0.70–1.42) | Very low |
| TTM 72h vs TTM 24h | 1.45 (0.86–2.43) | 1.61 (0.97–2.67) | 1.53 (1.06–2.19) | Low |
| TTM 72h vs TTM 48h | NA | 1.54 (1.06–2.22) | 1.54 (1.06–2.22) | Very low |
FIGURE 4: Forest plot of network estimate for survival

TTM 72h was associated with survival, compared with no TTM/normothermia, TTM 24h, or TTM 48h. We did not find any association in the other comparisons.

| Comparison                     | Number of studies | Within-study bias | Reporting bias | Indirectness | Imprecision | Heterogeneity | Incoherence | Confidence rating |
|--------------------------------|-------------------|-------------------|----------------|--------------|-------------|---------------|--------------|-------------------|
| TTM 24h vs Normothermia        | 2                 | Some concerns     | Not suggested  | No concerns  | Some concerns| No concerns   | No concerns   | Very low          |
| TTM 48h vs Normothermia        | 2                 | No concerns       | Not suggested  | No concerns  | Some concerns| No concerns   | No concerns   | Moderate          |
| TTM 72h vs Normothermia        | 2                 | Major concerns    | Not suggested  | No concerns  | No concerns  | No concerns   | No concerns   | Very low          |
| TTM 48h vs TTM 24h             | 0                 | Some concerns     | Not suggested  | No concerns  | Major concerns| No concerns   | No concerns   | Very low          |
| TTM 72h vs TTM 24h             | 1                 | Some concerns     | Not suggested  | No concerns  | No concerns  | Some concerns| No concerns   | Low               |
| TTM 72h vs TTM 48h             | 0                 | Some concerns     | Not suggested  | No concerns  | No concerns  | Some concerns| No concerns   | Very low          |

TABLE 9: Summary of confidence in network estimates for survival

| Treatment     | P-score for survival | P-score for favorable neurological outcome |
|---------------|-----------------------|-------------------------------------------|
| Normothermia  | 0.10                  | 0.10                                      |
| TTM 24h       | 0.44                  | 0.25                                      |
| TTM 48h       | 0.47                  | 0.78                                      |
| TTM 72h       | 0.99                  | 0.87                                      |

TABLE 10: P-scores of treatments
Favorable neurological outcomes at the longest timepoint of ≥6 months were reported in 4 studies including a total of 684 patients, with the network plot for favorable neurological outcomes shown in Figure 2. The pairwise comparisons are shown in Figure 5. Only 1 small observational study showed that 72h TTM was associated with a significantly higher rate of favorable neurological outcome than normothermia. Network estimates are shown in Table 11 and Figure 6. TTM 72h was associated with favorable neurological outcomes, compared with normothermia (RR 9.56 (95% CI 2.04-42.93)), or TTM 48h (RR 8.15 (95% CI 1.6-40.59)). TTM 24h was associated with favorable neurological outcomes, compared with normothermia (RR 8.02 (95% CI 1.28-50.50)). We did not find any association in the other comparisons. A summary of the confidence in the network estimates is shown in Table 12. The certainty in the network estimates was very low for all six comparisons. The P-scores for favorable neurological outcomes are shown in Table 10. The hierarchy for efficacy in favorable neurological outcome was TTM 72h (P-score 0.87) > TTM 48h (P-score 0.78) > TTM 24h (P-score 0.25) > normothermia (P-score 0.10).

**FIGURE 5: Forest plots for the pairwise comparison of favorable neurological outcomes**

TTM 72h was associated with a higher rate of favorable neurological outcomes compared to normothermia. We did not find any association in the other comparisons.
| Comparison                  | Direct estimate RR (95% CI) | Indirect estimate RR (95% CI) | Network estimate RR (95% CI) | Certainly of evidence for NMA |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-------------------------------|
| TTM 24h vs Normothermia     | NA                          | 8.02 (1.28–50.50)           | 8.02 (1.28–50.50)           | Very low                      |
| TTM 48h vs Normothermia     | 1.15 (0.69–1.92)            | NA                          | 1.15 (0.69–1.92)            | Very low                      |
| TTM 72h vs Normothermia     | 9.36 (2.04–42.91)           | NA                          | 9.36 (2.04–42.91)           | Very low                      |
| TTM 48h vs TTM 24h          | NA                          | 0.14 (0.02–0.97)            | 0.14 (0.02–0.97)            | Very low                      |
| TTM 72h vs TTM 24h          | 1.17 (0.42–3.28)            | NA                          | 1.17 (0.42–3.28)            | Very low                      |
| TTM 72h vs TTM 48h          | NA                          | 8.15 (1.6–40.59)            | 8.15 (1.6–40.59)            | Very low                      |

**TABLE 11: Network estimates of a favorable neurological outcome**

**FIGURE 6: Forest plot of network estimate for favorable neurological outcome**

TTM 72h was associated with favorable neurological outcomes, compared with no TTM/normothermia, or TTM 48h. TTM 24h was associated with favorable neurological outcomes, compared with no TTM/normothermia. We did not find any association in the other comparisons.
### TABLE 12: Summary of confidence in network estimates for favorable neurological outcome

| Comparison                  | Number of studies | Within-study bias | Reporting bias | Indirectness | Imprecision | Heterogeneity rating | Incoherence rating | Confidence rating |
|-----------------------------|-------------------|-------------------|----------------|--------------|-------------|----------------------|-------------------|-------------------|
| TTM 24h vs Normothermia     | 0                 | Major concerns    | Not suggested  | No concerns  | Major concerns | Very low             |                   |                   |
| TTM 48h vs Normothermia     | 2                 | No concerns       | Not suggested  | No concerns  | Major concerns | Very low             |                   |                   |
| TTM 72h vs Normothermia     | 1                 | Major concerns    | Not suggested  | No concerns  | Major concerns | Very low             |                   |                   |
| TTM 48h vs TTM 24h          | 0                 | Some concerns     | Not suggested  | No concerns  | Major concerns | Very low             |                   |                   |
| TTM 72h vs TTM 24h          | 1                 | Some concerns     | Not suggested  | No concerns  | Major concerns | Very low             |                   |                   |
| TTM 72h vs TTM 48h          | 0                 | Some concerns     | Not suggested  | No concerns  | Major concerns | Very low             |                   |                   |

**Discussion**

In the present study, 4 forms of TTM after ROSC post-cardiac arrest in children were compared using NMA: normothermia, duration of TTM below 55 °C for 24h, 48h, and 72h. The NMA suggested that TTM for 72h improved survival and neurological outcomes. In addition, the ranking analysis showed that a longer duration of therapeutic hypothermia may be associated with better survival and neurological outcomes. However, this result is largely due to a small number of observational studies showing better survival and neurological outcomes in the TTM 7h group and, therefore, there is only weak evidence to support prolonged therapeutic hypothermia. Overall, there are only a few high-quality studies on TTM after pediatric cardiac arrest and further studies are needed to determine the efficacy and duration of therapeutic hypothermia after pediatric cardiac arrest.

Our NMA showed that TTM 72h may improve survival. Seven studies with survival as an outcome were included in the NMA, and 7 evaluated qualitatively. An RCT (published in 2017) for patients who sustained an in-hospital cardiac arrest (IHCA) found no improvement in survival with 48h of therapeutic hypothermia compared to normothermia [11]. Several observational studies, including those that were not included in the quantitative analysis because of varying therapeutic hypothermia durations, also reported no significant difference in survival between therapeutic hypothermia and normothermia [13,18,19,21-23]. An RCT (published in 2015) of patients who sustained an out-of-hospital cardiac arrest (OHCA) also reported no significant difference in survival between 48h of therapeutic hypothermia and normothermia; however, the point estimate indicated that 48h of therapeutic hypothermia was dominant [10]. In addition, several observational studies also reported point estimate dominance of therapeutic hypothermia [15,20]. Two observational studies suggested that survival was improved after 72h of therapeutic hypothermia compared to normothermia [14,16]. One small RCT reported point estimate dominance of 72h of therapeutic hypothermia compared to 24 h [17]. Our NMA suggested that 72h of therapeutic hypothermia may improve survival, with the ranking analysis also showing a dose-response relationship between the length of therapeutic hypothermia and survival. However, the finding that 72h of hypothermia may be better for survival was largely due to the results of two small observational studies and the treatment effects estimated from the NMA were of low or very low certainty due to possible bias and heterogeneity. Therefore, the effectiveness of 72h of hypothermia is unknown and high-quality RCTs comparing long-length hypothermia to short-length hypothermia and normothermia are needed.

Our NMA showed that TTM 72h may improve neurological outcomes. However, the number of studies assessing neurological outcomes was small and the certainty of the NMA comparison was very low. Quantitative synthesis was only possible for 4 studies that assessed neurological outcomes, while a further 4 studies only be assessed qualitatively. The RCT for OHCA in 2015 and the RCT for IHCA in 2017 both compared therapeutic hypothermia for 48 h to normothermia, finding no significant differences in neurological outcome between hypothermia and normothermia [10,11]. However, consistent with our survival results, the point estimates in the RCT for OHCA suggested that therapeutic hypothermia for 48 h may be beneficial. Two relatively recent observational studies (therapeutic hypothermia 72h vs normothermia or therapeutic hypothermia variable vs. no TTM) have reported improved neurological outcomes with therapeutic hypothermia [16,24], with several studies reporting a dominance of therapeutic
hypothermia on point estimates [14,20]. However, other studies did not find any significant differences between therapeutic hypothermia and normothermia [13,17,19,21]. Overall, evidence regarding the effect of therapeutic hypothermia treatment on neurological outcomes in children with ROSC after cardiac arrest is lacking.

Experimental models suggest that a longer length of hypothermia therapy is more useful as a neuroprotective strategy than a shorter length [33-35]. A small RCT comparing 72h versus 24h therapeutic hypothermia after pediatric cardiac arrest reported lower biomarker concentrations of brain injury in the 72h therapeutic hypothermia group [17]. In neonates, 72h therapeutic hypothermia has been shown to be effective for hypoxic encephalopathy [36]. Overall, there were no high-quality studies on the length of therapeutic hypothermia following cardiac arrest in children, future studies on the benefit of prolonged therapeutic hypothermia are needed.

A problem in studies on cardiac arrest is the heterogeneity of patients included [12,37,38]. There are differences between OHCA and IHCA not only in terms of the location of the cardiac arrest but also in the likelihood of etiology and the presence of underlying diseases, amongst other factors [39,40]. OHCA is often respiratory in origin, whereas IHCA is often cardiac in origin and occurs in children with underlying diseases. Although there is no major difference in the treatment after resuscitation, the time to treatment also differs between OHCA and IHCA patients. The usefulness of therapeutic hypothermia has been reported to be greater for certain patient populations [41]. In our study, OHCA and IHCA were also present and their etiology varied; however, sub-analysis was not possible due to the small number of studies and patients and the inability to collect data by etiology and location of cardiac arrest. Future studies on the assessment and quantitative synthesis of the efficacy of therapeutic hypothermia in terms of the location and etiology of the cardiac arrest, together with the duration and temperature of the TTM, are needed.

Strengths and Limitations

To the best of our knowledge, there were no studies to compare the effectiveness of the duration of therapeutic hypothermia for children with ROSC after cardiac arrest using quantitative integration with NMA. Although previous meta-analyses have not reported conclusive findings either supporting or rejecting the use of therapeutic hypothermia in pediatric cardiac arrest, our study observed that longer therapeutic hypothermia, especially TTM for 72 h, may improve outcomes. A broad search was conducted for observational studies and RCTs without language restrictions, and qualitative evaluation and quantitative synthesis, using NMA, were conducted for the included studies.

However, the limitations of our study need to be acknowledged. First, quantitative synthesis included RCTs and observational studies without fully adjusting for confounders. Most of the comparisons on the certainty of evidence for NMA were "low" or "very low" due to the inclusion of observational studies and their inherent confounders and biases. Despite this limitation, we believe that our study is important as a pilot study to evaluate the effects of the length of therapeutic hypothermia. Second, we did not compare the temperatures of the therapeutic hypothermia in this study because there was not much difference in the therapeutic hypothermia because there was not much difference in the therapeutic hypothermia between the different studies. This could be an effect modifier or an interaction. Third, certain comparisons had only direct or indirect data. Future studies comparing the duration of hypothermia and NMAs that include such studies are needed.

Conclusions

Although prolonged therapeutic hypothermia might be effective in pediatric patients with ROSC after cardiac arrest, the evidence to support this result is only weak to very weak. There is no conclusive evidence regarding the effectiveness and length of therapeutic hypothermia. High-quality RCTs comparing long-length therapeutic hypothermia to short-length hypothermia and normothermia are needed.

Appendices
### Table 13: Search Strategy

| Database       | Search Strategy                                                                 |
|----------------|----------------------------------------------------------------------------------|
| MEDLINE via OVID | 1. MeSH descriptor: [Pediaics] explode all trees 2. MeSH descriptor: [Child] explode all trees 3. MeSH descriptor: [Infant] explode all trees 4. MeSH descriptor: [Adolescent] explode all trees 5. (infant" OR newbor" OR new-born" OR perinat" OR neonat" OR baby" OR babies OR toddler" OR minors" OR minor$ OR youth$ OR teen$ OR under$age$ OR pubescent$ OR pediatric$ OR paediatric$ OR preterm$ OR preterm$).mp. 13. 11 and 12 14. exp Cryotherapy/ 15. exp Body Temperature/ 16. exp Hypothermial/ (hypotherm$ OR normotherm$ OR cool$ OR cold$ OR temperature$ OR cryother$ OR cryogen$ OR cryotreat$ OR refrigeration OR "artificial hibernation").ti,ab, 18. 14 or 15 or 16 or 17 or 19. random?ed.ti,ab, 20. randomized controlled trial.pt, 21. controlled clinical trial.pt, 22. placebo.ab. 23. clinical trials as topic.sh. 24. randomly.ab. 25. trial.ti. 26. Comparative Study/ 27. 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 28. (animals not (humans and animals)).sh. 29. 27 not 28. 30. exp cohort studies/ 31. cohort$tw. 32. controlled clinical trial.pt. 33. epidemiologic methods/ 34. limit 33 to yr=1966-1989 35. exp case-control studies/ 36. (case$ and control$).tw. 37. observational.tw. 38. 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 39. 29 or 38 40. 13 and 18 and 39 |
| CENTRAL        | 1. MeSH descriptor: [Post-Cardiac Arrest Syndrome] explode all trees 14. (neuroprotection).ti,ab,kw 15. (asystole OR dysrhythmia OR ((heart OR cardiac OR ventricular OR circulatory) NEAR/3 arrest) OR (ventricular NEAR/5 fibrillation OR tachycardia OR arrhythmia)) OR "pulsless electrical activity" OR "electromechanical dissociation" OR "cardiopulmonary resuscitation" OR (PEA OR EMD) OR "non-perfusing rhythm").ti,ab,kw 16. (acls OR als OR (advanced adj3 support$)).tw. 17. 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 18. 6 AND 17 19. MeSH descriptor: [Cryotherapy] explode all trees 20. MeSH descriptor: [Body Temperature] explode all trees 21. MeSH descriptor: [Hypothermia] explode all trees 22. ((hypotherm$ OR normotherm$ OR cool$ OR cold$ OR temperature$ OR cryother$ OR cryogen$ OR cryotreat$ OR refrigeration OR "artificial hibernation").ti,ab,kw 23. 19 OR 20 OR 21 OR 22 24. 18 AND 23 |
| Clinicaltrials.gov | INFLECT EXACT "All Studies" [STUDY-TYPES] AND (asystole OR ((heart OR cardiac OR circulatory) AND arrest) OR (ventricular and fibrillation OR tachycardia)) OR "pulsless electrical activity" OR "electromechanical dissociation" OR "cardiopulmonary resuscitation" OR (PEA OR EMD) OR "non-perfusing rhythm") |
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