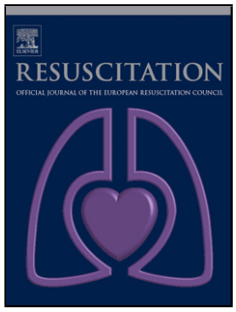

Title: Paediatric targeted temperature management post cardiac arrest: A systematic review meta-analysis

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Paediatric Targeted Temperature Management Post Cardiac Arrest: A Systematic Review Meta-Analysis

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Abstract

Introduction:

The International Liaison Committee on Resuscitation prioritized the need to update the review on the use of targeted temperature management (TTM) in paediatric post cardiac arrest care. In this meta-analysis, the effectiveness of TTM at 32-36°C was compared with no target or a different target for comatose children who achieve a return of sustained circulation after cardiac arrest.

Methods:

Electronic databases were searched from inception to December 13, 2018. Randomized controlled trials and non-randomized studies with a comparator group that evaluated TTM in children were included. Pairs of independent reviewers extracted the demographic and outcome data, appraised risk of bias, and assessed GRADE certainty of effects. A random effects meta-analysis was undertaken where possible.

Results:

Twelve studies involving 2,060 patients were included. Two randomized controlled trials provided the evidence that TTM at 32-34°C compared with a target at 36-37.5°C did not statistically improve long-term good neurobehavioural survival (risk ratio: 1.15; 95% CI: 0.69-1.93), long-term survival (RR: 1.14; 95% CI: 0.93-1.39), or short-term survival (risk ratio: 1.14; 95% CI: 0.96-1.36). TTM at 32-34°C did not show statistically increased risks of infection, recurrent cardiac arrest, serious bleeding, or arrhythmias. A novel analysis suggests that another small RCT might provide enough evidence to show benefit for TTM in out-of-hospital cardiac arrest.

Conclusion:

There is currently inconclusive evidence to either support or refute the use of TTM at 32-34°C for comatose children who achieve return of sustained circulation after cardiac arrest. Future trials should focus on children with out-of-hospital cardiac arrest.

PROSPERO: CRD4201808441

Keywords: Cardiac arrest; out-of-hospital cardiac arrest; in hospital cardiac arrest; survival; long-term outcome; systematic review; meta analysis

Introduction

Cardiac arrest is a catastrophic event in adults and in children.[1] Among children with return of sustained circulation (ROSC), hypoxic ischemic brain injury is the major cause of morbidity for which there are limited treatment options.[2] The development of an inflammatory response resulting in organ failure and fever may play a major part in the disease process of the post cardiac arrest syndrome.[3] The use of therapeutic hypothermia is one potential management strategy that reduces inflammation, reperfusion injury, oxygen consumption and apoptosis.[4] In adults post cardiac arrest, evidence has shown benefit from mild therapeutic hypothermia (32-36°C).[5] In newborns with birth anoxia, the use of mild therapeutic hypothermia has consistently shown to improve outcomes.[6]

There are numerous differences between adult and paediatric cardiac arrest, rendering indirect evidence from adults problematic for post arrest children.[7]

Several observational studies have shown both the safety and feasibility of using targeted temperature management (TTM) in children.[8] The benefits or harms of TTM in children post arrest was unclear, however, and these observational studies demonstrated that although some patients were receiving this therapy, the decision making for doing so was unclear. In 2015 and 2017, the first two RCTs were published on the use of TTM in paediatric cardiac arrest.[9, 10]

The International Liaison Committee on Resuscitation (ILCOR) evaluates the available resuscitation evidence through a transparent and rigorous evaluation process by a team of multi-disciplinary experts, culminating in publication of the consensus on science with treatment recommendations (CoSTR).[11] Temperature management of comatose children post cardiac arrest was last considered by the ILCOR Paediatric Life Support Task Force (PLS) in 2015, but new published evidence has prompted an update to the CoSTR.[12] This systematic review and meta-analysis (SRMA) was conducted in parallel and in collaboration with the ILCOR PLS Task Force to provide the evidence summary to inform the planned update to the CoSTR for the use of TTM in children who achieve ROSC after cardiac arrest.

Methods

Question

The specific question asked was: among paediatric patients (> 24 hours to 18 years of age) who achieve ROSC after a non-traumatic OHCA or IHCA (Population), does TTM with a target temperature of 32-36°C (Intervention), compared to no TTM or TTM at an alternative target temperature range (Comparator), change good neurobehavioral survival (GBS), survival, health-related quality of life (HRQoL) and in-hospital adverse outcomes (Outcomes), based upon randomized or observational studies (with a comparator group) (Study design), from any publication date to current (Timeframe)?

Protocol

This systematic review and meta-analysis was conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for meta-analysis in health care interventions (Supplementary Appendix 1).[13, 14] The protocol was registered in advance of article selection with the Prospective Register of Systematic Reviews (PROSPERO; registered September 10, 2018; CRD42018108441).

Outcomes

The selection and importance rating of patient-oriented outcomes for paediatric post cardiac arrest were determined in advance through discussion and consensus with the ILCOR PLS Task Force. The primary outcome was

long-term GBS defined as “good” paediatric overall performance category (POPC = 1-2), paediatric cerebral performance category (PCPC score = 1-2) or equivalent (eg: Vineland adaptive behavior scale-II ≥ 70).[15, 16] The secondary outcomes centred on GBS (at other time intervals), overall survival, and HRQoL at three time intervals: long-term (1-3 years), intermediate-term (3-6 months), and short-term (28-30 days or hospital discharge). HRQoL was defined using paediatric specific quality of life (QoL) tools (the Paediatric Quality of Life Inventory, the Infant Toddler QoL Questionnaire or equivalent). Potential in-hospital adverse outcomes were also captured including infection (culture proven), recurrent cardiac arrest, serious bleeding (red blood cell transfusion), and any arrhythmias (not leading to cardiac arrest).

Search Strategy

Medline, Embase, and all Evidence Based Medicine Reviews were searched by an Information Specialist using controlled language for medical subject headings and keywords from inception of the databases to July 18, 2018. The search was updated on December 13, 2018 *(*Supplementary Appendix 2*)*.[17] An iterative approach was used to ensure that key articles were found. References of all included studies, systematic reviews, 2010 and 2015 ILCOR CoSTR, and trial registries (the United States Clinical Trials Registry, www.clincaltrials.gov; and the International Clinical Trials Registry Platform, www.who.int/ictrp/en/) were searched.

Study Selection and Data Extraction

Randomized controlled trials (RCTs) and quasi-RCTs (allocation not truly random) were eligible. Additionally, non-randomized prospective and retrospective observational studies were eligible if they included a comparator group. Any study that did not report any of the primary or secondary outcomes, case reports, small case series (≤10 patients), review articles, editorials, commentaries and non-human studies were excluded. Duplicate publications on the same population were excluded, unless additional outcomes were reported or where distinct populations could be extracted. All languages were included if an English abstract was available. Articles only involving perinatal management of asphyxia or studies that focused on hypothermia management for cardiac surgery were excluded.

Covidence software was used for study selection in two steps (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia; www.covidence.org). Pairs of independent reviewers screened titles and abstracts. In the event of a disagreement at abstract screening, the full text was reviewed. Pairs of independent reviewers subsequently completed full-text review for eligibility. A third reviewer was involved for disagreements at the full-text stage and final decisions were determined by consensus. Inter-rater agreement for article selection was assessed using Cohen's kappa coefficient at the abstract and full-text stages.

Data Collection, Bias, and Certainty Assessment

For each study, pairs of authors independently extracted pre-determined study characteristics, patient characteristics, and study outcomes and then achieved consensus. Corresponding authors were contacted to request clarification and additional information as needed.

Pairs of authors independently evaluated risk of bias (RoB) using the Cochrane Risk of Bias Tool for RCTs and the CLARITY Tool for cohort studies.[13, 18] Similarly, two authors assessed the certainty of evidence for each outcome based upon the GRADE framework.[19] The RoB and GRADE assessments were then reviewed by ILCOR paediatric critical care content experts to achieve consistency and consensus.

Data Analysis

Covidence, GRADEPro and Review Manager software (RevMan 5.3, The Nordic Cochrane Centre, Copenhagen, Denmark, 2014) were used to abstract, summarize and analyse the data, respectively.

Clinical, methodologic and statistical heterogeneity was assessed. Statistical heterogeneity was evaluated using forest plots, and calculating the I^2 statistic.[20] If the data exhibited significant clinical, methodologic, or statistical heterogeneity formal pooling of results were inappropriate. Pre-

specified subgroup analyses were used to explore possible causes of heterogeneity.[21]

A meta-analysis was performed if two or more RCTs were available. As multiple small studies (<250 patients) were anticipated, a random effects (RE) model was used for analysis. Pooled unadjusted risk ratios (RR) and corresponding 95% confidence intervals (CI) using the Mantel-Haenszel method for dichotomous variables were reported. If pooling of adjusted analyses for observational studies were appropriate, adjusted odds ratios (OR) were reported using the generic inverse variance method. Forest plots were used for graphical representation of either the RR or OR.[21]

In post hoc exploratory analyses, the addition of hypothetical OHCA and IHCA studies with the same findings as the respective RCTs was considered to determine the size of a study required to change the statistical significance of the pooled primary outcome for these subgroups.

Prespecified subgroup analyses were planned, if relevant information was available, for location of cardiac arrest, age groups, presumed aetiology of cardiac arrest, and the use of extracorporeal membrane oxygenation (ECMO). Specific subgroup information was extracted, if available, or if ≥ 80% of patients met the subgroup criteria, the study was used.

Results

Literature Search and Study Selection

The search strategy identified a total of 1392 records. After removing 335 duplicates, 1057 records were screened by title and abstract. No additional studies were found via reference searches. A total of 80 full-text articles were assessed for eligibility, and 12 publications were included (Figure 1).[8-10, 22-30] The Cohen's kappa coefficient was 0.63 at the abstract stage and 1.0 at the full-text stage.

Search of clinical trial registries found 4 paediatric TTM registered trials. Two of these RCTs were included in this SRMA.[9, 10] One pilot RCT of 34 paediatric post-arrest patients compared TTM 32-34°C for 24 hours to 72 hours, but was excluded as it had no comparison to an alternative temperature TTM (or no TTM).[31] The last is an unpublished pilot multi-site RCT completed in 2010, the Hypothermia for Cardiac Arrest in Paediatrics, comparing TTM at 33-34°C to TTM at 36.5-37.5°C for 48 hours (NCT00754481).

Study Characteristics (Table 1)

Of the 12 included articles, there were 2 RCTs,[9, 10] 1 exploratory subgroup analysis of the OHCA RCT,[27] 8 retrospective observational cohort studies,[8, 22-24, 26, 28-30] and 1 additional pilot publication of an included

cohort study that provided additional information.[25] All further descriptions of the studies will reference the 2 RCTs and 8 cohort studies (and not the 2 additional publications included[25, 27]) unless otherwise noted.

A total of 2,060 patients were included in studies. Most studies were from the United States, Canada and the United Kingdom; they were published between 2009 and 2018 with patient recruitment from 2000-2017. The multi-centre RCTs compared active TTM at 32-34°C to active TTM normothermia at 36-37.5°C for 48 hours and then maintained active normothermia for a total of 120 hours in both arms.[9, 10, 27] The cohort studies had a variety of different TTM strategies in the intervention arm including 32-34°C,[22, 23, 25, 26, 28, 30] 33-35°C,[8] 34-35°C,[29] and < 35°C;[24] and compared to normothermia < 38°C,[28, 29] or no TTM[8, 22-24, 26, 30] for a variety of different times (12-72 hours).

The primary outcome of GBS was defined differently among the studies. The 2 RCTs reported their GBS as the number of patients with VABS-II score ≥ 70 at 1 year.[9, 10] Of the cohort studies that evaluated GBS, it was defined as either CPC ≤ 2,[22] PCPC ≤ 2,[25, 26] or PCPC 1-3.[24] Although one publication reported HRQoL measures, it was reported in a way that could not be extracted with comparative data.[29]

There were also differences in the reporting of in-hospital adverse outcomes. The RCTs allowed capture of severe bleeding as indicated by transfusion of packed red cells or whole blood, serious arrhythmias, and culture proven infection through 7 days.[9, 10, 27] Among the retrospective cohort studies there was greater variability in definition.[8, 22-24, 26, 28-30]

Patient Characteristics (Table 2)

Within each study, the intervention and comparator groups were reasonably similar in age and gender. However, there were considerable differences between studies with respect to patient's cardiac history, aetiology of arrest, and witnessed status. Of the two randomized control studies, one focused only on IHCA and the other on OHCA.[9, 10] For the observational studies, three included only OHCA,[22, 26, 28] one included only IHCA,[23] and the remaining had a mix of both IHCA and OHCA.[8, 24, 29, 30] Pre-existing cardiac history was variable between the studies, with some including only patients with cardiac history,[23] some excluding those with cardiac history,[8, 26, 27, 29] while others made no distinction. Similarly, the presumed cause of arrest varied between studies with some focusing on presumed cardiac and others presumed asphyxia[8, 10, 26, 28] or drowning.[27] Some studies had very few patients receiving ECMO,[8-10, 27, 28] while others had a much larger proportion.[23, 24, 29] Overall, the majority of studies reported less than 10% of children having an initial shockable rhythm.

Risk of Bias (Table 3)

The two RCTs were fully randomized and blinded for assessors (none were blinded for the intervention) and found to have a low overall RoB. All but one of the cohort studies were determined to have a high RoB, owing to the intervention being at the discretion of the treating physician (which was inadequately controlled or adjusted for in the primary analyses).[8, 22-24, 26, 28, 30] The remaining study was determined to have an unclear RoB due to uncertainty in their methodology.[29]

Certainty in the Point Estimates (GRADE Analysis) (Supplementary Appendix 3)

The majority of the outcomes extracted from the RCTs were downgraded for concerns with inconsistency and imprecision. The outcomes extracted from the cohort studies were downgraded due to concerns with risk of bias, inconsistency, indirectness and imprecision. This resulted in low or very low certainty for the majority of outcomes.

Outcome Analysis (Figure 2 & Supplementary Appendix 4)

The 2 RCTs had moderate clinical heterogeneity (different settings), low methodological heterogeneity (same methods and in-hospital management), and low or moderate statistical heterogeneity, allowing pooling of the results in the meta-analyses and separate subgroup analyses. As there were only 2 relatively small RCTs available, observational comparative data was

considered, but the RCT and non-RCT data were not combined. For the observational studies, only studies that reported adequately adjusted results were pooled, while non-adjusted results are shown, where relevant, without pooling.

Good Neurobehavioural Survival (Figure 2a & 2b)

For the primary outcome of long-term GBS (1 year), a pooled analysis of the two RCTs found no statistical benefit of TTM at 32-34°C compared to TTM at 36-37.5C (RR: 1.15; 95% CI: 0.69-1.93, I^2= 61%, n=517, low certainty).[9, 10] Two adjusted cohort studies found very low certainty of evidence of no statistical benefit in either intermediate-term (aOR: 0.50; 95% CI: 0.11-2.22, n=663)[24] or short-term GBS (aOR: 1.22; 95% CI: 0.59-2.51, n=79).[22]

Survival (Figure 2c & 2d)

For the secondary outcome of overall survival, a pooled analysis of the two RCTs found very low certainty of evidence of no statistical benefit of TTM at 32-34°C compared to TTM at 36-37.5°C in either long-term (RR: 1.14; 95% CI: 0.93-1.39, I^2= 9%, n=613) or short-term survival (RR: 1.14; 95% CI: 0.96-1.36, I^2= 18%).[9, 10] One retrospective cohort study found no benefit in adjusted intermediate-term survival (aOR: 0.50; 95% CI: 0.11-2.22, n=79, very low certainty).[24] Three cohort studies found no benefit in adjusted short-term survival (OR: 1.08; 95% CI: 0.53-2.17; I^2= 34%, n=341, very low certainty).[8, 22, 24]

Adverse Outcomes – Infection (Supplementary Appendix 4: Figure 1a)

A pooled analysis of the two RCTs found no statistical evidence of harm in culture-proven infection from TTM at 32-34°C compared to TTM at 36-37.5°C (RR: 1.08; 95% CI: 0.87-1.33; I^2= 0%, n=611, low certainty) .[9, 10] Four cohort studies reported on infection; unadjusted outcomes were not pooled, but none of the studies showed statistical harm.[8, 23, 24, 26]

Adverse Outcomes – Recurrent Cardiac Arrest (Supplementary Appendix 4: Figure 1b)

Pooled analysis of the two RCTs found no statistical harm of recurrent cardiac arrest from TTM at 32-34°C compared to TTM at 36-37.5°C (RR: 0.74; 95% CI: 0.4701.16; I^2= 0%, n=613, very low certainty) .[9, 10] Two cohort studies reported unadjusted recurrent cardiac arrest rates that could not be pooled; none of the individual studies showed statistical harm.[8, 24]

Adverse Outcomes – Serious Bleeding (Supplementary Appendix 4: Figure1c)

Pooled analysis of the two RCTs found no statistical harm for serious bleeding from TTM at 32-34°C compared to TTM at 36-37.5°C (RR: 0.97; 95% CI: 0.88-1.07; I^2= 0%, n=311, low certainty) .[9, 10] Two observational cohort studies reported unadjusted serious bleeding; none of the individual studies showed statistical harm.[8, 24]

Adverse Outcomes – Arrhythmias (Supplementary Appendix 4: Figure 1d)

Pooled analysis of the two RCTs found no statistical harm for arrhythmias from TTM at 32-34°C compared to TTM at 36-37.5°C (RR: 1.11; 95% CI: 0.73-1.69; I^2= 0%, n=611, very low certainty) .[9, 10] Five observational studies reported unadjusted outcomes for arrhythmias; one showed statistical harm and the other 3 showed no statistical benefit or harm.[8, 23, 24, 26, 28]

Subgroup Analysis - Location of Cardiac Arrest (Supplementary Appendix 4: Figures 2a-d)

For the predetermined subgroup analysis by location of arrest (OHCA or IHCA), no meta-analyses could be completed as there is only one RCT for each subgroup and the observational studies had methodologic heterogeneity.

For OHCA, the single RCT did not find statistical benefit of TTM.[10] One of the 3 cohort studies found unadjusted statistically significant benefit of 72 hours of TTM at 32-34°C compared with normothermia TTM for survival and GBS.[26] The other two studies did not find statistical benefit or harm.[22, 28] An exploratory analysis was conducted to determine if the addition of a hypothetical OHCA RCT that yielded similar results as the THAPCA OHCA study would change the pooled analysis confidence interval to favour TTM at

32-34°C.[10] Enrolment of 200 patients in such a hypothetical RCT would be associated with a statistically significant benefit of GBS at 1 year.

The RCT of IHCA did not find statistical benefit or harm of TTM at 32-34°C compared to TTM at 36-37.5°C.[9] The point estimates for the different observational cohort studies are on both sides of the null effect line.[23, 24, 29] An exploratory analysis indicated that an additional hypothetical RCT of 6000 patients with similar outcome to the IHCA THAPCA RCT[9] would be required to demonstrate a statistically significant harm of TTM at 32-34°C in GBS at 1 year compared to TTM at 36-37.5°C.

Subgroup Analysis - Aetiology of Arrest (Supplementary Appendix 4: Figures 3a-e)

Two retrospective observational cohort studies with presumed cardiac aetiology could not be pooled, but separately reported no significant benefit or harm in short-term survival of TTM at 32-35°C compared to TTM at 36-37.5°C (or no TTM).[23, 29]

Two observational cohort studies (and a pilot publication of one of those studies) reported on the GBS and survival outcomes for patients with predominantly (> 80%) presumed asphyxial aetiology.[8, 25, 26] High risk of bias and lack of adjusted outcomes precluded pooling of data. One OHCA observational study found a statistically significant benefit of TTM at 33°C for

72 hours for both GBS and survival.[26] All of the point estimates favoured TTM at 32-35°C.

The OHCA THAPCA study published a non-randomized subgroup analysis of drowning as an aetiology.[27] There was no statistically significant benefit of the intervention for survival or GBS.

Subgroup Analysis – ECMO (Supplementary Appendix 4: Figure 4)

Although some patients in several of the studies underwent ECMO, outcome data was only available from 2 studies. The THAPCA IHCA RCT (non-randomized co-intervention) found low certainty of evidence of no statistical benefit in long-term GBS (at 1 year) for TTM at 32-34°C compared to TTM at 36-37.5C (RR: 0.80; 95% CI: 0.48-1.32, I^2= N/A, n=157, low certainty).[9] In one observational cohort study, all patients received ECMO; they reported no statistical benefit in short-term survival.[29]

Discussion

In this SRMA, we identified 10 studies that compared the effectiveness of TTM at 32-35°C to either no TTM or TTM at 36-37.5°C for children who achieve ROSC after cardiac arrest. We identified 2 randomized trials and 8 retrospective observational cohort studies that provided comparative data on GBS, survival, and in-hospital adverse events.[8-10, 22-24, 26, 28-30] There

is inconclusive evidence to either support or refute the use of hypothermic TTM (compared to no TTM or an alternative temperature) for children who achieve ROSC after cardiac arrest.

Despite the low incidence of paediatric cardiac arrest, the public health burden is high given the number of potential life years lost.[32] Conducting research on paediatric cardiac arrest is challenging. Methodological heterogeneity makes synthesizing data problematic and difficult to interpret.[33, 34] Future studies should use standardized outcomes (eg: Utstein template) to help improve the amount of comparative data available.[15] In the THAPCA IHCA trial, of the nearly 2800 children who were screened for enrolment, 73% were excluded. Given the limited number of post arrest children, there needs to be greater enrolment of patients.[34] Parents may choose the standard care rather than participating in a research trial, especially when the risk/benefit ratio remains unknown.[35, 36] This was evident in both the IHCA and OHCA trials where 29% and 24% of families who were approached, declined to participate. An additional 18% and 6% of families, were not approached as the attending physician thought participation was inappropriate.[9, 10]

The current paediatric TTM literature is also limited by the differences between the OHCA and IHCA settings.[37, 38] These patients are often managed similarly once admitted to hospital but appear to be inherently

different. Among the IHCA studies, there was a greater number of patients with comorbidities and presumed cardiac aetiology of the arrest. Conversely, there was a high rate of presumed asphyxia cause of arrest in the OHCA studies. These very different aetiologies may benefit from different approaches to post ROSC care.

The impact of treatment by location of arrest and the aetiology of arrest is a current knowledge gap. However, the individual OHCA studies and the studies with presumed asphyxial cause of arrest all have point estimates that favour mild hypothermic TTM. The hypothetical study analysis for OHCA indicated that only one additional RCT with 200 patients with the same results as the THAPCA OHCA study would be required to provide a pooled statistically significant benefit. Using Bayesian analysis may also allow a statistically significant outcome with a smaller sample size.[39] Conversely, the evidence for IHCA does not favour hypothermic TTM and a much larger study (n=6000) would be required to confirm either pooled benefit or harm. These factors may influence sample size calculations for future studies.

Other differences in the location of arrest relate to the differences in response times. In IHCA, the shorter time to arrest recognition, initiation of CPR, defibrillation, and advanced life support may substantially affect survivability and GBS. The rate of shockable rhythms is very low in OHCA compared to IHCA, and this may be partly related to the delay to initial rhythm

interpretation in OHCA patients, but also different aetiologies (higher cardiac aetiology in IHCA patients). Additionally, the greater availability of technologies such as ECMO to re-establish circulation may be started much sooner in the IHCA population compared to the OHCA patients.

The current available evidence on use of TTM in children involves different comparators. Paediatric IHCA registry data have shown a strong association between the presence of fever post-resuscitation and poor neurologic outcome.[40] While the two THAPCA studies were designed in such a way that patient temperature in the normothermic comparison arm of the studies was actively controlled at 36-37.5°C and preventing fever,[9, 10] most cohort studies that have compared hypothermia to 'normothermia' have generally not included active TTM in the control arm to prevent hyperthermia. This failure to prevent inadvertent fever (or at least failure to adjust for it statistically) in the 'normothermic' comparison group is a significant limitation of the retrospective data.

Although pooling of the current studies to date does not find a statistical benefit to TTM at one year, in the pooled RCT analysis, [9, 10] fewer deaths from heart failure, and fewer death or poor neurological prognosis were seen in the mild hypothermia group during the first 3 days post arrest, compared to the therapeutic normothermia group.[41] The difference in early neurological deaths may be artefactual from delayed prognostication in patients who

undergo mild therapeutic hypothermia. There were no differences in survival at longer time intervals. Similarly, one cohort study showed a mean 2.9 day longer duration of stay in paediatric intensive care unit (PICU) for non-surviving children receiving TTM 32-34°C compared to those receiving TTM 36-37.5°C.[28] There was no difference in PICU length of stay for children surviving to hospital discharge. The authors attribute this to a change in timing for neurological and brain death testing for TTM 32-34°C patients. Since over 70% of post ROSC children included in these studies did not survive to hospital discharge, an increased length of stay in the PICU may produce increased costs for uncertain benefit.

Strengths and Limitations

Our systematic review and meta-analysis has a number of strengths. We brought together a multidisciplinary team, which included content experts, methodologists and systematic reviewers assisted by an experienced research librarian. We used a rigorous search strategy and adhered to the PRISMA standards and Cochrane methods.[13, 14, 21] We also included numerous subgroups, which we believe will be relevant to clinicians to help in their decision making.

Our review also has some limitations. Our question included comparators with both active normothermia TTM and no documentation of active TTM. Active management of normothermia is inherently different than permissive

fever. We included 8 retrospective observational studies that had varying methodologies, clinical heterogeneity, different treatment protocols with respect to duration and temperature targets and had different definitions of the adverse events. These studies were also rated to be a high risk of bias owing to the intervention being performed at the discretion of the treating physician.

Conclusions

Since publication of the 2015 ILCOR CoSTR, additional evidence has been published on the use of TTM in comatose children post ROSC. Despite 2 recently published RCTs, and a total of 8 observational cohort studies, there is inconclusive evidence to support or refute the use of TTM at 32-34°C following cardiac arrest in children. Gaps in knowledge that may be most beneficial to study are the use of TTM 32-34°C for children following OHCA or asphyxial arrest and the use of TTM at 36-37.5°C in IHCA patients.

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Conflicts of Interests

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Legends to Figures

Figure 1. PRISMA Flow Chart of included studies

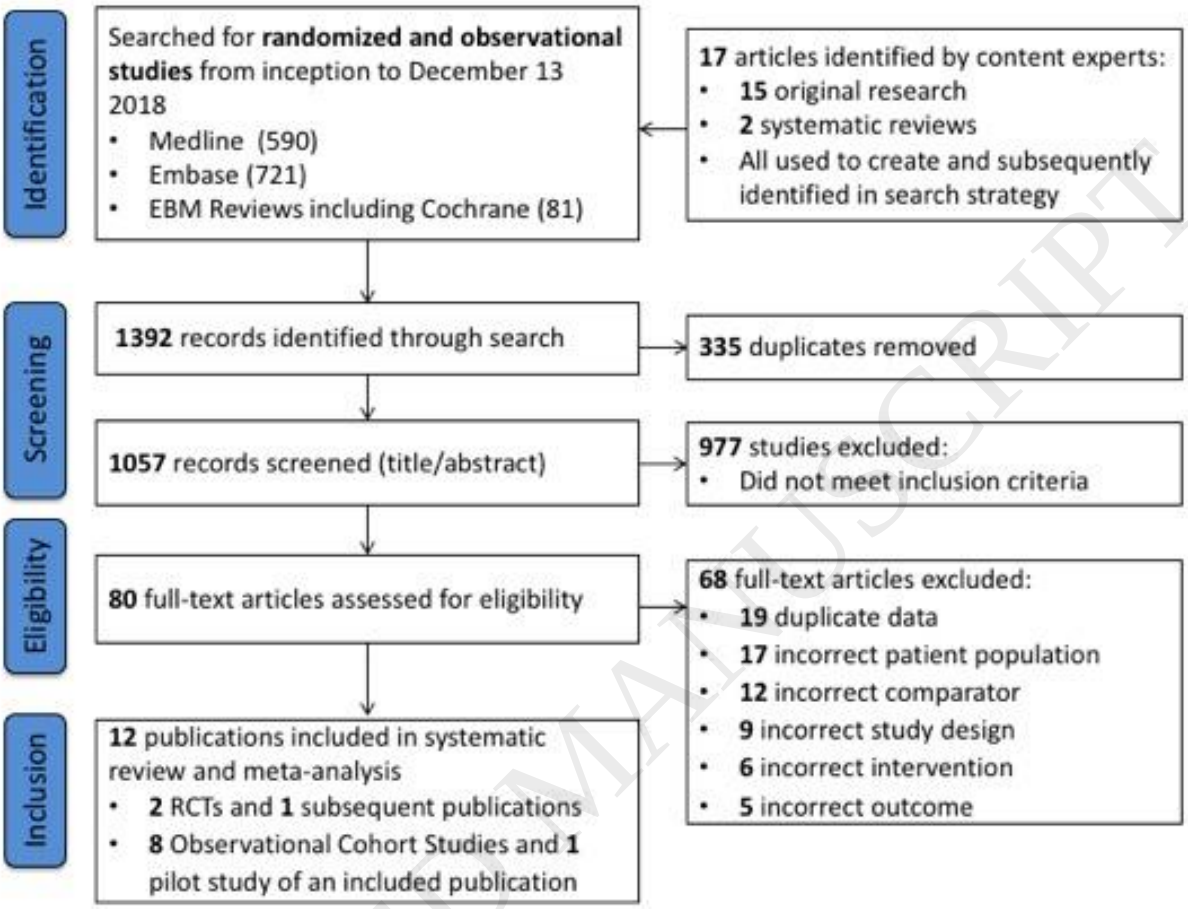
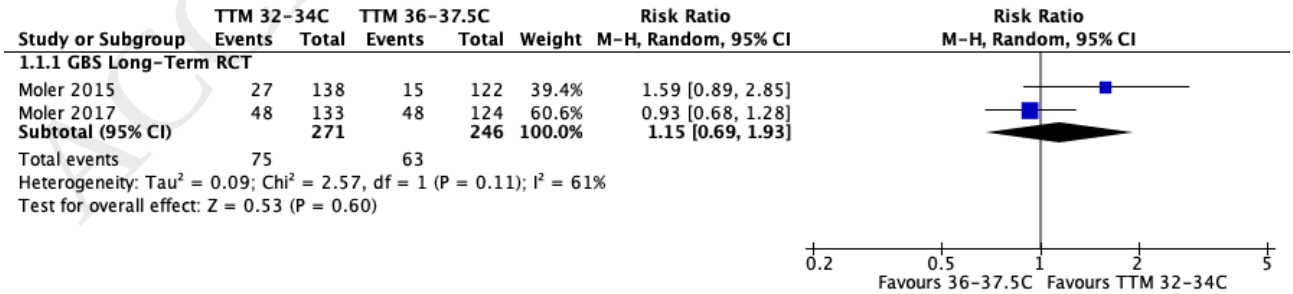


Figure 2. Summary of results forest plots: a. Good Neurobehavioral Survival RCTs; b. Good Neurobehavioral Survival Observational Studies; c. Survival RCTs; d. Survival Observational Studies

(a)



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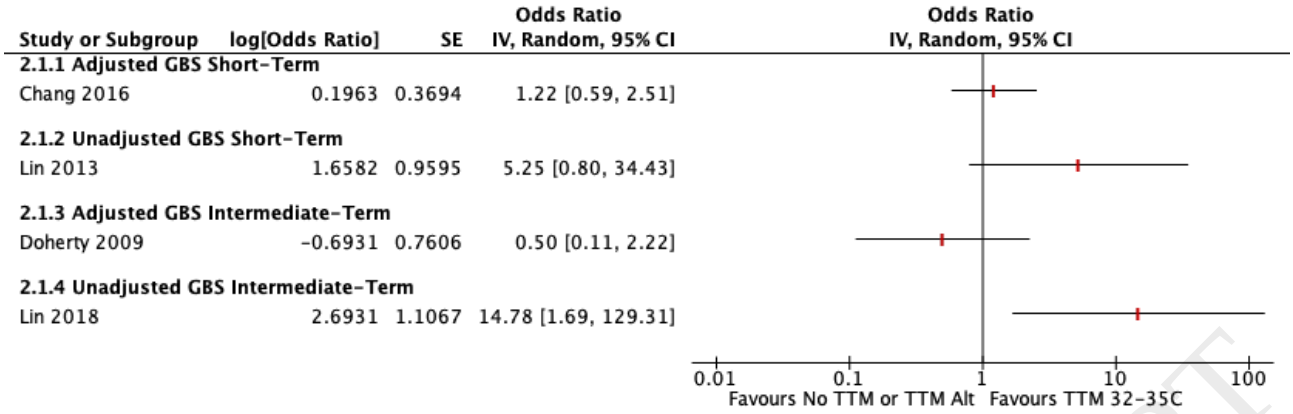

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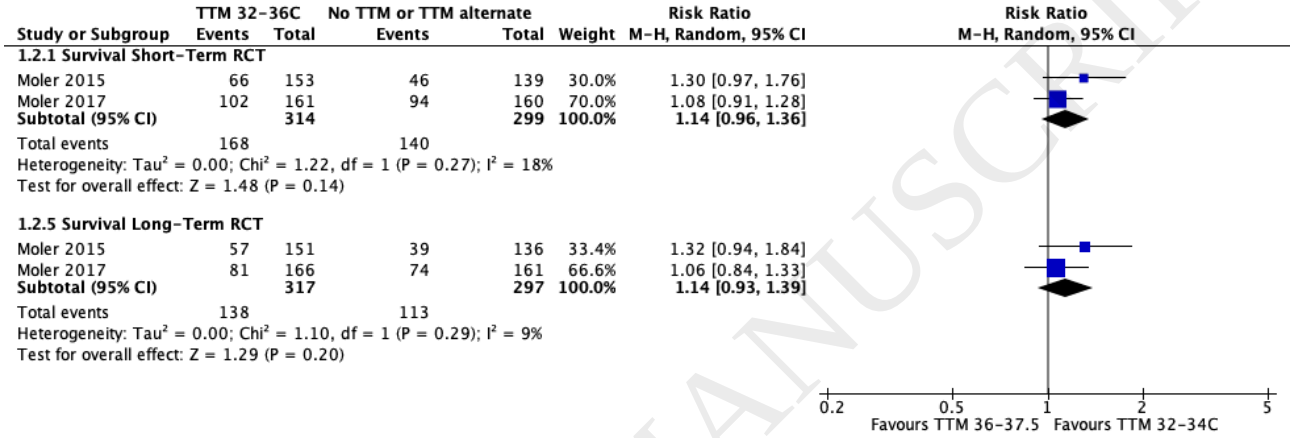

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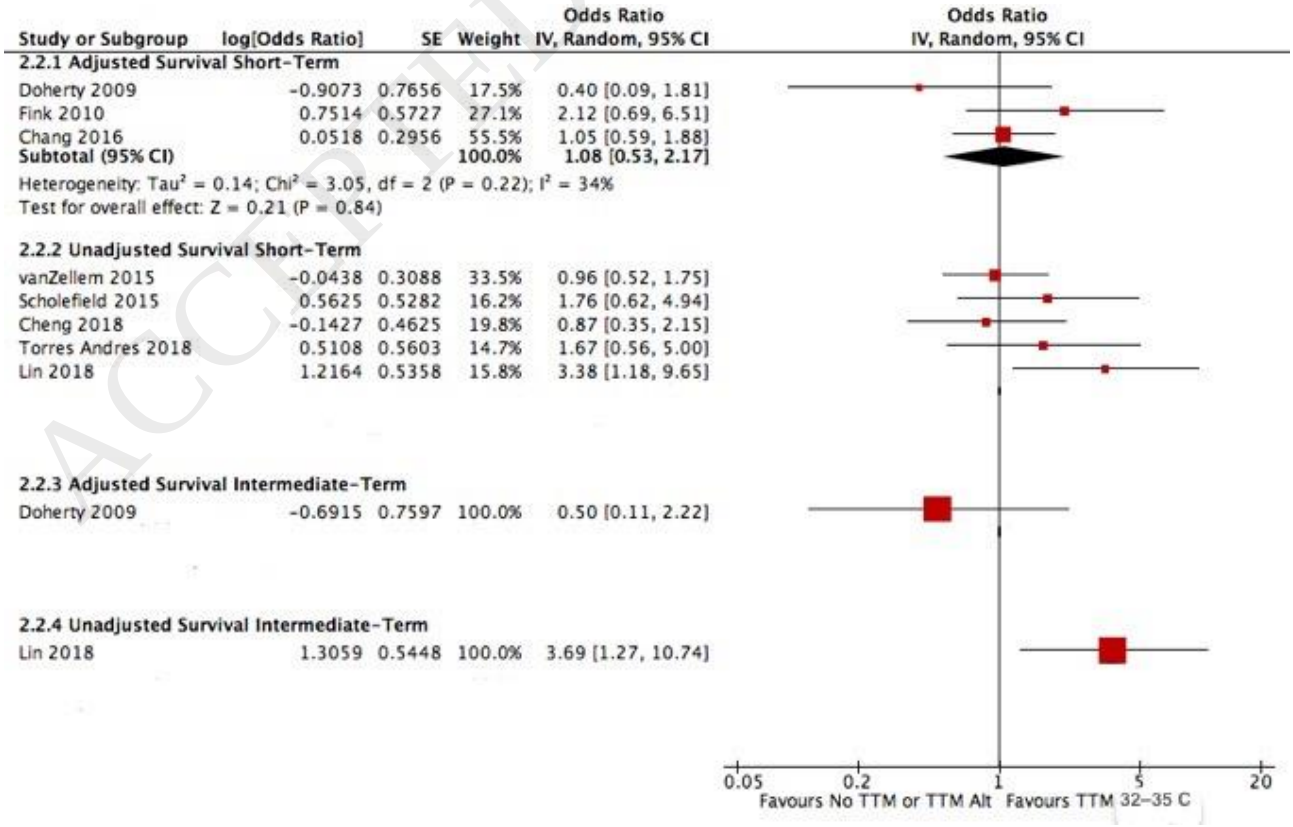

Table 1. Study Characteristics

Study	Study Characteristics			Number	Patients by Treatment (N)		Intervention Definition		Length of TTM				Neurological Outcome Tool
	Years of Recruitment	Country of Recruitment	Multi or Single center		TTM	Comparato			12 h	24 h	48 h	72 h	
Randomized Control Trials													
Moler 2015	2009-2012	USA & Canada	Multi	295	155	140	TTM	TTM 32-34°C for 48h then 36-37.5°C for total 120h			✓*		VABS-II score ≥ 70
							Comparator	TTM 36-37.5°C for 120 hours					
Moler 2017	2009-2010	US, Canada, & UK	Multi	329	166	163	TTM	TTM 32-34°C for 48h then 36-37.5°C for total 120h			✓*		VABS-II score ≥ 70
							Comparator	TTM 36-37.5°C for 120 hours					
Moler 2016 **	2009-2012	USA & Canada	Multi	64	46	28	TTM	TTM 32-34°C for 48h then 36-37.5°C for total 120h			✓*		VABS-II score ≥ 70

							Comparator	TTM 36-37.5°C for 120 hours					
Retrospective Cohort Studies													
Doherty 2009	2001-2003	Canada & UK	Multi	79	29	50	TTM	TTM <35°C	Variable				PCPC 1-3
							Comparator	No TTM					
Fink 2010	2000-2006	USA	Single	181	40	141	TTM	TTM 33-35°C	Variable				N/A
							Comparator	No TTM					
Lin 2013***	2010-2012	Taiwan	Single	43	15	28	TTM	TTM 32-34°C				✓	PCPC score ≤ 2
							Comparator	No TTM					
Scholefield 2015	2004-2010	UK	Single	73	38	35	TTM	TTM 32–34°C		✓			N/A
							Comparator	Normothermia <38°C					
vanZellem 2015	2002-2011	The Netherlands	Single	200	63	137	TTM	TTM 32–34°C		✓			N/A
							Comparator	No TTM					
Chang 2016	2008-2014	Korea	Multi	663	81	582	TTM	TTM 32-34°C	Variable			CPC score ≤ 2	
							Comparator	No TTM					
Cheng 2018	2012-2013 2013-2015	USA	Single	75	26	49	TTM	TTM 32-34°C			✓ (> 1 y)	✓ (< 1 y)	N/A
							Comparator	No TTM					
Lin 2018		Taiwan	Single	64	25	39	TTM	TTM 32-34°C					

	2010-2017						Comparator	No TTM				✓	PCPC score ≤ 2
Torres-Andres 2018	2007-2015	USA	Single	58	28	30	TTM	TTM 34-35°C	Not reported			N/A	
							Comparator	Normothermia < 38°C					

*TTM randomized for first 48 hours, but active normothermia (36-37.5°C) for total 120 hours
** Moler 2016 is an exploratory non-randomized sub-group analysis of Moler 2015 RCT
*** Lin 2013 is a pilot study of Lin 2018 - only good neurobehavioural Survival at hospital discharge included as all other outcomes as per Lin 2018

Abbreviations: CPC= cerebral performance category; GOS=Glasgow outcome score; h= hours; N= number; N/A= not applicable; PCPC= paediatric cerebral performance category; TTM= targeted temperature management; UK= United Kingdom; VABS-II= Vineland adaptive behavior scale-II

Table 2. Patient characteristics

Study	Targeted Temperature Management	N	Age (Years) (mean, SD)	Male Gender (%)	Cardiac History (%)	Presumed Cardiac Cause of Arrest (%)	Presumed Asphyxia Cause of Arrest (%)	In-Hospital Cardiac Arrest IHCA (%)	Out-of-Hospital Cardiac Arrest OHCA (%)	Initial Shockable Rhythm (%)	Witnessed arrest (%)	Bystander CPR (%)	Duration of CPR (minutes) (IQR)
Moler 2015	TTM	155	2.1 (0.6-10.1)*	102 (66)	14 (9)	14 (9)	111 (72)	0 (0)	155 (100)	14 (9)	58 (40)	101(68)	23 (15-35)
	Comparator	140	1.6 (0.4-7)*	94 (67)	21 (15)	18 (13)	102 (73)	0 (0)	140 (100)	9(6)	51 (38)	85 (63)	28 (19-45)
Moler 2017	TTM	166	1.4 (0.3-5.7)*	97 (58)	163 (98)	89 (54)	45 (27)	166 (100)	0 (0)	17 (10)	N/A	166 (100)	23 (7-42)
	Comparator	163	0.6 (0.2-6.3)*	99 (61)	146 (90)	74 (45)	55 (34)	163 (100)	0 (0)	17 (10)	N/A	163 (100)	22 (7-51)
Moler 2016**	TTM	46	2.4 (1.5-5.9)	28 (61)	N/A	0 (0)	46 (100)	0 (0)	46 (100)	0 (0)	8 (18)	40 (87)	21 (14-34)
	Comparator	28	3.6 (1.9-8.2)	22 (79)	N/A	0 (0)	28 (100)	0 (0)	28 (100)	2 (7)	4 (15)	18 (72)	32 (16-55)
Doherty 2009	TTM	29	N/A	16 (55)	19 (66)	21(72)	5 (17)	28 (97)	1 (3)	2 (7)	N/A	N/A	30 (23-42)
	Comparator	50	N/A	23 (44)	37 (74)	34 (68)	11 (22)	47 (94)	3 (6)	11 (22)	N/A	N/A	10 (5-30)
Fink 2010	TTM	40	2.4 (0.4-11.8)*	24 (60)	N/A	5 (13)	35 (88)	16 (40)	24 (60)	3 (9)	25 (64)	N/A	15 (8-26)

	Comparator	141	2.9 (1.1-11.1)*	80 (57)	N/A	11 (8)	129 (92)	78 (55)	63 (45)	16 (13)	111 (79)	N/A	9 (4-20)
Lin 2013	TTM	15	N/A	10 (67)	0 (0)	1 (7)	14 (83)	6 (40)	9 (60)	1 (7)	N/A	N/A	21 (6)‡
	Comparator	28	N/A	18 (64)	2 (7)	0 (0)	28 (100)	8 (29)	20 (71)	0 (0)	N/A	N/A	25 (22)‡
Scholefield 2015	TTM	38	1.5 (0-5.8)*	17 (45)	1 (3)	4 (11)	14 (37)	0 (0)	38 (100)	5 (14)	23 (62)	30 (81)	40 (N/A)
	Comparator	35	1 (0-4)*	8 (23)	3 (9)	1 (3)	11 (31)	0 (0)	35 (100)	1 (3)	22 (69)	15 (47)	29 (N/A)
vanZellem 2015	TTM	63	3.96 (0.09-17.67)*	43 (68)	10 (53)	60 (30)	95 (48)	19 (30)	44 (70)	11 (18)	11 (19)	48 (81)	N/A
	Comparator	137	1.87 (0.08-21.88)*	67 (49)	33 (54)			83 (61)	54 (39)	10 (8)	13 (10)	119 (90)	N/A
Chang 2016	TTM	81	15 (10-18)*	25 (31)	5 (6)	44 (54)	N/A	0 (0)	81 (100)	19 (24)	50 (62)	29 (36)	N/A
	Comparator	582	7 (1-15)*	199 (34)	16 (3)	298 (51)	N/A	0 (0)	582 (100)	44 (8)	310 (53)	118 (20)	N/A
Cheng 2018	TTM	26	0.5 (0.08-2.28)*	12 (46)	26 (100)	N/A	N/A	26 (100)	0 (0)	N/A	N/A	N/A	22 (14-40)
	Comparator	49	0.21 (0.04-1.1)*	33 (67)	49 (100)	N/A	N/A	49 (100)	0 (0)	N/A	N/A	N/A	21 (13-33)
Lin 2018	TTM	25	N/A	21 (84)	0 (0)	0 (0)	25 (100)	0 (0)	25 (100)	0 (0)	12 (48)	4 (16)	26 (15) ‡
	Comparator	39	N/A	28 (72)	0 (0)	0 (0)	39 (100)	0 (0)	39 (100	0 (0)	25 (64)	8 (21)	26 (17)‡
	TTM	28			N/A	46 (79)	3 (5)	55 (95)	3 (5)	N/A	N/A	N/A	N/A

Torres-Andres 2018***	Comparator	30	0.29 (0.08-4.42)*	35 (60)	N/A					N/A	N/A	N/A	N/A

* Reports median with IQR
**Moler 2016 is an exploratory non-randomized sub-group analysis of Moler 2015 RCT
*** This study only gives total characteristics, not broken down by TTM or not

‡Reports mean and SD

Abbreviations: C-Section= cesarean section, CPC= cerebral performance category; CPR= cardiopulmonary resuscitation; GOS=Glasgow outcome score; h= hours; IQR=interquartile range; min= minutes; N= number; N/A= not available; SD=standard deviation; TTM= targeted temperature management;

Table 3. Risk of Bias

Table 3a. Risk of Bias for Randomized Controlled Studies

Cochrane Risk of Bias for RCTs									
Study		**Sequence Generation**	**Allocation Concealment**	**Blinding of Participants and Personnel**	**Blinding of Outcome Assessors**	**Incomplete Outcome data**	**Selective Outcome Reporting**	**Other Sources of Bias**	**Overall Bias**
Moler	2015	LOW	LOW	HIGH	LOW	LOW	LOW	LOW	LOW
Moler	2017	LOW	LOW	HIGH	LOW	LOW	LOW	UNCERTAIN	LOW
Moler	2016	LOW	LOW	HIGH	LOW	LOW	LOW	HIGH	HIGH

Abbreviations: RCT= randomized controlled trial

Table 3b. Risk of Bias for Observational Cohort Studies

CLARITY Tool to Assess Risk of Bias in Cohort Observational Studies										
Study		**Population selection**	**Assessment of exposure**	**Absence of the outcome of interest at the start of the study**	**Matching or adjusted analysis for key prognostic variables**	**Assessment for prognostic factors**	**Assessment of outcome**	**Adequacy of follow-up**	**Similarity of co-interven-tions**	**Overall Bias**
Doherty	2009	LOW	LOW	LOW	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	HIGH	HIGH
Fink	2010	LOW	UNCLEAR	UNCLEAR	HIGH	UNCLEAR	UNCLEAR	LOW	HIGH	HIGH
Lin	2013	LOW	LOW	LOW	HIGH	UNCLEAR	UNCLEAR	LOW	UNCLEAR	HIGH
Scholefield	2015	LOW	LOW	LOW	HIGH	UNCLEAR	LOW	LOW	LOW	HIGH
van Zellem	2015	UNCLEAR	LOW	LOW	HIGH	UNCLEAR	LOW	LOW	UNCLEAR	HIGH
Chang	2016	LOW	LOW	LOW	HIGH	UNCLEAR	UNCLEAR	LOW	UNCLEAR	HIGH

Cheng	2018	UNCLEAR	LOW	UNCLEAR	HIGH	UNCLEAR	LOW	LOW	UNCLEAR	HIGH
Torres-Andres	2018	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	LOW	LOW	UNCLEAR	UNCLEAR
Lin	2018	LOW	LOW	LOW	HIGH	LOW	LOW	LOW	UNCLEAR	HIGH