# Targeted temperature management after cardiac arrest: Updated meta-analysis of all-cause mortality and neurological outcomes ☆

Mohammed Abdalla [a,*,1], Abdelnasir Mohamed [a,1], Wiam Mohamed [b,1], Khlwd Khtab [b,1], Hugo Cattoni [a,1], Mohammed Salih [c,1]

[a] Saint Francis Hospital, Evanston, IL, United States
[b] University of Khartoum, Sudan
[c] Hurley Medical Center, Flint, MI, United States

## ABSTRACT

Background: Cardiac arrest carries high mortality and morbidity burden. Different studies showed conflicting data regarding outcomes of targeted temperature management (TTM) for cardiac arrest. The purpose of this meta-analysis is to systematically determine the effect of TTM on all-cause mortality and neurological outcomes after cardiac arrest.
Methods: We conducted a systematic search for randomized controlled trials in Pubmed, Cochrane & ScienceDirect. Primary outcomes were neurological outcome and all-cause mortality.
Results: Nine randomized controlled trials utilizing data for in-hospital and out-of-hospital cardiac arrest were selected for meta-analysis. Total number of patients included was 1592. Mortality was lower in targeted temperature management group (OR 0.637, 95% CI 0.436–0.93, p-value 0.019, $I^2 = 44.78\%$, n = 1592). Therapeutic hypothermia group also demonstrated reduction in poor neurological outcomes (OR 0.582, 95% CI 0.363–931, p-value 0.024, $I^2 = 56.79\%$, n = 1567). Subgroup analysis was conducted, after excluding in-hospital cardiac arrest patients, and demonstrated reduction in poor neurological outcome (OR 0.562, 95% CI 0.331–0.955, p-value 0.033, $I^2 = 61.78\%$, n = 1480) and mortality in out-of-hospital cardiac arrest patients (OR 0.674, 95% CI 0.454–999, p-value 0.049, $I^2 = 43.8\%$, n = 1505).
Conclusion: Targeted temperature management after cardiac arrest may be associated with improvement in all-cause mortality and reduction in poor neurological outcome.

## 1. Introduction

Cardiac arrest carries a high burden of mortality and morbidity. In the United States, 356,500 patients suffer from out-of-hospital cardiac arrest every year. It is estimated that around 209,000 patients receive treatment for in-hospital cardiac arrest annually. Survival to hospital's discharge is 12% for all age groups regardless of the initial rhythm [1]. Survivors of cardiac arrest suffer from severe sequelae including anoxic brain injury resulting in poor neurological recovery which is the major contributor to death and higher mortality rates in cardiac arrest victims irrespective of first recorded rhythm. [2].

Measures to decrease the neurological consequences following cardiac arrest include targeted temperature management (TTM) which is an attempt to improve the neurological outcomes for the survivors of cardiac arrest by controlling the core body temperature to target temperature range between 32 °C to 36 °C.

Generally, hyperthermia is unfavorable post cardiac arrest and should be avoided. This is because increased body temperature is associated with increased mortality rates and neurological injury. Each degree above 37 °C carries a higher risk of death in the first 48 h post cardiac arrest [3].

Multiple randomized controlled trials were conducted to measure outcomes of patients who underwent TTM post cardiac arrest, however the data from these studies were conflicting regarding the end points. Additionally, our study included data for both in-hospital and out-of-hospital cardiac arrest victims, while other meta-analyses were focused on out-of-hospital cardiac arrest [4]. Also we analyzed databases up to January 2019 [5].

The purpose of this meta-analysis is to systematically analyze the outcomes of randomized controlled trials that were conducted on cardiac arrest survivals who were managed with TTM initiated soon after return of spontaneous circulation. The major end points assessed were all-cause mortality and poor neurological outcomes.

## 2. Methods

### 2.1. Data sources and searches

We conducted a systematic search on January 2019 utilizing electronic databases, we searched Pubmed, ScienceDirect and Cochrane database of systematic reviews using the terms "Targeted Temperature Management" or "TTM" or "therapeutic hypothermia" or "TH" or "induced hypothermia" and "Cardiac arrest" or "Arrest". We searched for human studies in English language in these databases since inception to the date. Our analysis was performed according to guidelines of Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [6]. Identified abstracts were reviewed to determine their eligibility to be included. The criteria for inclusion were: randomized controlled trials, conducted in adults, evaluating mortality and neurological outcomes comparing TTM vs control for both in-hospital and out-of-hospital cardiac arrest patients.

### 2.2. Study selection

Two authors (MA and AM) independently conducted the search and selected the studies, any disagreements were resolved by third author (WM). Flow chart for selection of studies for meta-analysis is shown in Fig. 1. The preliminary search yielded 2371 articles. We excluded 2079 articles as they didn't meet the inclusion criteria. Detailed review of article' titles and abstracts of 292 studies resulted in exclusion of 278 studies due to nonadherence to the inclusion criteria. Fourteen studies were selected for further review and full manuscripts of these papers and their references list were assessed for further publications. Three studies were excluded as the outcomes in TTM group vs control were not clearly determined. Another three studies were conducted in the same population so one was chosen for the analysis and the other two studies were excluded [7–9]. Nine randomized controlled trials were included in the meta-analysis utilizing data for in-hospital and out-of-hospital cardiac arrest patients [9,12–18].

### 2.3. Data extraction

Two reviewers (MA and AM) independently extracted the data for meta-analysis, and discrepancies were resolved by third reviewer (WM) and by consensus. We extracted the study year, study's sample size, mortality in control group, mortality in TTM group, poor neurological outcome in control, poor neurological outcome in TTM group, age, male percentage, witnessed cardiac arrest, time to cardiopulmonary resuscitation, time to return of spontaneous circulation, goal temperature of TTM in the study, shockable rhythm, and location of cardiac arrest.

### 2.4. Statistical analysis

We performed meta-analyses to assess all-cause mortality and neurological outcome in control group vs TTM group using data from 9 studies for in-hospital and out-of-hospital cardiac arrest patients. Additionally, we performed subgroup analysis after we excluded data for in-hospital cardiac arrest patients.

Odds ratios for each trial were calculated. Mantel-Haenzel method was utilized to calculate the pooled odds ratio for fixed effect and DerSimonian and Laird model for random-effects. We used $I^2$ statistic to assess for heterogeneity, and was considered as low, moderate or high for 25%, 50%, and 75%, respectively. Publication bias was assessed by visual inspection of funnel plot and formal testing (Egger's test, Begg's test). We calculated 95% confidence interval for different variables. We considered results significant if p-value less than 0.05. Meta-analysis was performed using software program (Comprehensive Meta-Analysis Version 3.3).
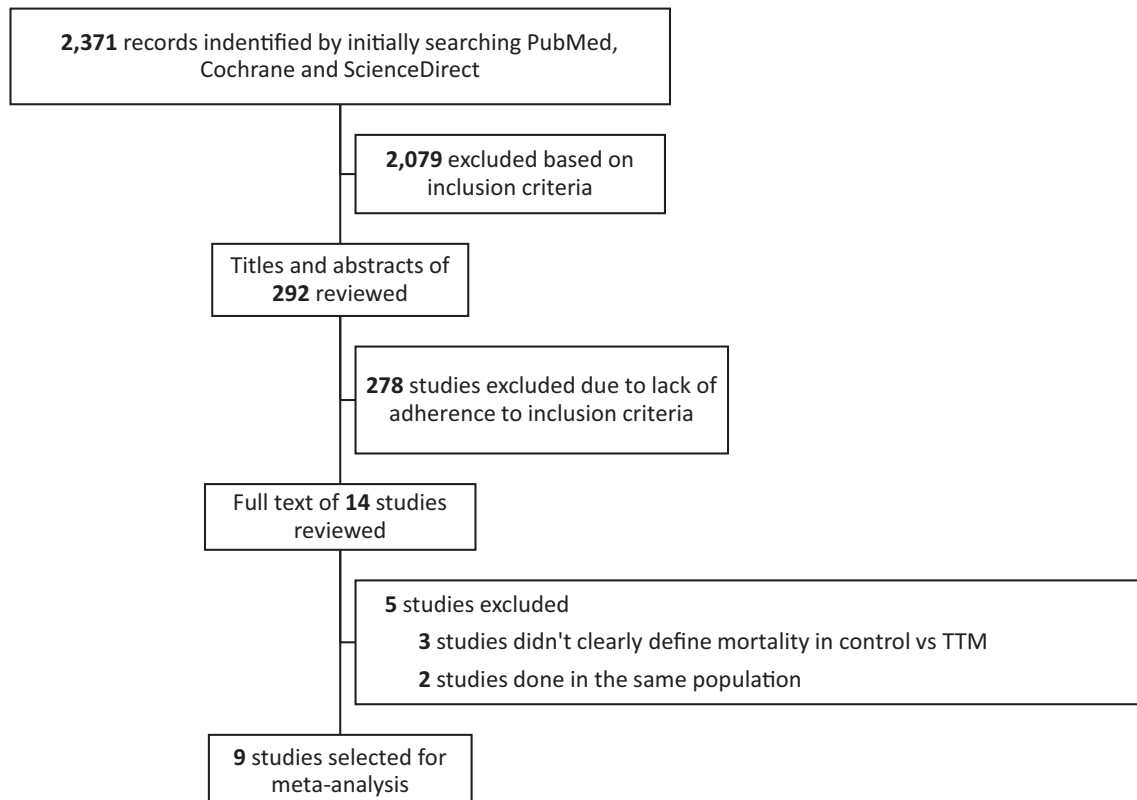


Fig. 1. Flow chart for selection of studies for meta-analysis.

**Table 1**
Extracted data from the selected studies.

| Study | Year | Study population size | TTM mortality | Control mortality | TTM poor neuro outcome | Control neuro outcome | Goal TTM in study | Cardiac arrest location |
|---|---|---|---|---|---|---|---|---|
| Look et al | 2018 | 87 | 27/45 | 33/42 | 33/45 | 34/42 | 33 | In & out of hospital |
| Nielsen et al | 2013 | 939 | 226/473 | 220/466 | 251/473 | 242/466 | 33 | Out of hospital |
| Laurent et al | 2005 | 42 | 15/22 | 11/20 | 15/22 | 11/20 | 33 | Out of hospital |
| Hachimi-Idrissi | 2005 | 28 | 6/14 | 8/14 | 8/14 | 11/14 | 33 | Out of hospital |
| Bernard et al | 2002 | 77 | 22/43 | 23/34 | 22/43 | 25/34 | 33 | Out of hospital |
| HACA | 2002 | 275 | 56/137 | 76/138 | 61/137 | 83/138 | 32 | Out of hospital |
| Hachimi-Idrissi | 2001 | 30 | 13/16 | 13/14 | 14/16 | 14/14 | 34 | Out of hospital |
| Tiainen et al | 2007 | 70 | 8/36 | 12/34 | 2/27 | 4/18 | 33 | Out of hospital |
| Bernard et al | 1997 | 44 | 10/22 | 17/22 | 11/22 | 19/22 | 33 | Out of hospital |

TTM = targeted temperature management, CPR = cardiopulmonary resuscitation, ROSC = return of spontaneous circulation.

## 3. Results

Nine randomized controlled trials were selected for meta-analysis. Data extracted shown in Table 1. Eight of these studies investigated outcomes of implementing TTM only in out-of-hospital cardiac arrest patients. One study examined data from both in-hospital and out-of-hospital cardiac arrest. The total number of patients included in the meta-analysis was 1592 (808 in TTM group; 784 controls). Mortality was lower in TTM group (OR 0.637, 95% CI 0.436–0.93, p-value 0.019, $I^2 = 44.79\%$, n = 1592) as shown in Fig. 2. Therapeutic hypothermia group also demonstrated reduction in poor neurological outcomes (OR 0.582, 95% CI 0.363–931, p-value 0.024, $I^2 = 56.8\%$, n = 1567) as shown in Fig. 3.

For subgroup analysis, after excluding in-hospital cardiac arrest patients, results showed improvement in poor neurological outcomes in out-of-hospital cardiac arrest patients treated with TTM and the results were statistically significant (OR 0.562, 95% CI 0.331–0.955, p-value 0.033, $I^2 = 61.79\%$, n = 1480) as shown in Fig. 4. Furthermore, all-cause mortality was lower in the group who had TTM after out-of-hospital cardiac arrest (OR 0.674, 95% CI 0.454–999, p-value 0.049, $I^2 = 43.84\%$, n = 1505) as demonstrated in Fig. 5. No publication bias was detected by inspection of funnel plot (Fig. 6) or with formal testing (Begg's test p-value = 0.83, Egger's test p-value = 0.065).

## 4. Discussion

Targeted temperature management is part of post-cardiopulmonary resuscitation bundle after achievement of return of spontaneous systemic circulation. It is an attempt to alleviate the effect of the damage caused by anoxic brain injury secondary to the decreased cerebral
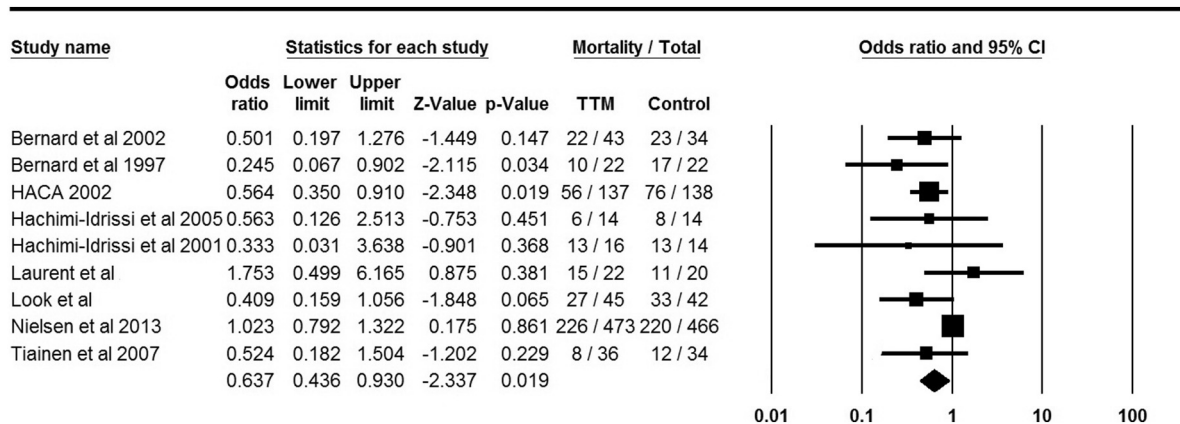


| Study name | Odds ratio | Lower limit | Upper limit | Z-Value | p-Value | Mortality / Total TTM | Control |
|---|---|---|---|---|---|---|---|
| Bernard et al 2002 | 0.501 | 0.197 | 1.276 | -1.449 | 0.147 | 22 / 43 | 23 / 34 |
| Bernard et al 1997 | 0.245 | 0.067 | 0.902 | -2.115 | 0.034 | 10 / 22 | 17 / 22 |
| HACA 2002 | 0.564 | 0.350 | 0.910 | -2.348 | 0.019 | 56 / 137 | 76 / 138 |
| Hachimi-Idrissi et al 2005 | 0.563 | 0.126 | 2.513 | -0.753 | 0.451 | 6 / 14 | 8 / 14 |
| Hachimi-Idrissi et al 2001 | 0.333 | 0.031 | 3.638 | -0.901 | 0.368 | 13 / 16 | 13 / 14 |
| Laurent et al | 1.753 | 0.499 | 6.165 | 0.875 | 0.381 | 15 / 22 | 11 / 20 |
| Look et al | 0.409 | 0.159 | 1.056 | -1.848 | 0.065 | 27 / 45 | 33 / 42 |
| Nielsen et al 2013 | 1.023 | 0.792 | 1.322 | 0.175 | 0.861 | 226 / 473 | 220 / 466 |
| Tiainen et al 2007 | 0.524 | 0.182 | 1.504 | -1.202 | 0.229 | 8 / 36 | 12 / 34 |
| | 0.637 | 0.436 | 0.930 | -2.337 | 0.019 | | |

**Fig. 2.** Forest plot for mortality in targeted temperature group (TTM) vs control.



| Study name | Odds ratio | Lower limit | Upper limit | Z-Value | p-Value | TTM | Control |
|---|---|---|---|---|---|---|---|
| Bernard et al 2002 | 0.377 | 0.143 | 0.993 | -1.973 | 0.048 | 22 / 43 | 25 / 34 |
| Bernard et al 1997 | 0.158 | 0.036 | 0.691 | -2.450 | 0.014 | 11 / 22 | 19 / 22 |
| HACA 2002 | 0.532 | 0.329 | 0.859 | -2.582 | 0.010 | 61 / 137 | 83 / 138 |
| Hachimi-Idrissi et al 2005 | 0.364 | 0.069 | 1.909 | -1.196 | 0.232 | 8 / 14 | 11 / 14 |
| Hachimi-Idrissi et al 2001 | 0.200 | 0.009 | 4.540 | -1.010 | 0.312 | 14 / 16 | 14 / 14 |
| Laurent et al | 1.753 | 0.499 | 6.165 | 0.875 | 0.381 | 15 / 22 | 11 / 20 |
| Look et al | 0.647 | 0.235 | 1.785 | -0.841 | 0.400 | 33 / 45 | 34 / 42 |
| Nielsen et al 2013 | 1.047 | 0.810 | 1.352 | 0.348 | 0.728 | 251 / 473 | 242 / 466 |
| Tiainen et al 2007 | 0.280 | 0.045 | 1.727 | -1.372 | 0.170 | 2 / 27 | 4 / 18 |
| | 0.582 | 0.363 | 0.931 | -2.260 | 0.024 | | |

**Fig. 3.** Forest plot for poor neurological outcome in targeted temperature group (TTM) vs control.

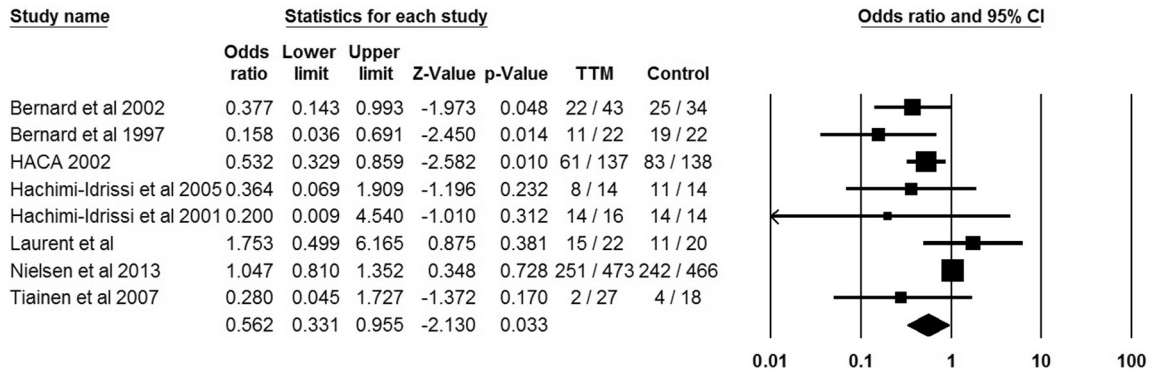| Study name | Statistics for each study | | | | | | | Odds ratio and 95% CI |
|---|---|---|---|---|---|---|---|---|
| | Odds ratio | Lower limit | Upper limit | Z-Value | p-Value | TTM | Control | |
| Bernard et al 2002 | 0.377 | 0.143 | 0.993 | -1.973 | 0.048 | 22 / 43 | 25 / 34 | |
| Bernard et al 1997 | 0.158 | 0.036 | 0.691 | -2.450 | 0.014 | 11 / 22 | 19 / 22 | |
| HACA 2002 | 0.532 | 0.329 | 0.859 | -2.582 | 0.010 | 61 / 137 | 83 / 138 | |
| Hachimi-Idrissi et al 2005 | 0.364 | 0.069 | 1.909 | -1.196 | 0.232 | 8 / 14 | 11 / 14 | |
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| Nielsen et al 2013 | 1.047 | 0.810 | 1.352 | 0.348 | 0.728 | 251 / 473 | 242 / 466 | |
| Tiainen et al 2007 | 0.280 | 0.045 | 1.727 | -1.372 | 0.170 | 2 / 27 | 4 / 18 | |
| | 0.562 | 0.331 | 0.955 | -2.130 | 0.033 | | | |

**Fig. 4.** Forest plot for poor neurological outcome in targeted temperature group (TTM) vs control in out-of-hospital cardiac arrest.

perfusion during cardiac arrest. The neurological injury is the main etiology and a major contributor to mortality in cardiac arrest after return of spontaneous systemic circulation is achieved.

Consequently, TTM also aims to limit mortality in cardiac arrest patients through decreasing the injury to the nervous system. Our meta-analysis examined the outcomes of TTM in post cardiac arrest patients.

After thorough search through electronic databases, we selected nine studies, with total number 1592 patients, to be included.

In this meta-analysis, the effect of TTM on neurological outcomes was measured by looking into the outcomes of 1567 patients. In our study TTM improved the neurological outcomes significantly. This is contrary to previous studies that showed worse neurological outcomes
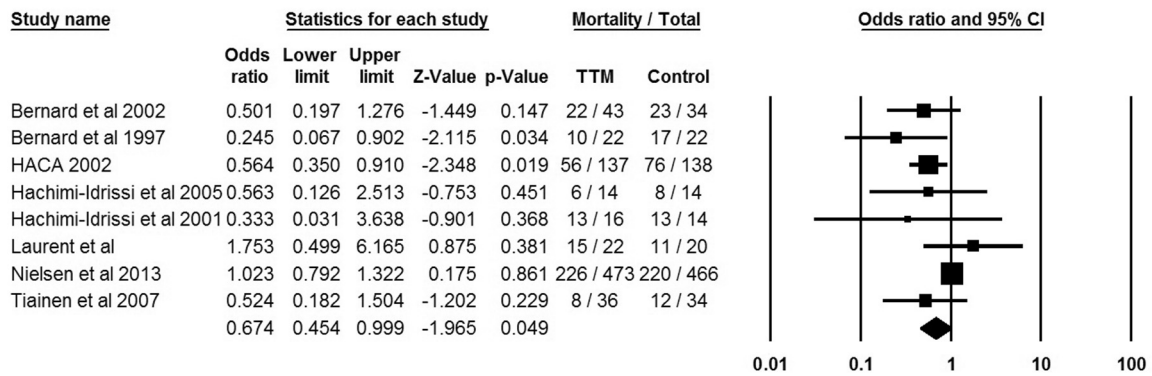
| Study name | Statistics for each study | | | | | Mortality / Total | | Odds ratio and 95% CI |
|---|---|---|---|---|---|---|---|---|
| | Odds ratio | Lower limit | Upper limit | Z-Value | p-Value | TTM | Control | |
| Bernard et al 2002 | 0.501 | 0.197 | 1.276 | -1.449 | 0.147 | 22 / 43 | 23 / 34 | |
| Bernard et al 1997 | 0.245 | 0.067 | 0.902 | -2.115 | 0.034 | 10 / 22 | 17 / 22 | |
| HACA 2002 | 0.564 | 0.350 | 0.910 | -2.348 | 0.019 | 56 / 137 | 76 / 138 | |
| Hachimi-Idrissi et al 2005 | 0.563 | 0.126 | 2.513 | -0.753 | 0.451 | 6 / 14 | 8 / 14 | |
| Hachimi-Idrissi et al 2001 | 0.333 | 0.031 | 3.638 | -0.901 | 0.368 | 13 / 16 | 13 / 14 | |
| Laurent et al | 1.753 | 0.499 | 6.165 | 0.875 | 0.381 | 15 / 22 | 11 / 20 | |
| Nielsen et al 2013 | 1.023 | 0.792 | 1.322 | 0.175 | 0.861 | 226 / 473 | 220 / 466 | |
| Tiainen et al 2007 | 0.524 | 0.182 | 1.504 | -1.202 | 0.229 | 8 / 36 | 12 / 34 | |
| | 0.674 | 0.454 | 0.999 | -1.965 | 0.049 | | | |

**Fig. 5.** Forest plot for mortality in targeted temperature group (TTM) vs control in out-of-hospital cardiac arrest.
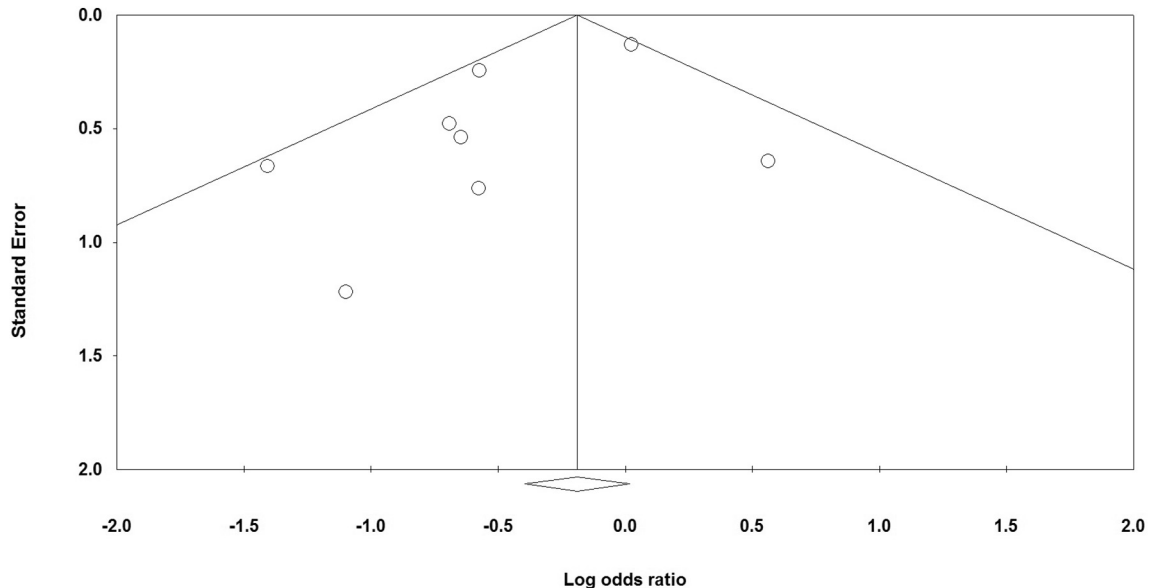


**Fig. 6.** Funnel plot.

in TTM patients [19,20], and in accordance with Pang et al. [11]. The randomized trials selected for this analysis had data for in-hospital and out-of-hospital cardiac arrest patients.

Cerebral perfusion and oxygen supply are compromised in cardiac arrest. Furthermore, Depletion of glucose and energy reserve ensue following cardiac arrest. In addition, when cerebral perfusion is restored following return of spontaneous circulation, free radicals may be produced. These free radicals may induce further neurological insult. These factors collectively may result in loss of normal cellular function and integrity. TTM after cardiac arrest reduces cerebral oxygen demand by decreasing the metabolic rate of the brain. Furthermore, TTM decreases the production of oxygen free radicals and the subsequent cellular damage [21,22].

All-cause mortality was one of the outcomes that was investigated in our analysis. Pooled data from nine controlled trials, with 1592 cardiac arrest victims, were analyzed. The data was from both in-hospital and out-of- hospital cardiac arrest patients. Meta-analysis of these data revealed that all-cause mortality was lower in TTM group in contrast with control group, this effect was statistically significant. In contrast other studies showed that TTM has higher mortality, for example Bhattacharjee et al. and Chan et al. [19,20]. As we suggested above; this effect in mortality is most likely due to the reduction in cerebral neurological damage as it's the number one culprit in death for post cardiac arrest patients.

One of the selected studies had data for in-hospital cardiac arrest patients [10], we excluded this study in order to analyze the data to perform subgroup analysis in out-of-hospital cardiac arrest patients. Again, this analysis investigated all-cause mortality and the neurological outcomes. Subgroup meta-analysis showed reduction in mortality and improvement in neurological outcomes for out-of-hospital cardiac arrest patients. Generally, the outcomes TTM is better for out-of-hospital cardiac arrest in comparison with in-hospital cardiac arrest patients [19].

Limitations of our analysis include limited number of in-hospital cardiac arrest patients as there is paucity of randomized controlled trials conducted to assess outcomes of TTM for in-hospital cardiac arrest. Additionally, small number of studies limited our ability to evaluate publication bias in a better way and to perform sensitivity analysis. Finally, lack of comprehensive patients' data hindered a full evaluation of factors that can affect the outcomes from TTM.

## 5. Conclusion

Targeted temperature management after cardiac arrest may be associated with improvement in all-cause mortality and reduction in poor neurological outcome.

## Declaration of Competing Interest

The authors have no conflict of interest to disclose.

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