

Therapeutic whole-body hypothermia reduces mortality in severe traumatic brain injury if the cooling index is sufficiently high: meta-analyses of the effect of single cooling parameters and their integrated measure

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Abstract

Therapeutic hypothermia was investigated repeatedly as a tool to improve the outcome of severe traumatic brain injury (TBI), but previous clinical trials and meta-analyses found contradictory results. We aimed to determine the effectiveness of therapeutic whole-body hypothermia on the mortality of adult patients with severe TBI by using a novel approach of meta-analysis.

We searched the PubMed, EMBASE, and Cochrane Library databases from inception to February 2017. The identified human studies were evaluated regarding statistical, clinical, and methodological designs to ensure inter-study homogeneity. We extracted data on TBI severity, body temperature, mortality, and cooling parameters; then we calculated the cooling index, an integrated measure of therapeutic hypothermia.

Forest plot of all identified studies showed no difference in the outcome of TBI between cooled and not cooled patients, but inter-study heterogeneity was high. On the contrary, by meta-analysis of RCTs which were homogenous with regards to statistical, clinical designs and precisely reported the cooling protocol, we showed decreased odds ratio for mortality in therapeutic hypothermia compared to no cooling. As independent factors, milder and longer cooling, and rewarming at $< 0.25^{\circ}\text{C}/\text{h}$ were associated with better outcome. Therapeutic hypothermia was beneficial only if the cooling index (measure of combination of cooling parameters) was sufficiently high.

We conclude that high methodological and statistical inter-study heterogeneity could underlie the contradictory results obtained in previous studies. By analyzing methodologically homogenous studies, we show that cooling improves the outcome of severe TBI and this beneficial effect depends on certain cooling parameters and on their integrated measure, the cooling index.

Introduction

Traumatic brain injury (TBI) is recognized as a significant cause of mortality and morbidity predominantly in the young population.¹ TBI is estimated to affect 10 million people annually worldwide and by 2020 it can be one of the major causes of death and disability, posing a global health and financial burden for the society.² Among the leading causes of TBI are motor vehicle accidents in both more and less developed countries, most frequently involving young males.^{2,3} Mild head injuries may recover fully without any specific treatment, whereas severe injuries are often rapidly fatal or leave survivors with disabilities.⁴ Severe TBI constitutes a major health and socio-economic problem worldwide.⁵

The pathomechanisms underlying severe TBI are complex and often involve focal as well as diffuse changes.⁶ Focal lesions include contusional damages of the brain parenchyma, most commonly in the frontal and temporal lobes, as well as disruptions in vasculature, resulting in intracerebral and extracerebral hematomas.^{5,6} In a typical case like the one presented in Table S1, focal lesions are diagnosed with routine imaging techniques, such as computed tomography (see Fig. S1). The primary head injury can initiate a number of pathophysiological processes which will determine the extent and the duration of the damage. These mechanisms involve ischemia, swelling (edema), neurotransmitter release (excitotoxicity), formation of free radicals, ionic flux-mediated damage, metabolic and mitochondrial dysfunction, and neuroinflammatory responses.⁴⁻⁶

Many of the pathological mechanisms associated with TBI are temperature-sensitive,⁷ suggesting that at a lower deep body temperature the adverse processes can be decelerated and neuroprotective effects can be achieved. Therapeutic hypothermia has been investigated as a possible neuroprotective strategy to attenuate the harmful effects of severe TBI. In animal models of TBI, beneficial effects of therapeutic hypothermia have been shown repeatedly,⁸⁻¹¹ but clinical studies provided contradictory results. The first report of the use of hypothermia in TBI was in 1943,¹² while randomized controlled studies appeared only at the end of the 1990s.¹³ Over the last 25 years, numerous clinical trials have been conducted to assess the effects of induced hypothermia in severe TBI.¹³⁻³¹ Cooling of patients with severe TBI improved the outcome in several of these studies,^{14,17,}

21, 23, 25, 26, 29-32 while other trials suggested weak or no evidence for the use of therapeutic hypothermia following TBI.^{16, 20, 27, 33-35} It has to be noted that the study design (*e.g.*, randomization), inclusion criteria of patients, and the applied cooling protocol varied substantially among the trials, which differences could have contributed to the contradictory findings in the human studies.

As attempts to ultimately answer the question of whether therapeutic hypothermia improves the outcome of TBI, several meta-analyses have also been performed.³⁶⁻⁴² However, the different analyses provided contradictory results. While, about half of them showed that therapeutic hypothermia might be effective in the treatment of TBI and could reduce mortality,^{36, 38, 39, 41} the other half indicated that it did not decrease the mortality rate.^{37, 40, 42} It can be assumed that the high inter-study variability in the statistical and clinical designs of the trials, which were included in some of the meta-analyses and the different study selection protocols were responsible for the contradictory results. Indeed, high inter-study heterogeneity was reported in all of the performed meta-analyses so far.³⁶⁻⁴²

In the present study, we used a novel approach to determine the efficacy of therapeutic hypothermia in TBI. In our meta-analysis, we carefully evaluated all studies identified by literature search based on statistical design, patient inclusion criteria, and the applied cooling protocol, thereby we identified studies which were homogeneously designed from three aspects: statistically (randomization), clinically (whole-body cooling versus no temperature management of patients with severe TBI), and methodologically (cooling protocols precisely reported). Then, we conducted meta-analyses of these studies to evaluate the effects of therapeutic hypothermia as well as that of the individual parameters of the cooling protocol on the mortality rate of patients with severe TBI. We introduced the cooling index, an integrated measure of therapeutic hypothermia calculated from three different cooling parameters, and studied its relation to mortality in severe TBI.

Methods

Our meta-analysis was conducted in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (Table

S2).⁴³ The analysis was based on the Participants, Intervention, Comparison, Outcome (PICO) model: in severe TBI population, we aimed to assess the effect of therapeutic whole-body hypothermia compared to no cooling on the mortality ratio. This meta-analysis has been registered with PROSPERO International Prospective Register of Systematic Reviews (CRD42017056535).

Literature Search

A systematic search of the PubMed, EMBASE, and Cochrane Library databases was performed from inception to February 2017 with using the following Medical Subject Headings and search terms: (“hypothermia” OR “cooling”) AND (“traumatic brain injury” OR “TBI”) AND (“mortality” OR “death” OR “survival”). Then, the “human” filter was selected. We restricted our search to original studies published in English without time period limitations. We included journal articles of the following study types: clinical study, clinical trial, comparative study, controlled clinical trial, controlled study, multicenter study, observational study, and randomized controlled trial.

The search for the articles was conducted separately by two authors (EO and AG), who also assessed study eligibility, and extracted data from the selected studies independently. Disagreements were resolved by consensus with the help of a third author (ZR).

Data Extraction

Only those studies were included in the meta-analyses, in which the effect of therapeutic hypothermia was compared with no cooling interventions on the mortality ratio of adult patients with severe TBI. Nineteen RCTs^{13, 14, 16, 18, 20-31, 44-46} and eight articles^{15, 17, 19, 34, 47-50} of other study types were eligible for meta-analysis. The relevant data were extracted from these studies by two investigators (EO and AG) independently into Microsoft Excel software (Microsoft Corporation, Redmond, WA, USA). The following information was collected from each of the selected articles: authors’ names and date of publication, study type and randomization, characteristics of patient population [*e.g.*, mean age, sample size, intracranial pressure (ICP), and Glasgow coma score (GCS) at admission], methods of whole-body cooling (target temperature, duration of hypothermia,

and rate of rewarming), interventions in the no cooling group, and mortality rates in the study groups.

Data evaluation protocols

The collected data were evaluated based on a statistical and a biomedical approach. Statistically, we assessed the randomization of the collected studies based on the authors' statements, Jadad analysis, and detailed evaluation of the randomization protocol described in the study (see Quality assessment). In the biomedical evaluation, we narrowed the list of eligible studies to those that dealt with the effects of therapeutic whole-body hypothermia compared with no temperature management, therefore, we excluded those articles, in which selective brain cooling,^{44, 46, 51} or fever control with antipyretics^{34, 47, 48} was used, or when patients with spontaneous hypothermia were involved in the study.^{49, 52} Eligible studies resulting from the statistical or the biomedical refinement or both were compared with the random effect model of meta-analysis for odds ratio (OR) as effect size. To assess which parameters of the cooling methods have the biggest impact on the outcome of severe TBI, the studies were divided into subgroups based on target cooling temperature, cooling duration, and speed of rewarming. Target cooling temperatures were classified *a priori* as "moderate" (32-33°C)⁵³ and "mild" (33-35°C).^{29, 53} Cooling duration was divided into short (24-48h) and long (>48h) subgroups.⁵⁴ According to recent recommendations about the use of very slow (0.1-0.2°C/h) rewarming rates in patients with severe TBI,^{55, 56} the speed of rewarming was divided into either of 2 subgroups: 0.25-1°C/h and less than 0.25°C/h, also including passive. Rewarming was determined passive if the cooling process ensued without induction of any cooling or rewarming device within the next 18-24 hours.^{57, 58} For quantification purposes, the speed of passive rewarming was considered to equal 0.06°C/h.^{57, 58}

In addition to analyzing the effect of each cooling parameter individually, the influence of the used combinations of the three parameters together was also assessed on the outcome of severe TBI. When all three parameters, *i.e.*, target cooling temperature, cooling duration, and speed of rewarming, were reported in the same study, we calculated the integrated measure of cooling and named it as the cooling index. The cooling index

represents the area between the body temperature curve of cooled patients and a hypothetical horizontal line corresponding to a normal body temperature of 36.5°C (Fig. S2). The following formula was used: “cooling index” = $\Delta T \times t + (\Delta T \times \Delta T/R)/2$, where “ ΔT ” is the magnitude of hypothermia, *i.e.*, the difference between normal (36.5°C) and target cooling temperatures expressed in °C; “ t ” is duration of the maintenance of hypothermia in hours; and “ R ” is the rate of rewarming (°C/h); see also Fig. S2A. The impact of the rewarming rate was incorporated in the cooling index as the area of the triangle, which represents the change in body temperature during the rewarming phase. It has to be noted that due to the relatively narrow range (0.06-1°C/h) of the rewarming rates used in the analyzed studies, this area had the smallest contribution to the final value of the cooling index, while depth and duration of the cooling were more dominant contributors. The cooling index corresponds with the integrated measure of the magnitude and duration of therapeutic hypothermia. For example, a similarly high cooling index can result from short and deep cooling with rewarming at 0.25°C/h (Fig. S2B), as well as from longer, but milder cooling with slower, passive rewarming (Fig. S2A). A moderate cooling index can result from mild and short cooling followed by slow rewarming at $\sim 0.08^\circ\text{C/h}$ (Fig. S2C), while cooling index is low if cooling duration is brief and rewarming is faster (1°C/h) even if target cooling temperature is very low (Fig. S2D). For meta-analysis, the included studies were evenly distributed ($N = 4$) into subgroups with low ($< 160^\circ\text{C} \times \text{h}$), moderate (160-200°C × h), and high ($> 200^\circ\text{C} \times \text{h}$) cooling index. Examples for the assessment of the cooling index in each of the three subgroups are presented in Figure S2.

In five of the analyzed studies,^{14, 25, 26, 29, 31} the cooling protocol was changed depending from the ICP. Thus, we also compared whether the outcome of TBI differed between the group of studies which reported adjustments in the cooling protocol based on ICP and the group of studies which did not.

Quality assessment

To evaluate the quality of the included trials, two independent reviewers (EO and ZR) assessed the bias of the included studies according to the Cochrane Handbook.⁵⁹ The methodology described for random sequence generation, allocation concealment, blinding

of participants and personnel, blinding of outcome assessment, completeness of outcome data, and selective outcome reporting was assessed during the analysis. Due to the nature of the studies eligible for our meta-analyses, the blinding method could not be assessed. The Jadad score, a five-point quality scale was used also to analyze the quality of the articles.⁶⁰ Furthermore, an additional three-step evaluation of the randomization used in each study was performed, which was more relevant for such studies included in our meta-analysis. The first two questions of this evaluation were similar to those of the Jadad score, viz., whether the use of randomization was stated and whether the randomization procedure was appropriate and reported in the study. In the third step, the level of randomization was determined as good, if the use of randomization, and its exact protocol was reported in the study. If the use of randomization was stated, but the exact method was not described, the randomization level was assessed as medium, while in cases when the authors did not mention randomization, the level of randomization was considered low. This evaluation was necessary, because there were several studies in which the use of randomization was stated, but the exact method was not described,^{21, 23, 25, 27-31} which leaves the statement open for questions.

Statistical Analysis

The statistical analysis was performed according to the standard methods of meta-analysis. The primary effectiveness outcome was all-cause mortality. OR with 95% confidence intervals (CI) for mortality in the adult patients with severe TBI were calculated in a random-effects model of meta-analysis. Summary effect estimates were stratified by study design and the between-groups effects were assessed.

Publication bias was assessed with funnel plots by using the Duval and Tweedie trim and fill method⁶¹ and the Egger's test (Egger's test values of less than 0.1 were considered as indicators of significant small-study effect) (see Supplementary material). Between-study heterogeneity was tested with Q homogeneity test (p values of less than 0.05 were considered as indicators of significant heterogeneity) and with I^2 statistical test, where I^2 is the proportion of total variation attributable to between-study variability (an I^2 value of more than 50 was considered as indicating considerable heterogeneity). Results of

the meta-analyses are depicted as forest plots. All analyses were performed using the Comprehensive Meta-Analysis software (version 3.3; Biostat, Inc., Engelwood, MJ, USA).

Results

Study selection

The flow chart of the study selection is presented in Figure 1. Until February 23, 2017 the literature search identified altogether 709 studies from the PubMed, EMBASE, and Cochrane databases. After enabling filters for human studies and English language and using additional filters (study types) 321 studies remained, which were screened for title and abstract for inclusion criteria. 273 articles were excluded because of insufficient data reporting or because children were studied. 48 studies were included in qualitative synthesis. A further 21 articles were excluded due to the lack of mortality data. 27 studies were included and pooled for quantitative synthesis.

When we compared the effects of therapeutic hypothermia with no cooling by including all 27 identified studies in the meta-analysis (Fig. S3), we did not find a significant difference in the OR for mortality between the groups. Importantly, the included studies were methodologically quite heterogeneous with regards to both statistical and clinical designs ($Q = 167$, $p < 0.001$; $I^2 = 84$).

As a statistical approach to reduce heterogeneity, we analyzed separately those nineteen studies which could be considered as RCTs (Fig. S4). Therapeutic hypothermia tended to improve the outcome in patients with severe TBI, but the difference did not reach the level of significance ($OR = 0.782$; $p = 0.075$). However, between-study heterogeneity was still reasonably high as indicated by the nearly significant result of the Q homogeneity test ($p = 0.053$). Based on detailed quality assessment of the randomization protocols in the studies, the level of randomization was assessed as good in 3 studies, medium in 9 studies, and low in 2 studies (Table S3). The remaining 5 RCTs were not included in this assessment, as they did not pass the criteria set for homogenous clinical and methodological designs (see below). The use of therapeutic hypothermia significantly decreased the risk of mortality in the subgroup of medium randomization level ($OR = 0.676$; $p = 0.041$), while no significant difference was found between cooling versus no

cooling in the other two subgroups (Fig. S5). When the good and medium subgroups were merged, their pooled OR remained significantly lower than 1 (OR = 0.66, $p = 0.003$), which indicated better outcome in therapeutic hypothermia, but clinically, the inter-study heterogeneity was still considerably high.

We evaluated the studies based on clinical and methodological designs. Our goal was to study the effect of therapeutic hypothermia applied to the whole body of patients with severe TBI, but without spontaneous hypothermia and without temperature control. Therefore, 3 trials using selective brain cooling,^{44, 46, 51} 2 articles including cases of spontaneous hypothermia,^{49, 52} and 3 studies applying fever control^{34, 47, 48} had to be excluded from the analysis. Further 4 studies could not be included in the final analyses, because the applied cooling methods were not reported in sufficient details.^{15, 18, 19, 22} In one of the trials GCS of the included patients ranged between 3-15,¹⁶ which sample also includes mild (GCS = 13-15) and moderate cases of TBI (GCS = 9-12), therefore it also had to be excluded from further analysis (Fig. 1).

As result of the combined (statistical and physiological) evaluation of the studies identified by our literature search, 14 full-text publications (involving 1,786 adult patients with severe TBI; 896 in the therapeutic hypothermia group and 890 in the no cooling group), were included in the next steps of our analysis. The descriptive statistics of the age, GCS, ICP, and injury severity score in the patient populations from these 14 studies are presented in Table 1. These data reported from a big patient population ($N > 1,700$) correspond with the clinical parameters observed in the patient presented in Table S1. The publication years of the studies ranged from 1993 to 2017. All of them can be considered as randomized trials, in which the exact cooling methods of the whole body (target temperature, cooling duration, and speed of rewarming) are reported, and the effect of therapeutic hypothermia on mortality was compared with patients without temperature management in severe TBI. The homogeneity of the studies was verified by Egger's test, Q , and I^2 statistics, which showed no significant difference in inter-study variability (Egger's $p = 0.509$; $Q = 17$, $p = 0.224$; $I^2 = 21$). Meta-analysis of these studies revealed that therapeutic hypothermia significantly improved the outcome of severe TBI (OR = 0.675; $p = 0.004$) (Fig. 2).

Next, we studied the different parameters of the cooling protocol *viz.*, target temperature, cooling duration, and speed of rewarming. Based on target cooling temperatures 4 studies used “moderate” (equal or less than 33°C) and 7 studies “mild” (33-35°C) hypothermia, while in 3 studies the reported target temperature range overlapped between the moderate and mild groups (Fig. 3). We found that the use of mild therapeutic hypothermia considerably improved the outcome (decreased the risk of death) as compared with no cooling (OR = 0.627; $p = 0.050$). No significant differences were found in the moderate hypothermia and the overlapping target temperature groups (Fig. 3). With regards to cooling duration, in 9 studies short (24-48h) hypothermia was used, while in 5 studies cooling was longer than 48 hours (Fig. 4). The effect of long-term hypothermia was beneficial on the mortality rate of patients with severe TBI compared to patients with no temperature management (OR = 0.534; $p < 0.001$), while in case of short-term hypothermia the effect was not significant (Fig. 4). Based on the speed of rewarming, the studies were divided into subgroups using rewarming rates of either 0.25-1°C/h or less than 0.25°C/h. We found that therapeutic hypothermia improved the outcome of severe TBI when the rewarming rate was below 0.25°C/h (OR = 0.58; $p = 0.014$), while there was only a tendency for the better outcome when rewarming rate was $\geq 0.25^\circ\text{C}/\text{h}$ (OR = 0.74; $p = 0.085$) (Fig. 5). These results suggest that certain parameters of the cooling protocol can be associated with more beneficial effects of therapeutic hypothermia on the mortality of patients with severe TBI, but how the combination of the different parameters together, *i.e.*, the total extent of cooling, contributes to the outcome could not be firmly established.

In our next approach, we studied the integrated effect of the cooling parameters on the outcome of the disease. From the cooling parameters reported in the studies with medium and good level of randomization (Table S3), the cooling index was assessed by considering all three variables, *viz.*, target temperature, cooling duration, and speed of rewarming, in the formula (for details, see Methods and Fig. S2A). The reported parameters and the cooling index derived from these data are shown in Table 1. By calculating the cooling index, we were able to compare the effect of the overall extent of hypothermia among studies which used different cooling parameters in their protocols. The OR (estimated expected average) in the subgroups with low ($< 160^\circ\text{C} \times \text{h}$), moderate

(160-200°C × h), and high (> 200°C × h) cooling index was 0.831 ($p = 0.535$), 0.754 ($p = 0.340$), and 0.470 ($p = 0.035$), respectively (Fig. 6). Importantly, the only significant effect for an OR of less than 1, *i.e.*, when cooling was beneficial compared to no cooling, was observed in the subgroup of studies with high cooling index. These results suggest that in addition to the different independent contribution of each cooling parameter, the integrated measure of the magnitude and duration of therapeutic hypothermia (as indicated by the cooling index) can play a decisive role in determining whether the applied cooling protocol will decrease the risk of death in patients with severe TBI.

We also evaluated whether adjustments of the cooling parameters depending from the ICP of the patients impacts the outcome in severe TBI. When we compared the outcome of TBI between the group of studies which adjusted the cooling protocols based on ICP with the group of studies which did not, we found that when ICP was taken into account, the effect of therapeutic hypothermia was beneficial on the mortality rate of patients with severe TBI compared to patients with no temperature management (OR = 0.53; $p < 0.001$), while the beneficial effect was not significant when the cooling protocol was not changed depending from ICP (OR = 0.85; $p = 0.265$) (Fig. 7). These results support the necessity of monitoring ICP and adjusting the cooling parameters depending from ICP during therapeutic hypothermia.

Discussion

In the present study, we show that whole-body cooling decreases the risk of death in patients with severe TBI by conducting meta-analysis of clinical studies, which were homogenous with regards to statistical, clinical, and methodological designs. By analyzing the individual cooling parameters, we reveal that milder and longer cooling and slower rewarming speed than 0.25°C/h are the most important to improve the outcome of severe TBI. We introduce the cooling index to assess the overall extent of cooling, and show that therapeutic hypothermia is beneficial in severe TBI only if the cooling index is sufficiently high.

Our findings are in line with several clinical trials showing a beneficial effect of therapeutic hypothermia on the outcome of severe TBI,^{13, 14, 17, 21, 23, 25, 26, 29-31} whereas they

contradict other trials which found no or even adverse effect of whole-body cooling in TBI.^{20, 24, 27, 28} Differences in statistical, clinical, and methodological designs among the studies can be assumed to account for the contradictory results. The highest quality human studies are RCTs, while observational studies and retrospective analyses provide lower level of evidence. Among RCTs the randomization protocol can vary (see Table S3), which results in different levels of statistical bias involved in the trials. Three multi-center clinical trials^{20, 27, 28} found either no change or worse mortality rates in the cooled groups of patients with TBI, whereas all of the single-center studies^{13, 14, 17, 21, 23, 25, 26, 29-31} showed that therapeutic hypothermia was associated with a lower mortality rate. Differences between results from single-center versus multi-center trials have been observed earlier with regards to therapeutic hypothermia.⁶² Large multi-center trials are usually considered as higher quality studies than single-center trials mostly when pharmacological treatments are investigated, however, when precise execution of the studied intervention is crucial as in the case of therapeutic hypothermia, then the different protocols used in different centers can lead to heterogeneous results, which can mask the differences between the treated and control groups. The study type and randomization level should be taken into account when the findings of a study are evaluated and, especially, when several studies are compared with meta-analysis.

At least in some cases the clinical design of the studies could clearly contribute to mask the effects of therapeutic hypothermia on the outcome. In the study by Andrews et al.¹⁶ an adverse effect of therapeutic hypothermia on the outcome of TBI was found, however, patients with GCS of 3-15 were included in the trial and subgroup analysis for the different severities of TBI was not performed. Furthermore, it can be assumed that the deleterious effects of cooling on the outcome could be attributable to the different conventional treatments, which were not controlled for between groups.⁶³ Clifton et al.³⁰ could not confirm the efficacy of therapeutic hypothermia in TBI, which contradicted the results of an earlier phase 2 trial.²⁷ However, patients with spontaneous hypothermia were also included in the study,³⁰ which could have influenced the results. As opposed to therapeutic hypothermia when deep body temperature decreases due to forced cooling, spontaneous hypothermia is regarded as a regulated, adaptive mechanism in response to

severe forms of a disease (e.g., systemic inflammation),⁶⁴ and it is often associated with worse outcome.⁶⁵ In some studies the authors used fever control,^{34, 47, 48} which could also influence the results. Most of the antipyretics (e.g., NSAIDs) do not only reduce fever, but also exert anti-inflammatory and other effects. It has been shown that unlike the use of antipyretics, fever was not associated with mortality in systemic inflammation,⁶⁶ suggesting different biological and clinical implications of fever and antipyretics.⁶⁶ Since inflammatory processes are also involved in the pathomechanism of severe TBI,⁴⁻⁶ the use of antipyretics in the control (no cooling) group could change the outcome of the disease.

Methodologically, studies using selective brain cooling^{44, 46, 51} should be distinguished from those applying whole-body hypothermia, because selective brain cooling is occasionally invasive, and if maintained for several hours, it may induce systemic hypothermia.⁶⁷ A critical appraisal of published clinical studies showed that the methods of therapeutic hypothermia were heterogeneous in terms of timing, depth, duration, and rewarming rate.⁶⁸ The impact of the different cooling methods on the outcome can be reduced if exclusively those studies are compared, in which the cooling parameters are precisely reported, and the role of the parameters is also analyzed.

Previous meta-analyses of the available data from the clinical trials lead to contradictory results regarding the efficacy of therapeutic hypothermia in TBI.³⁶⁻⁴² It can be assumed that the substantial heterogeneity among the trials included in these meta-analyses could be a crucial factor, which influenced the outcome of the analysis. By using meta-analysis, weighting of the included results can be based only on the deviation reported in a trial. The more uncertain data (greater variability, smaller sample) are taken into account with a lesser weight, but the selection of the studies cannot be accounted for. The novel approach in our meta-analysis is that we extended the conventionally used protocols for study selection by detailed evaluation of the statistical, clinical, and methodological design of the studies. As a result, we identified a group of studies which were homogenous with regard to all three evaluated aspects of the design. By analyzing the results reported in these studies, we found that therapeutic hypothermia improves the outcome of severe TBI and its beneficial effect can be associated with certain cooling parameters (milder and longer cooling, and slower rewarming than 0.25°C/h). Our results

about the importance of slow rewarming are well in agreement with data obtained from experimental animals showing that hypothermia followed by slow rewarming provides maximal neuroprotective effect,^{69, 70} and further support the current recommendations about the use of very slow (0.1-0.2°C/h) rewarming rates in patients with severe TBI.^{55, 56} On the contrary, the use of uncontrolled rewarming may potentially offset the benefits of hypothermia, particularly because it may cause rebound intracranial hypertension.^{13, 30} Nevertheless, it also has to be noted that since the reported rewarming rates covered only a narrow range, an extended analysis, which would take in account fast, moderate, and slow rewarming of the patients, could not be performed in our study and that the contribution of rewarming to the cooling index was smaller than that of the other two cooling parameters. Importantly, different combinations of the studied parameters can be also advantageous if the total extent of hypothermia (cooling index) is sufficiently high. A high cooling index (~ 230°C × h), thereby beneficial effect of therapeutic hypothermia could be achieved by different combinations of the cooling parameters, *e.g.*, by short (48h) and deep (32.5°C) cooling followed by rewarming at a rate of 0.25°C/h,³⁰ as well as by longer (72h) and milder (34°C) cooling followed by slower (0.06°C/h) rewarming²³ (also compare with Fig. S2A and B). By looking at the single cooling parameters used in the two studies,^{23, 30} the effect of therapeutic hypothermia on the outcome could seem controversial, as moderate and short cooling³⁰ with slower rewarming²³ were not beneficial, while milder and longer hypothermia²³ with not so slow rewarming³⁰ improved the outcome in severe TBI. However, if the integrated measure of the magnitude and the duration of cooling is considered, *viz.*, the cooling index, then a high extent of hypothermia can be demonstrated in both studies,^{23, 30} resulting in a beneficial effect of whole-body cooling on the outcome of severe TBI as seen in the subgroup with high cooling index (OR = 0.47; Fig. 6). Since the clinical data of the patient presented in Table S1 are similar to the analyzed patient population, it is tempting to speculate that cooling of this patient with the methods specified above could have improved the outcome in his case. Our meta-analysis included data from a total of 1,786 adult patients with severe TBI, but due to the nature of this method, we have studied the reported mean in populations of patients, rather than the association in individual subjects. Therefore, precisely designed clinical trials are needed to confirm our results in clinical settings. The design of such trials should

include appropriate randomization protocols, targeted population of patients (severe TBI, no pre-existing thermoregulatory disorders, no differences between the study and control groups in medical-surgical treatment), and precise cooling protocols (a combination of parameters with sufficiently high cooling index). By validation of our findings in clinical trials, it would be possible to identify a subpopulation of patients with TBI, in which well-controlled therapeutic cooling could improve the outcome.

The addition of further patient characteristics (*e.g.* ICP, age, comorbidities) and methodological parameters (*e.g.*, initiation time of cooling) to the inclusion criteria of such trial, could help to accurately specify the patient population which can benefit the most from precisely conducted therapeutic hypothermia. Increased ICP can be regarded as both an indicator of the actual brain damage and as a cause of additional pathological changes in severe TBI.⁵⁵ A strong body of evidence supports that therapeutic hypothermia is a useful tool to decrease ICP in TBI, however this does not necessarily improve the outcome of the disease.⁶⁸ The contradiction between the management of intracranial hypertension and the lack of improvement in the outcome can be due to inadequate maintenance of the hypothermia-induced lower ICP, because of the applied cooling protocol. Rebound increases of ICP are more common in patients with TBI if the cooling duration is too short and the rate of rewarming is too fast.⁵³ To avoid the adverse changes in ICP, five of the analyzed studies reported that the designed cooling protocol was adjusted based on the ICP.^{14, 25, 26, 29, 31} Here, we showed that in these studies therapeutic hypothermia significantly improved the outcome in severe TBI compared to those trials which followed the protocol regardless of ICP.^{8, 13, 17, 20, 23, 24, 27, 28, 30} These results highlight the importance of continuous ICP monitoring during therapeutic hypothermia and warrant for the need of adjustments in the cooling protocol based on ICP. Unfortunately, the data about the deviations from the set protocols were not reported in sufficient details in any of the studies, in order to account for the changes in our calculation of the cooling index. It would also be interesting to study how pharmacological tools can be implemented in the induction of hypothermia in addition to external cooling of the body. Ideal candidates for such drugs could be among the new generation of the antagonists of the transient receptor potential vanilloid-1 channel, which were developed as painkillers, but can cause

marked hypothermia.⁷¹ These additional parameters could not be included in the present meta-analysis because of insufficient data availability. Due to the same reason, the upper limit of the cooling index, *i.e.*, above which the harmful effect of hypothermia would dominate over the beneficial effects, could not be determined in our analysis. In the included trials, even from which the highest cooling indices were calculated, cooling of the patients improved the outcome.^{21, 23, 29, 30} It can be expected that the upper safety limit of the cooling index would need to be established separately for the different study populations. Identification of the exact cooling protocol for a specified patient population would be in line with recent paradigms in the treatment of TBI, suggesting the need for targeted management of individuals or subsets of patients to improve the outcome.^{72, 73}

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Table 1 Characteristics of the patient groups with severe TBI in the studies included in the meta-analyses.

Study	Mean age (years)	GCS	Treatment	Number of patients (N)	ICP (mmHg)	ISS	Cooling duration (h)	Target temperature (°C)	Rewarming rate (°C/h)	Cooling index (°C × h)	Cooling index subgroup
Clifton (1993)	29.1	4-7	Cooling	24	14.5	NR	48	32-33	0.25	224	high
			No cooling	22	16.4	NR					
Clifton (2001)	31.5	3-8	Cooling	190	18.1	28 ± 9	48	32.5-34	0.25	177	moderate
			No cooling	178	17.9	28 ± 8					
Clifton (2011)	28.5	3-8	Cooling	52	NR	30 ± 6	48	33-34	0.25	162	moderate
			No cooling	45	NR	30 ± 9					
Hashiguchi (2003)	34.1	3-8	Cooling	9	11.1 ± 4.8	30.7 ± 5.6	48	33.5-34.5	~ 0.08	159	low
			No cooling	8	11.9 ± 4.2	33.0 ± 6.4					
Jiang (2000)	41.4	3-8	Cooling	43	29.6 ± 2.2	NR	72-336	33-35	1	243	high
			No cooling	44	30.3 ± 3.0	NR					

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 reduces mortality in severe traumatic brain injury if the cooling is initiated within 8 hours of the injury (DOI: 10.1089/neu.2018.5649)
 reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

Liu (2015)	NR	3-8	Cooling	110	27.5 ± 16.9	NR	72-288	35-36	< 0.25	-	-
			No cooling	110	26.8 ± 17.5	NR					
Marion (1997)	33.5	3-7	Cooling	40	15.4	NR	24	32-33	1	104	low
			No cooling	42	19.7	NR					
Polderman (2002)	36.7	3-8	Cooling	64	37.0 ± 20.0	NR	24	32	0.08	-	-
			No cooling	72	< 20.0	NR					
Shiozaki (1993)	35.4	<8	Cooling	16	35.4 ± 12.0	NR	48	33.5-34.5	passive	172	moderate
			No cooling	17	36.9 ± 12.1	NR					
Shiozaki (2001)	38.5	3-8	Cooling	45	NR	NR	48	33.5-34.5	~ 0.08	159	low
			No cooling	46	NR	NR					
Smrcka (2005)	41.0	3-8	Cooling	35	NR	11.8 ± 5	72	34	passive	232	high
			No cooling	37	NR	17.6 ± 7					
Tang (2017)	41.1	3-8	Cooling	30	NR	NR	48	32-35	0.25	162	moderate
			No cooling	30	NR	NR					
Zhao (2011)	37.2	3-8	Cooling	40	15.9 ± 4.3	NR	72	32.5-33	passive	387	high
			No cooling	41	17.1 ± 5.0	NR					
Zhi (2003)	42.5	3-8	Cooling	198	26.9 ± 4.6	NR	24-168	32-35	0.25	138	low
			No cooling	198	26.6 ± 4.9	NR					

-, not applicable; GCS, Glasgow coma score; ICP, intracranial pressure; ISS, injury severity score; NR, not reported.

FIGURE LEGENDS

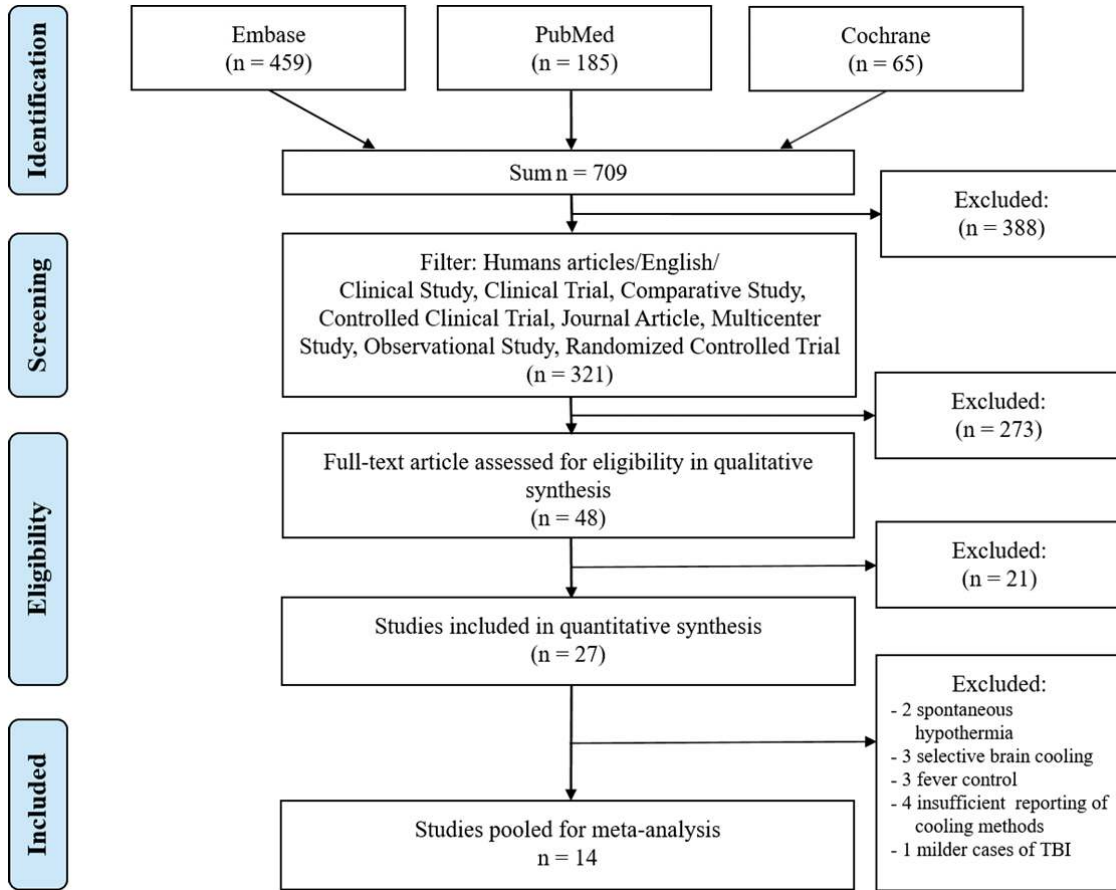


Figure 1 Flow chart of study selection and inclusion.

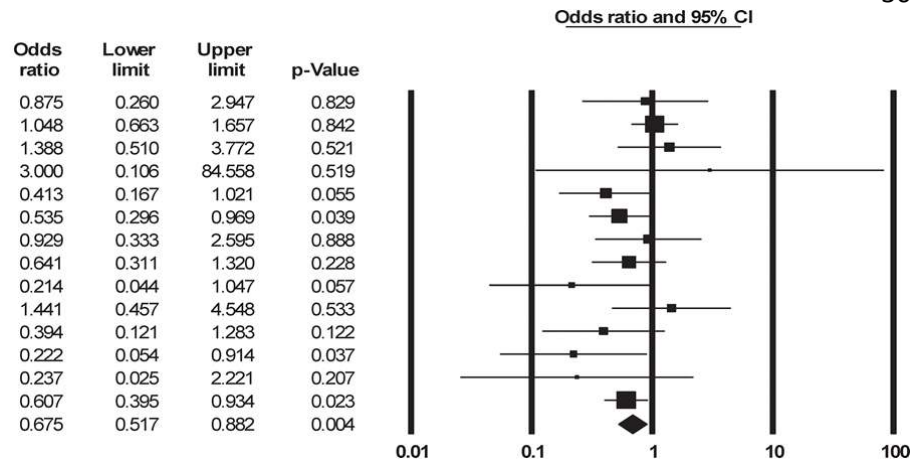


Figure 2 Forest plot of the odds ratios for mortality rate between cooled and not cooled groups of patients with severe TBI using random-effects model in statistically, clinically, and methodologically homogenous RCTs.

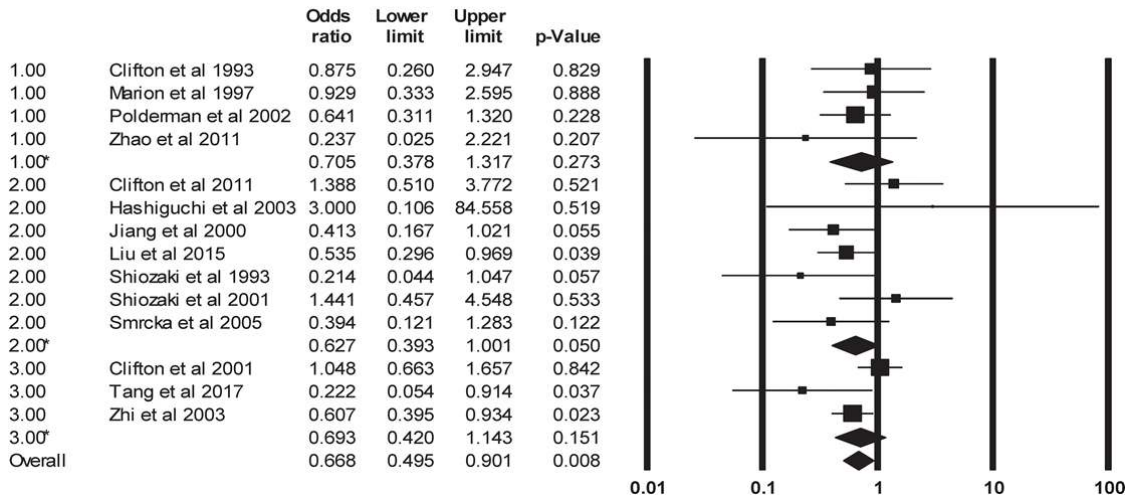


Figure 3 Forest plot of the odds ratios for mortality rate between cooled and not cooled groups of patients with severe TBI using random-effects model in RCTs divided into moderate (32-33°C; group label 1), mild (33-35°C; group label 2), and overlapping (32-35°C; group label 3) hypothermia subgroups based on target cooling temperature. Here and in Figures 4-6, the lines marked with * denote the mean values of the respective subgroups.

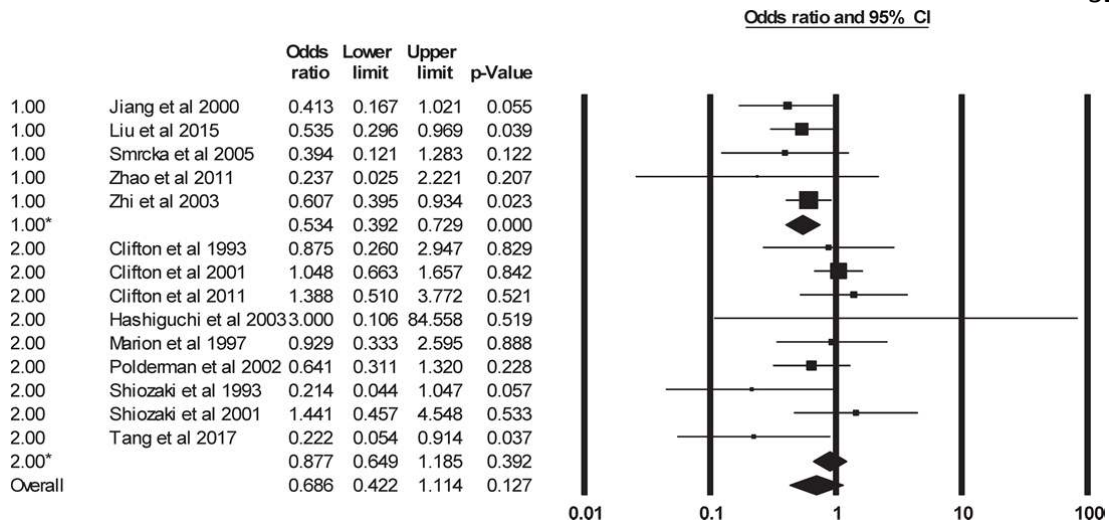


Figure 4 Forest plot of the odds ratios for mortality rate between cooled and not cooled groups of patients with severe TBI using random-effects model in RCTs divided into long (> 48h; group label 1) and short (24-48h; group label 2) subgroups based on cooling duration.

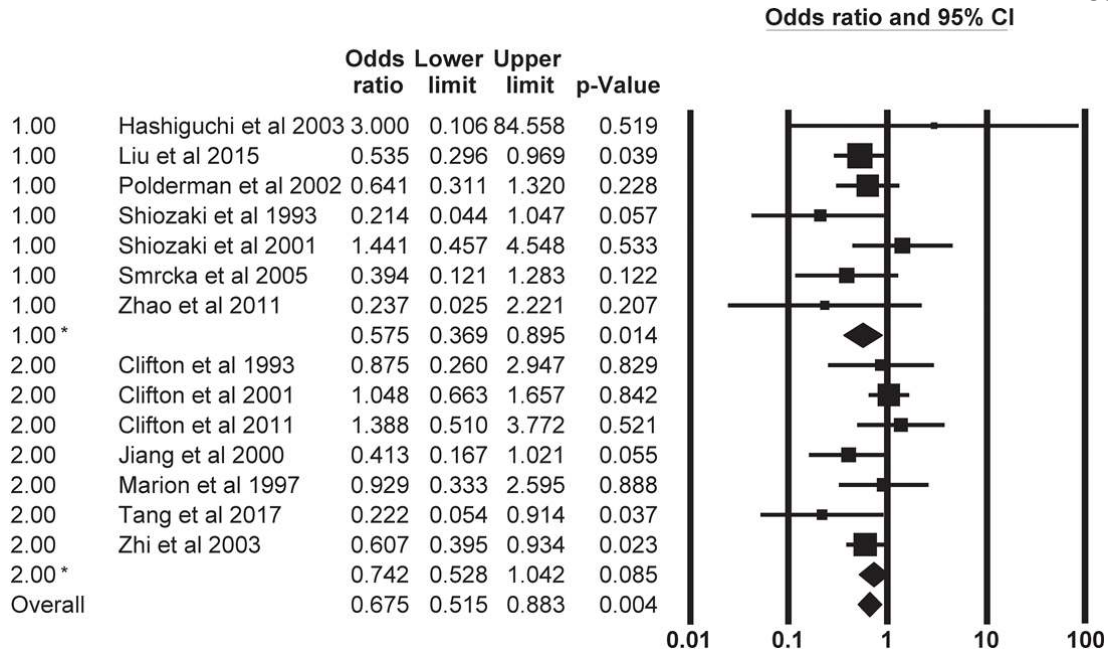


Figure 5 Forest plot of the odds ratios for mortality rate between cooled and not cooled groups of patients with severe TBI using random-effects model in RCTs divided into 2 subgroups based on rewarming rate: less than 0.25°C/h (group label 1) and 0.25-1°C/h (group label 2).

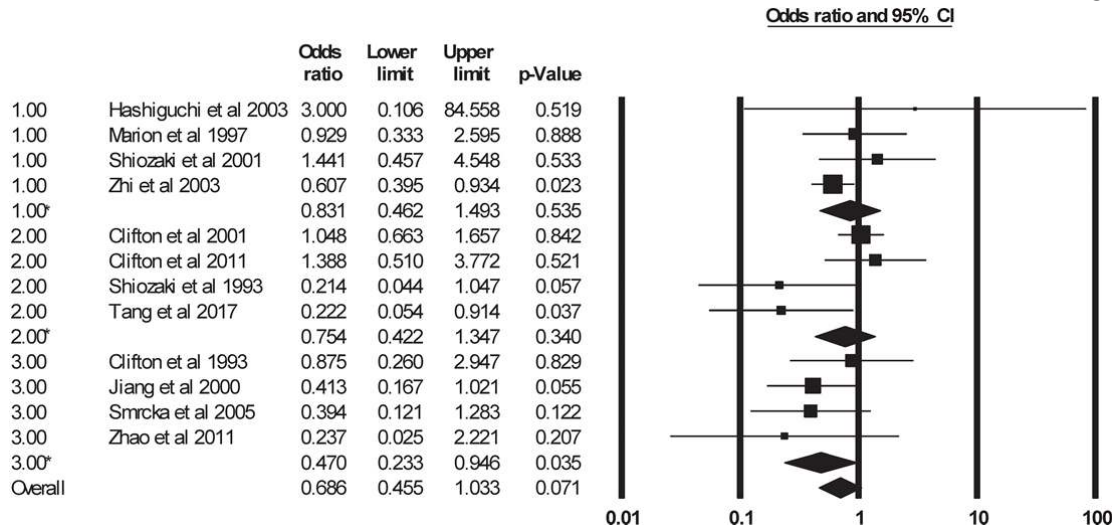


Figure 6 Forest plot of the odds ratios for mortality rate between cooled and not cooled groups of patients with severe TBI using random-effects model in RCTs divided into low (< 160°C × h; group label 1), moderate (160-200°C × h; group label 2), and high (> 200°C × h; group label 3) subgroups based on the cooling index.

		Odds ratio	Lower limit	Upper limit	p-Value
1.00	Jiang et al 2000	0.413	0.167	1.021	0.055
1.00	Polderman et al 2002	0.641	0.311	1.320	0.228
1.00	Shiozaki et al 1993	0.214	0.044	1.047	0.057
1.00	Tang et al 2017	0.222	0.054	0.914	0.037
1.00	Zhi et al 2003	0.607	0.395	0.934	0.023
1.00*		0.530	0.383	0.734	0.000
2.00	Clifton et al 1993	0.875	0.260	2.947	0.829
2.00	Clifton et al 2001	1.048	0.663	1.657	0.842
2.00	Clifton et al 2011	1.388	0.510	3.772	0.521
2.00	Hashiguchi et al 2003	3.000	0.106	84.558	0.519
2.00	Liu et al 2015	0.535	0.296	0.969	0.039
2.00	Marion et al 1997	0.929	0.333	2.595	0.888
2.00	Shiozaki et al 2001	1.441	0.457	4.548	0.533
2.00	Smrcka et al 2005	0.394	0.121	1.283	0.122
2.00	Zhao et al 2011	0.237	0.025	2.221	0.207
2.00*		0.849	0.636	1.133	0.265
Overall		0.675	0.425	1.070	0.095

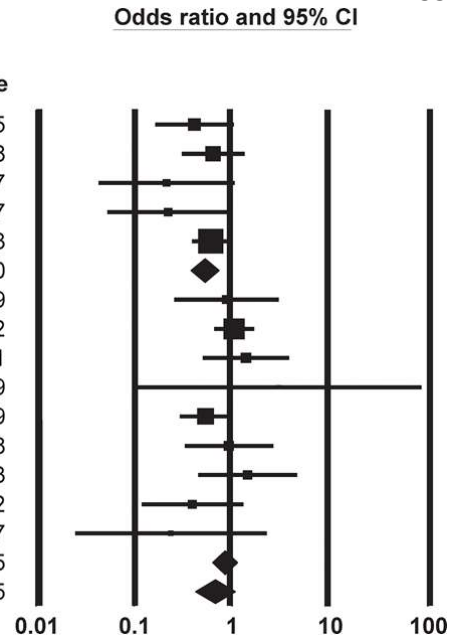


Figure 7 Forest plot of the odds ratios for mortality rate between cooled and not cooled groups of patients with severe TBI using random-effects model in RCTs divided into 2 subgroups: cooling protocol adjustments based on ICP (group label 1) and no ICP-based changes in the protocol (group label 2).

Supplementary material

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Table S1. Characteristics of a patient with severe TBI admitted to one of our centers (St. Joseph's Hospital).

Age (year)	35
Gender	male
Mechanism of Injury	Motor vehicle collision
GCS	3
CSF opening pressure (cm H ₂ O)	6
Injury Severity Score	38
Temperature on admission (°C)	38.4
Peak temperature during hospitalization (°C)	39.1
Description of Brain Injury	Fig S1
Associated Injuries	Bilateral multiple rib fractures, bilateral scapula fractures, bilateral pneumothoraces, T8 and T9 vertebral body fractures, comminuted nasal bone and osseous nasal septal fractures, fracture of right ethmoid air cells, segmental fracture of right lamina papycea
Hospital Course	<p>Patient underwent orotracheal intubation for depressed mental status, and bilateral chest tube placement for pneumothoraces.</p> <p>Transferred to level 1 trauma center for definitive evaluation and treatment. ICP monitor and ventriculostomy placed.</p> <p>He was admitted to the Neuro Intensive Care Unit, and underwent continuous EEG and ICP monitoring. He developed increasing ICPs, managed initially with pressor support to augment cerebral perfusion pressure. Barbiturate-induced coma was initiated on hospital day #5 for refractory elevated ICP.</p> <p>On hospital day #7, the patient's family elected to initiate palliative care secondary to poor neurologic prognosis, and patient died on hospital day #7.</p>

Table S2. PRISMA checklist.

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	7
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7-8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7, Figure 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7-10
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7-10
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	10-11

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	11-12
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I ²) for each meta-analysis.	7-10
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	10-11
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	11-12
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	13-14; Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	14-15
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	13-14; Table S3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	13-17; Figures 2-7 and S3-S5
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	13-17; Figures 2-7
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	13-15; Table S3
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	16-17; Figures 6 and S2
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	18-23
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	18-19
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	22-23
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	24

Table S3. Detailed quality assessment of the studies included in the meta-analysis according to the Cochrane Handbook and the Jadad score. In the own quality assessment of the randomization protocols, the level of randomization was assessed as good, medium and low.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias	Jadad score	Own assessment
Clifton 1993	?	+	-	-	?	-	?	2	?
Clifton 2001	?	+	-	-	?	?	?	2	?
Clifton 2011	+	+	-	+	?	?	?	3	+
Hashiguchi 2003	?	?	-	-	?	?	?	1	?
Jiang 2000	?	?	-	-	?	?	?	1	?
Liu 2015	-	-	-	-	?	?	?	1	-
Marion 1997	+	+	-	+	?	?	?	3	+
Polderman 2002	-	-	-	-	?	?	?	1	-
Shiozaki 1993	?	?	-	-	?	-	?	1	?
Shiozaki 2001	?	?	-	-	?	-	?	1	?
Smrcka 2005	?	?	-	-	?	-	?	1	?
Tang 2017	+	+	+	?	?	-	?	4	+
Zhao 2011	?	-	-	-	?	-	?	1	?
Zhi 2003	?	-	-	-	?	-	?	1	?



Figure S1. Axial CT image of the patient admitted with severe TBI, obtained at time of arrival to level 1 trauma center. TBI comprised diffuse bilateral subarachnoid hemorrhage, bilateral frontal contusions, small right subdural hematoma, and effacement of basal cisterns secondary to cerebral edema.

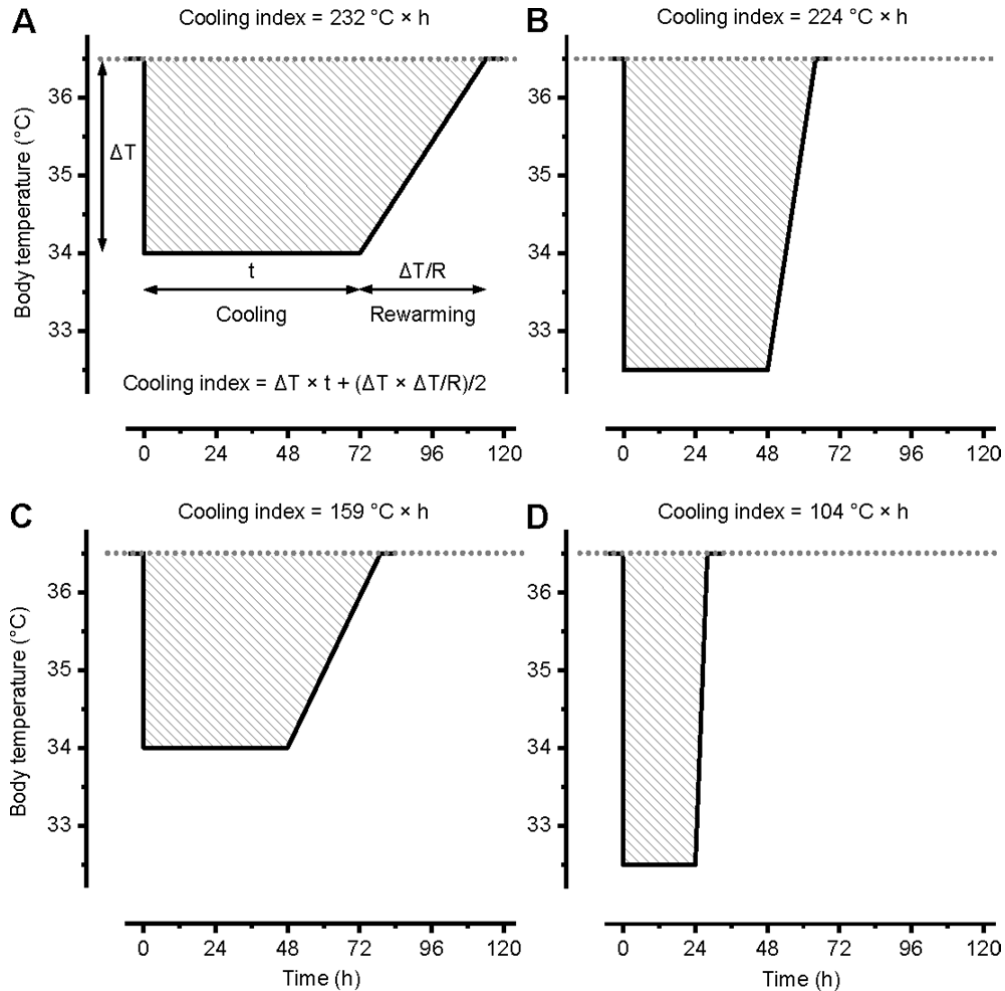


Figure S2. Calculation method of the cooling index and examples for high (**A** and **B**), moderate (**C**), and low (**D**) calculated values. The shown examples were calculated from the cooling parameters reported by Smrcka et al. (2005) (**A**), Clifton et al. (1993) (**B**), Shiozaki et al. (2001) (**C**), and Marion et al. (1997) (**D**). In all panels, the striped area represents the cooling index; the calculated values are indicated. Dotted gray line illustrates normal (not cooled) deep body temperature considered as 36.5°C . ΔT , difference between normal body temperature and cooling target temperature; t , cooling duration; R , rate of rewarming. See main text for detailed explanation.

	Odds ratio	Lower limit	Upper limit	Upper limit
Andrews et al 2015	1.480	0.958	2.287	2.287
Balvers et al 2016	3.796	2.655	5.427	5.427
Bukur et al 2012	1.653	1.446	1.890	1.890
Clifton et al 1993	0.875	0.260	2.947	2.947
Clifton et al 2001	1.048	0.663	1.657	1.657
Clifton et al 2011	1.388	0.510	3.772	3.772
Harris et al 2009	2.250	0.439	11.522	11.522
Hashiguchi et al 2003	3.000	0.106	84.558	84.558
Hifumi et al 2016	4.817	1.268	18.302	18.302
Jiang et al 2000	0.413	0.167	1.021	1.021
Lee et al 2010	0.500	0.041	6.166	6.166
Liu et al 2006	0.367	0.105	1.281	1.281
Liu et al 2015	0.535	0.296	0.969	0.969
Maekawa et al 2015	1.820	0.822	4.031	4.031
Marion et al 1997	0.929	0.333	2.595	2.595
Polderman et al 2002	0.641	0.311	1.320	1.320
Qiu et al 2007	0.603	0.223	1.630	1.630
Rincon et al 2014	22.484	11.173	45.246	45.246
Shiozaki et al 1993	0.214	0.044	1.047	1.047
Shiozaki et al 2001	1.441	0.457	4.548	4.548
Smrcka et al 2005	0.394	0.121	1.283	1.283
Suehiro et al 2014	1.167	0.599	2.273	2.273
Suehiro et al 2015	2.012	0.883	4.588	4.588
Tanget al 2017	0.222	0.054	0.914	0.914
Tohme et al 2014	2.054	1.377	3.064	3.064
Zhao et al 2011	0.237	0.025	2.221	2.221
Zhi et al 2003	0.607	0.395	0.934	0.934
	1.164	0.840	1.611	1.611

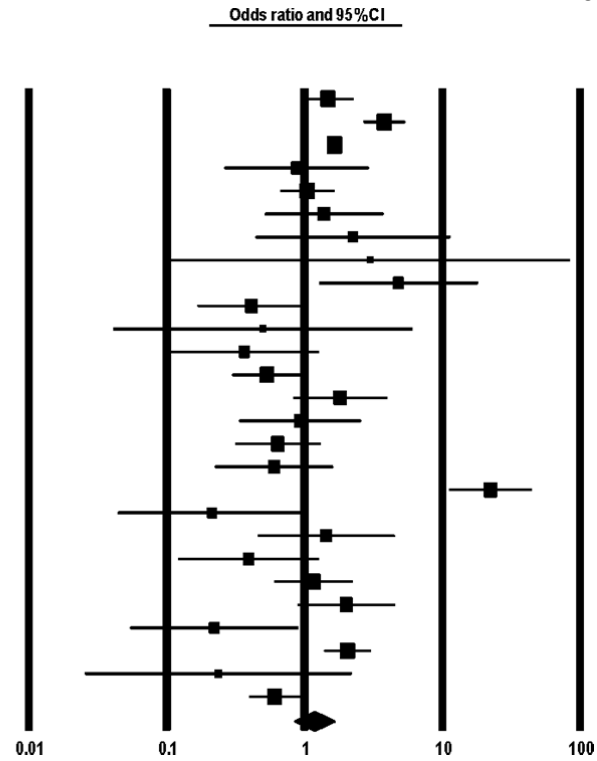


Figure S3. Forest plot of the odds ratios for mortality rate between cooled and not cooled groups of patients with severe TBI using random-effects model in 27 trials of all study types.

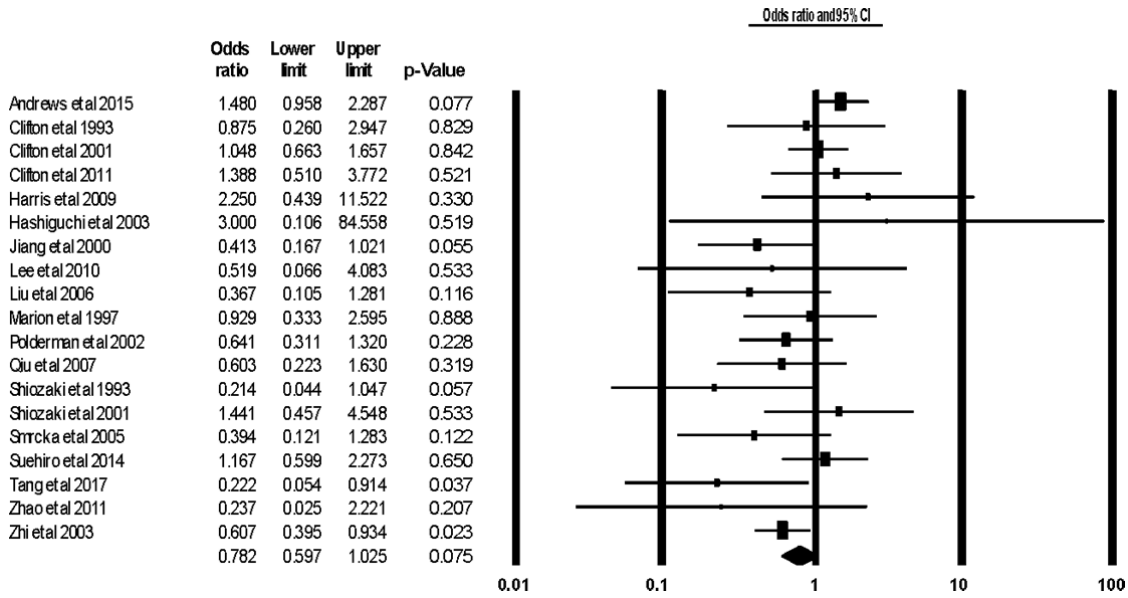


Figure S4. Forest plot of the odds ratios for mortality rate between cooled and not cooled groups of patients with severe TBI using random-effects model in all RCTs.

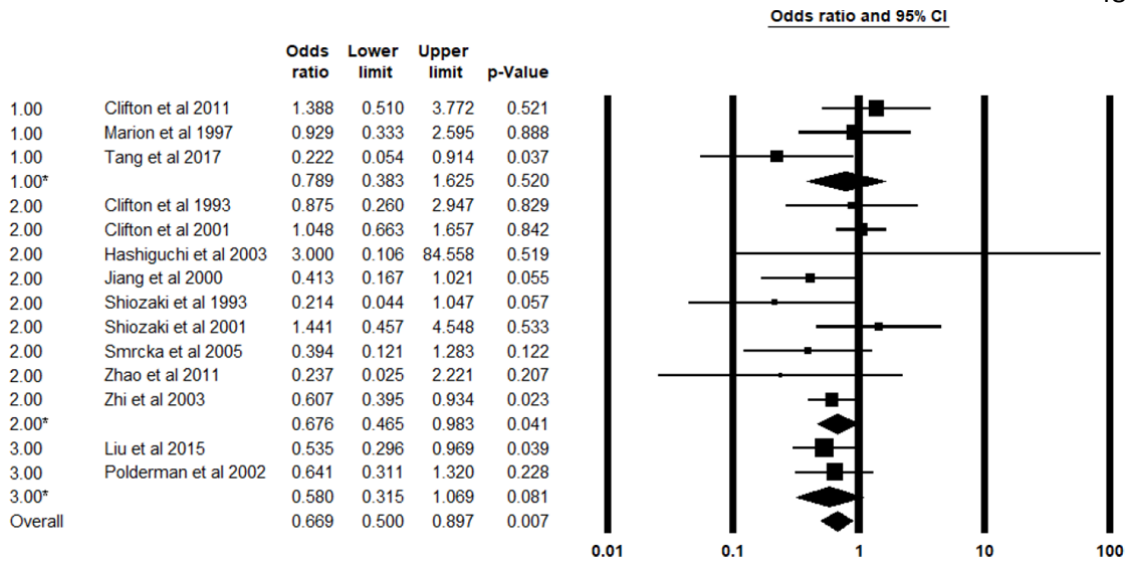


Figure S5. Forest plot of the odds ratios for mortality rate between cooled and not cooled groups of patients with severe TBI in RCT subgroups of good (group label 1), medium (group label 2), and low (group label 3) level of randomization protocols. The lines marked with * denote the mean values of the respective subgroups.

Funnel Plot of Standard Error by Log odds ratio

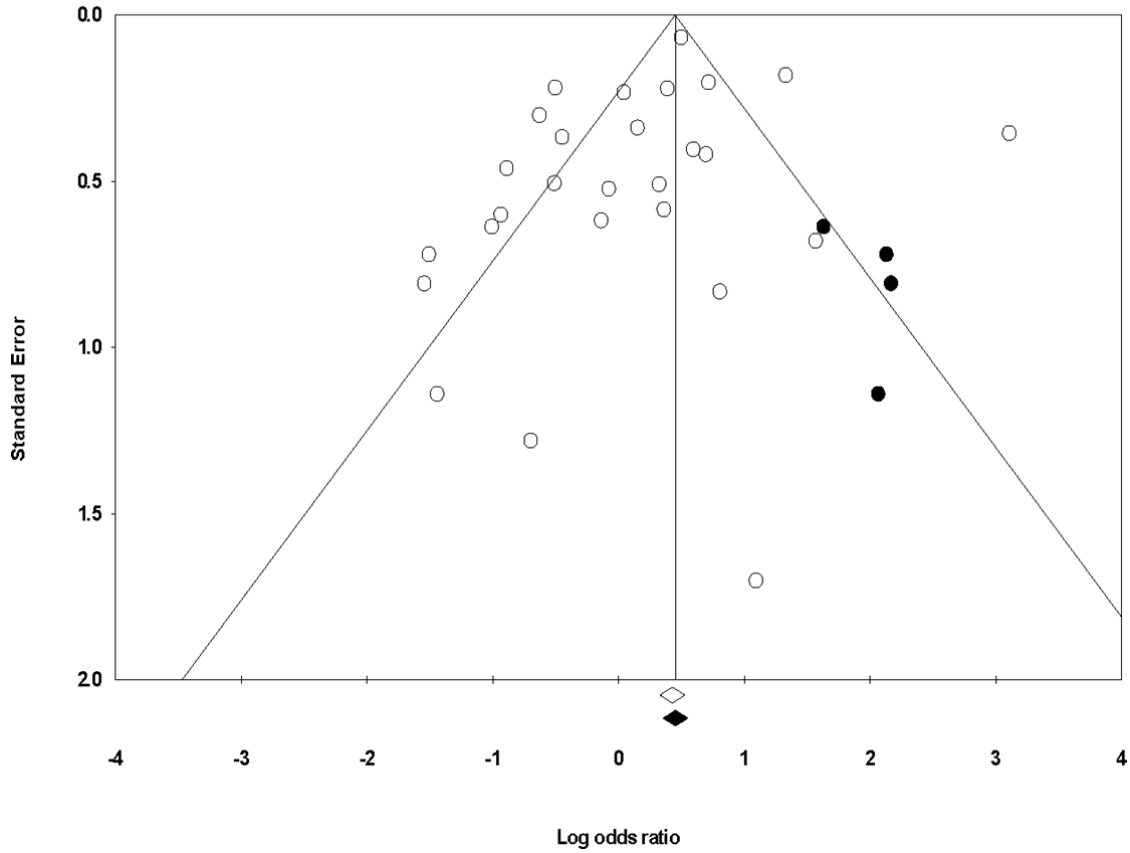


Figure S6. Funnel plot of 27 studies included in Figure S3.

Here, and in Figures S7-S9, open circles represent results from studies included in the forest plot, while closed circles indicate studies that appeared to be missing according to the trim and fill method of Duval and Tweedie. Open and closed diamonds represent the average estimated effect size without (open diamond) and with trim and fill correction (closed diamond). Duval and Tweedie corrected value: 1.37 (95% CI, 1.00, 1.88).

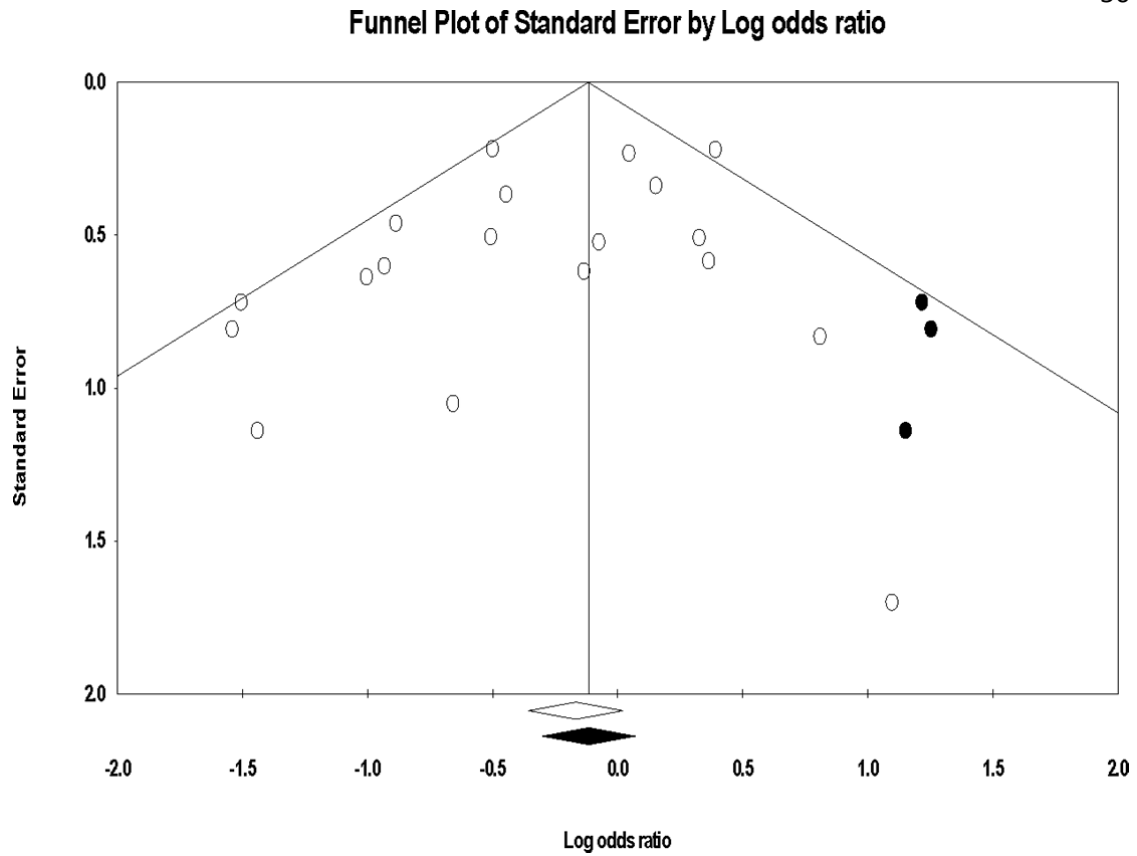


Figure S7. Funnel plot of 19 studies included in Figure S4. Duval and Tweedie trim and fill corrected value: 0.86 (95% CI, 0.65, 1.13).

Funnel Plot of Standard Error by Log odds ratio

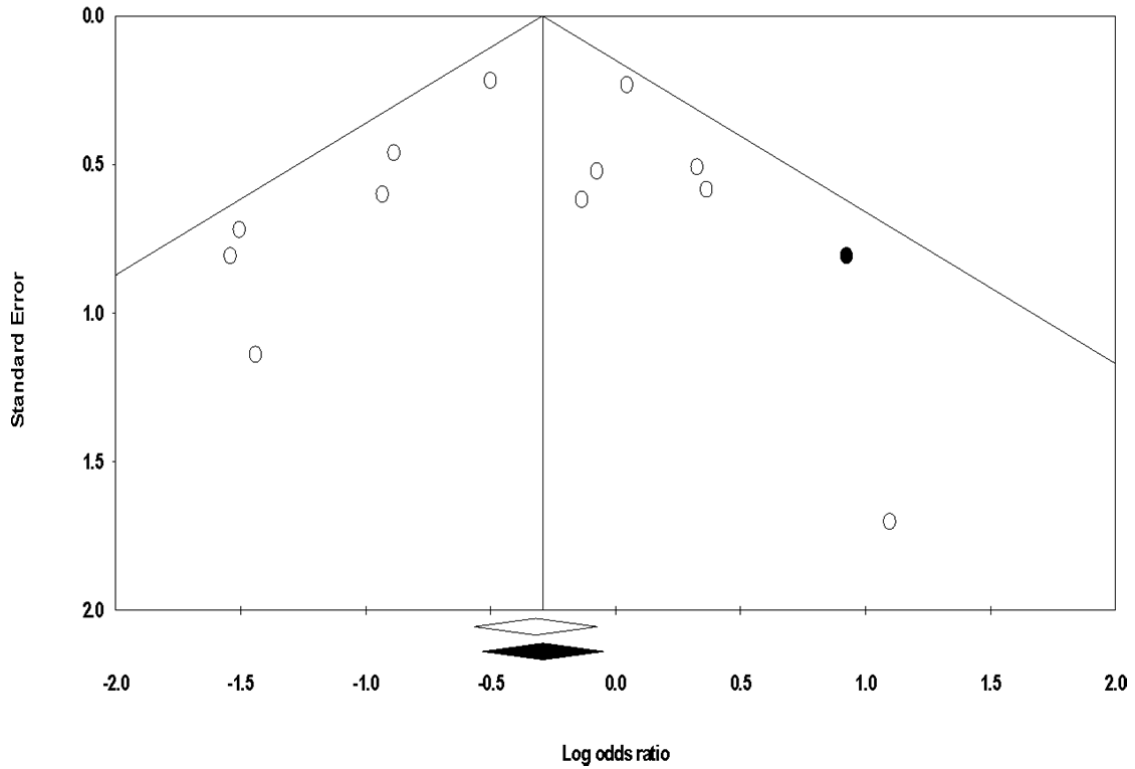


Figure S8. Funnel plot of 14 studies included in Figures 2-5, 7, and S5. Duval and Tweedie trim and fill corrected value: 0.70 (95% CI, 0.53, 0.92); $p = 0.509$ with Egger's test.

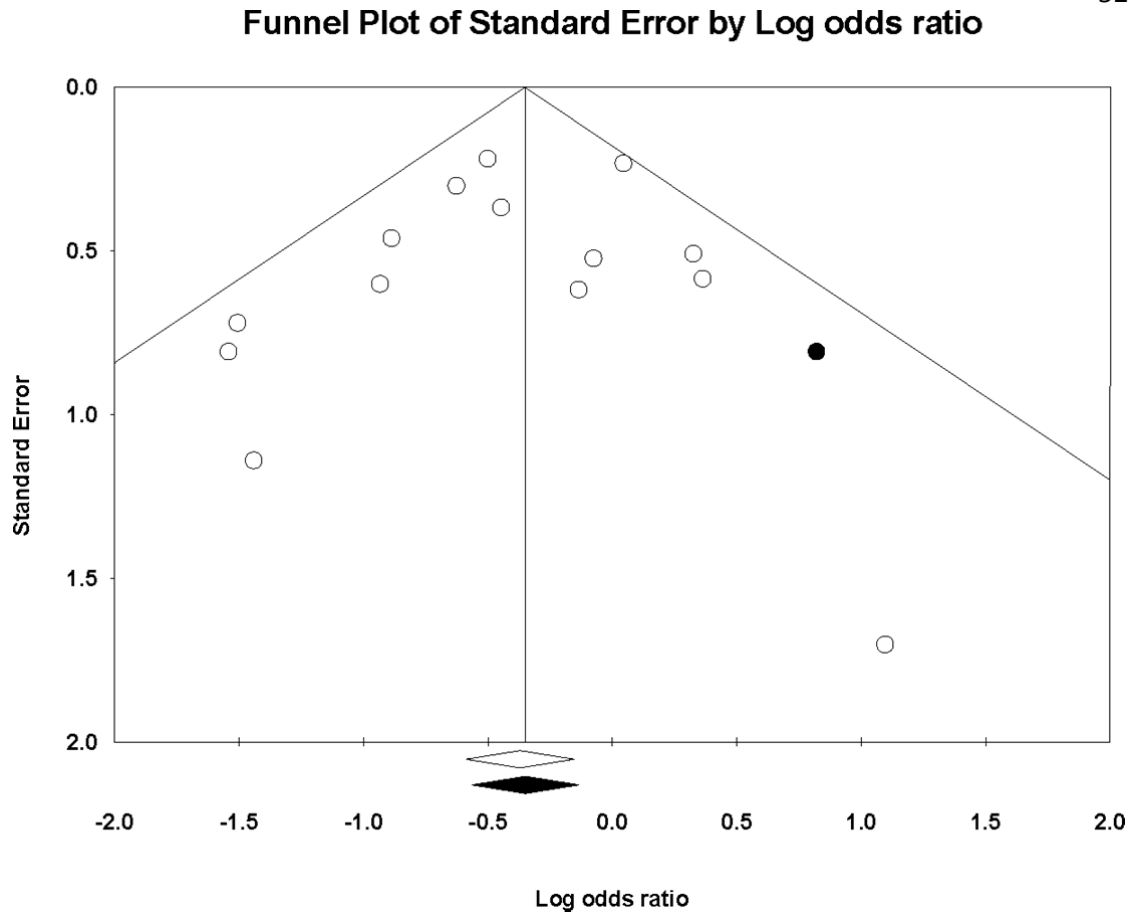


Figure S9. Funnel plot of 12 studies included in Figure 6. Duval and Tweedie trim and fill corrected value: 0.73 (95% CI, 0.52, 1.03); $p = 0.474$ with Egger's test.