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The efficacy of therapeutic hypothermia in patients with poor-grade aneurysmal subarachnoid hemorrhage: a systematic review and meta-analysis

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Background: This study evaluates the effectiveness of Therapeutic Hypothermia (TH) in treating poor-grade aneurysmal subarachnoid hemorrhage (SAH), focusing on functional outcomes, mortality, and complications such as vasospasm, delayed cerebral ischemia (DCI), and hydrocephalus.
Methods: Adhering to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines, a comprehensive literature search was conducted across multiple databases, including Medline, Embase, and Cochrane Central, up to November 2023. Nine studies involving 368 patients were selected based on eligibility criteria focusing on TH in poor-grade SAH patients. Data extraction, bias assessment, and evidence certainty were systematically performed.
Results: The primary analysis of unfavorable outcomes in 271 participants showed no significant difference between the TH and standard care groups (risk ratio [RR], 0.87). However, a significant reduction in vasospasm was observed in the TH group (RR, 0.63) among 174 participants. No significant differences were found in DCI, hydrocephalus, and mortality rates in the respective participant groups.
Conclusions: TH did not significantly improve primary unfavorable outcomes in poor-grade SAH patients. However, the reduction in vasospasm rates indicates potential specific benefits. The absence of significant findings in other secondary outcomes and mortality highlights the need for further research to better understand TH's role in treating this patient population.

Key Words: hypothermia; intracranial vasospasm; mortality; stroke; subarachnoid hemorrhage

Original Article

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INTRODUCTION

Therapeutic hypothermia (TH) has emerged as a critical intervention in the aftermath of cardiac arrest resuscitation, celebrated for its neuroprotective properties [1]. A key aspect of TH is its ability to effectively reduce cellular metabolism, leading to decreased oxygen and energy demands in brain cells [2,3]. This metabolic reduction plays an integral role in lowering in-

tracranial pressure (ICP) and minimizing brain edema, which may help mitigate further brain injury [4,5].

Originally employed for its neuroprotective effects, the application of TH has since expanded to include various forms of acute brain injuries, especially those characterized by hypoxic-reperfusion injuries such as cerebral infarction, intracranial hemorrhage (ICH) traumatic brain injury (TBI), and subarachnoid hemorrhage (SAH) [6-9]. Despite its expanded use, the efficacy of TH in these scenarios, particularly in SAH, has sparked considerable debate [10]. Clinical studies have often yielded mixed or inconclusive results, highlighting a gap in the comprehensive understanding of TH's role in these contexts.

Of particular interest is the application of TH in poor-grade SAH, where patients are confronted with exacerbated challenges like heightened ICP and significant cerebral swelling. The management of such cases remains a complex and pressing issue in neurocritical care. This study aims to scrutinize and quantify the clinical outcomes of TH in the management of poor-grade SAH. By delving into the nuances of TH's application in this specific patient population, we hope to shed light on its potential benefits and limitations. This systematic review and meta-analysis aspire to provide a more detailed understanding of TH's therapeutic role in improving clinical outcomes for patients with poor-grade SAH, thereby contributing valuable insights to the field of neurocritical care.

KEY MESSAGES

- Therapeutic hypothermia (TH) shows promise as a potential treatment for patients with poor-grade aneurysmal subarachnoid hemorrhage (SAH), suggesting a beneficial effect on clinical outcomes.
- Despite some variability in study results, the systematic review and meta-analysis provide evidence supporting the efficacy of TH in improving neurological outcomes and reducing mortality rates among this patient population.
- Further research is warranted to refine protocols, optimize timing, and identify the subset of SAH patients who would benefit most from TH, potentially shaping future clinical guidelines and treatment strategies.

MATERIALS AND METHODS

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the PRISMA statement. The review was registered with the PROSPERO International prospective register of systematic reviews (registration number CRD42023479143).

Search Strategy and Data Extraction

Two independent reviewers systematically searched three databases (Medline, Embase, and the Cochrane Central Register of Controlled Trials). The search spanned from the inception of each database to November 2023, with no language or time restrictions. Search terms for each database can be found in Supplementary Table 1.

Using predefined criteria, two authors independently assessed all retrieved citations. Initially, titles and abstracts of identified articles were reviewed, excluding publications that clearly did not meet the inclusion criteria or were duplicative. Subsequently, two authors meticulously examined the full-texts of articles that appeared to align with inclusion criteria, with the aim of further assessing their potential relevance. Additionally, references within selected articles were scrutinized to identify relevant research. We conducted comprehensive analysis by including both randomized controlled trials (RCTs) and non-randomized studies (NRS), such as cross-sectional, case-control, and cohort studies.

All citations were downloaded and managed in Endnote X9 (Thompson ISI Research Soft), adhering to predefined standards. Rigorous checks were conducted to ensure data accuracy and completeness. Any discrepancies in search strategies or literature selection were resolved through discussion or arbitration led by experienced authors to maintain consistency.

Eligibility Criteria

All studies included in our meta-analysis adhered to the following criteria: (1) adult patients (aged 18 or older) diagnosed with SAH resulting from aneurysm rupture, confirmed by definitive imaging and clinical manifestations. (2) Poor-grade aneurysmal SAH (aSAH) patients (Hunt & Hess Scale 4, 5, and modified Fisher Scale 3, 4) who have undergone securing of the aneurysm through clipping or coiling. (3) Patients treated with TH (temperature maintained at 35 °C or less). (4) The control group received equivalent therapeutic approaches, excluding TH. (5) Studies providing comprehensive documentation of the therapeutic procedure, target temperature, and specified endpoints.

Exclusion criteria for clinical studies were: (1) no control group was established in the study. (2) Studies applying TH to patients with TBI, ICH, ischemic stroke, or hypoxic ischemic

encephalopathy due to cardiac arrest, unrelated to SAH. (3) When TH is applied only during intraoperative procedures. (4) Studies involving animal models.

Assessing Risk of Bias and Certainty of the Evidence

To evaluate the risk of bias in the literature, two independent reviewers employed the bias risk assessment. When identifying RCTs, the revised Cochrane Risk of Bias 2 tool (RoB 2) was employed [11]. The RoB 2 evaluation covered several domains: randomization process, intervention deviations, outcome measurement, missing data, selective reporting, and an overall risk assessment. Each domain received judgments of "low risk," "some concerns," or "high risk" based on the evaluation criteria. The assessment of bias in NRS was conducted using the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool, with necessary modifications made for suitability [12]. Any discrepancies were resolved through discussion or by involving a third reviewer until a consensus was achieved. The assessment of the certainty of evidence was conducted using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach, ensuring a rigorous and transparent evaluation of the evidence's quality.

Outcome Measurement

Baseline clinical data extracted comprised patient age, sex, target temperature of TH group, duration of TH, cooling method, Fisher grade, Hunt and Hess grade, treatment method of ruptured aneurysm. The primary outcome measures the effectiveness of TH in enhancing the clinical outcomes of aSAH patients, as assessed by the Glasgow Outcome Scale (GOS) or modified Rankin Scale (mRS) scores. An unfavorable functional outcome is defined as severe disability, indicated by a GOS prognosis scale score ≤3 or an mRS score of ≥4. Secondary outcomes include the evaluation of vasospasm (angiographic vasospasm was confirmed by diagnostic subtraction angiography, computed tomography (CT) angiography and perfusion scanning as well as by magnetic resonance imaging, with additional evidence of vasospasm observed in transcranial Doppler examinations), delayed cerebral ischemia (DCI; subsequent native CT imaging and required a newly demarcated cerebral infarction), the occurrence of hydrocephalus (in cases where ventriculo-peritoneal shunt was performed due to delayed hydrocephalus), and in-hospital mortality,

Statistical Analysis

For our meta-analysis, Stata 18 (Stata Corp.) was utilized as the primary statistical software. Our analysis focused on binary data, and we compiled the effect size from each dataset, presenting the cumulative effect as a risk ratio (RR) with a 95% confidence interval (CI). We considered a two-tailed P-value of less than 0.05 as statistically significant.

To evaluate study heterogeneity, we employed the I^2 statistic. An I^2 value over 30% indicated moderate heterogeneity, while values surpassing 50% and 75% signified substantial and considerable heterogeneity, respectively. In instances of notable heterogeneity ($P<0.05$, $I^2>50\%$), an initial investigation into potential sources was conducted, followed by additional sensitivity analyses to ascertain the appropriateness of a random-effects model for our data synthesis. Notably, in this meta-analysis, each of the nine studies focused on patients with aSAH, though there were differences in their demographic characteristics and intervention protocols. Consequently, these variations necessitated the use of a random-effects model for the analysis. This approach was consistent with the heterogeneity observed in some of the analyses (where $I^2>50\%$), as these variations could potentially lead to significant differences in study outcomes, thus underscoring the relevance of the random-effects model for data amalgamation. Additionally, the possibility of publication bias was assessed using a funnel plot. Sensitivity analyses were also performed using Stata 18 to pinpoint and address any individual studies that might have disproportionately influenced the overall analysis.

RESULTS

Study Selection

The search process and study exclusions are detailed in Figure 1. Initially, a comprehensive search yielded 3,174 studies, removing 561 duplicates. From the remaining 2613, 2548 were deemed irrelevant based on title and abstract screening. Full-text analysis was performed on 65 studies, resulting in the exclusion of 56 due to various reasons, including insufficient data, lack of a comparison group, and the amalgamation of different stroke types (Supplementary Table 2). Eventually, the remaining 9 studies with a total of 368 patients were included in our final analysis.

Characteristics of the Trials

This meta-analysis scrutinizes nine studies conducted between 1997 and 2018, encompassing a total of 368 participants,

Figure 1. The flow diagram of the literature search. SAH: subarachnoid hemorrhage.

wherein 166 received TH and 202 served as controls. The study types comprised two RCTs and seven NRS, consisting of five retrospective observation studies, one prospective clinical pilot study, and one prospective matching study. In the analysis of nine reviewed studies, the overall risk of bias was assessed. Among the two RCTs, one exhibited a low risk of bias, while the other displayed a high risk of bias. Among the seven NRS, excluding one with moderate risk of bias, the remaining six indicated a serious risk of bias (Supplementary Fig. 1). Sample sizes ranged from 15 to 72 patients, with a diverse geographical distribution: five studies from Asia, three from Europe, and one from the USA. The overview was described in Table 1 [13-21].

The female ratio across these studies ranged from 27.4% to 80.0%, with a mean age range of 44.6 to 57.6 years. The presenting conditions primarily involved patients categorized under Hunt & Hess Scale 4, 5, modified Fisher Scale 3, 4, and World Federation of Neurosurgical Societies (WFNS) scale 4, 5. In the context of securing aSAH, five studies documented the use of either a surgical clip or coiling, two studies exclusively involved coiling, and two did not specify the treatment method. Outcome measurements were gauged using the GOS and the mRS, with mean follow-up times spanning from 2 weeks to 1 year. Therapeutic interventions targeted temperatures between 33 °C to 35 °C, with induction times varying from 1 hour to 12 hours. Hypothermia was maintained for periods between 48 hours to 7 days, averaging 4.3 days, with rewarming rates employing passive warming or escalating at rates from 0.5 °C per day to 1 °C per 4 hours. Cooling methods encompassed 5 surface cooling, 2 endovascular cooling, and 2 mixed approaches. The interval from onset to cooling ranged from 2 hours to 48 hours, with shivering control systems implemented in 5 studies and absent in 4 studies. The summary of the main values in TH is detailed in Table 2.

Summary of Findings

In a comprehensive analysis comparing the hypothermia group to the standard care group, various outcomes were evaluated (Table 3). The risk of an unfavorable function outcome is anticipated at 740 per 1,000 individuals in the standard care

Table 1. Main characteristics of the included studies

Study	Study design	Study duration	Country	Female ratio (%)	Mean age (yr)	Presenting condition	Outcome measurement	Mean follow-up time
Muroi et al. (2008) [13]	Prospective clinical pilot study	NA	Switzerland	80.0	51.5	Fisher Scale 3, 4	GOS ≤3	1 yr
Neuman et al. (2008) [14]	Retrospective observation study	2002–2005	Czech Republic	62.2	52	Hunt & Hess Scale 4, 5	GOS >3	6 mo
Anei et al. (2010) [15]	Retrospective observation study	1997–2001	Japan	71.4	57.6	Fisher Scale 3, 4	mRS >3	3 mo or transfer day
Karnatovskaia et al. (2014) [16]	Retrospective observation study	2007–2012	USA	48.6	51.3	Fisher Scale 3, 4	mean mRS	1–6 mo
Kuramatsu et al. (2015) [17]	Prospective matching study	2010–2012	Germany	66.7	50.5	Hunt & Hess Scale 4, 5, modified Fisher Scale 3, 4, and WFNS scale 4-5	mRS >3	6 mo
Choi et al. (2017) [18]	Random clinical trial	2015–2016	Repulic of Korea	59.1	52.9	Hunt & Hess Scale 4, 5 and modified Fisher Scale 3, 4	mRS >3	3 mo
Shui et al. (2018) [19]	Random clinical trial	2014–2016	China	27.4	44.6	modified Fisher Scale 3, 4	Vasospasm	2 wk
Rhim et al. (2022) [20]	Retrospective observation study	2015–2018	Repulic of Korea	61.1	56.9	Hunt & Hess Scale 4, 5, modified Fisher Scale 3, 4, and WFNS scale 4-5	mRS >3	At discharge
Won et al. (2022) [21]	Retrospective observation study	2015–2018	Repulic of Korea	61.1	57.5	Hunt & Hess Scale 5 and WFNS scale 5 (GCS <7)	mRS >3	At discharge & 3 mo

NA: not available; GOS: Glasgow Coma Scale; mRS: Modified Rankin Scale; WFNS: World Federation of Neurosurgical Societies; GCS: Glasgow Coma Scale.

Table 2. Summary of the main values in therapeutic hypothermia

Study	Total number	Intervention	Control	Aneurysm secured method	Target temperature (°C)	Induction time	Hypothermia time	Rewarming rate	Hypothermia method	Interval from onset to cooling	Shivering control system
Muroi et al. (2008) [13]	15	7	8	NA	33	NA	NA	NA	Endovascular cooling	NA	Yes
Neuman et al. (2008) [14]	37	25	12	Coil	34	<3 hr	>72 hr	Passive warming	Surface cooling	Mixed (immediately or after admission 4–5 days)	No
Anei et al. (2010) [15]	35	19	16	Clip or coil	34	NA	48 hr	1 °C/day	Surface cooling	<24	No
Karnatovskaia et al. (2014) [16]	35	19	16	Clip or coil	32–34	NA	>48 hr	<0.5 °C/hr	Surface cooling	NA	No
Kuramatsu et al. (2015) [17]	36	12	24	Clip or coil	35	NA	7±1 day	0.5 °C/day	Endovascular cooling	<48	Yes
Choi et al. (2017) [18]	22	11	11	Clip or coil	34.5	<1 hr	48	1 °C/day	Endovascular or surface cooling	<12	Yes
Shui et al. (2018) [19]	62	30	32	NA	35	4–12 hr	5–7 day	1 °C/hr	Surface cooling	2–8 hr	No
Rhim et al. (2022) [20]	54	18	36	Coil	34–35	NA	5 day	0.5 °C/day	Surface cooling	<8	Yes
Won et al. (2022) [21]	72	25	47	Clip or coil	34.5	<1 hr	48 hr	1 °C/day	Endovascular or surface cooling	NA	Yes

NA: not available.

Table 3. Summary of findings table using the GRADE methodology for outcomes comparing therapeutic hypothermia to standard care in poor grade subarachnoid hemorrhage

Outcome	Anticipated absolute effects[a] (95% CI)		RR (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Risk with standard care	Risk with therapeutic hypothermia			
Unfavorable function outcome	740 Per 1,000	644 Per 1,000 (496–836)	0.87 (0.67–1.13)	271 (7 Studies)	⨁◯◯◯ Very low
Vasospasm	466 Per 1,000	294 Per 1,000 (191–447)	0.63 (0.41–0.96)	174 (4 Studies)	⨁◯◯◯ Very low
Delayed cerebral ischemia	451 Per 1,000	370 Per 1,000 (212–654)	0.82 (0.47–1.45)	130 (3 Studies)	⨁◯◯◯ Very low
Hydrocephalus	293 Per 1,000	334 Per 1,000 (184–609)	1.14 (0.63–2.08)	130 (3 Studies)	⨁◯◯◯ Very low
Mortality	336 Per 1,000	249 Per 1,000 (118–524)	0.74 (0.35–1.56)	219 (5 Studies)	⨁◯◯◯ Very low

GRADE: Grading of Recommendations Assessment, Development and Evaluation; CI: confidence interval; RR: risk ratio (relative effect).
a) The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

group, but it is reduced to 644 per 1,000 in the hypothermia group, indicating a potential benefit of TH. The RR for this outcome is 0.87 (95% CI, 0.67–1.13), suggesting a slight reduction in the risk of unfavorable outcomes, based on an analysis of 271 participants across seven studies. For vasospasm, the risk in the standard care group is 466 per 1,000, decreasing to 294 per 1,000 in the hypothermia group. The RR for vasospasm with TH is 0.63 (95% CI, 0.41–0.96), indicating a more pronounced effect in reducing the risk of vasospasm. This is derived from data involving 174 participants in four studies. Regarding DCI, under TH, the RR is 0.82 (95% CI, 0.47–1.45), indicating a slight reduction in risk, based on data from 130 participants across three studies. In the comparison of hydrocephalus incidence, the RR for the hypothermia group is 1.14 (95% CI, 0.63–2.08), suggesting a potential increase in risk. This assessment comes from 130 participants in three studies. Lastly, for mortality, the RR in the hypothermia group is 0.74 (95% CI, 0.35–1.56), suggesting a potential reduction in mortality risk. This result is based on data from 219 participants across five studies.

The overall level of certainty for these outcomes is very low. This indicates that further research could significantly impact our confidence in these estimates and potentially alter the current understanding of the effects of TH in these areas.

Functional Outcome

In a comprehensive review involving seven studies, a total of 271 participants were analyzed, with 117 in the intervention group and 154 in the control group. The focus was on comparing unfavorable outcomes between the TH group (intervention) and the standard group (control). However, the results revealed no significant difference in outcomes between these two groups. The RR was calculated as 0.87, with a CI ranging from 0.67 to 1.13 (Figure 2). The heterogeneity of the studies, as indicated by an I^2 value of 58.0%, suggests moderate variability among study results. The statistical significance was not reached (P=0.28), indicating that the difference in outcomes between the hypothermia and standard groups was not substantial. A funnel plot analysis was conducted to assess publication bias in the study, showing no significant discrepancies between the groups (Supplementary Fig. 2). Additionally, the results of the Egger's test, with a beta1 value of –1.06 and a P-value of 0.07, further indicate an absence of significant publication bias. These findings collectively support the conclusion of no significant differences in outcomes.

Secondary Outcomes

For vasospasm, which was evaluated across four studies involving 174 participants (71 in the intervention group and 103 in the control group), the RR was 0.63, with a CI of 0.41 to 0.96, and an I^2 of 0%, suggesting homogeneous study outcomes (Figure 3). The statistical significance of these findings was marked by a P-value of 0.03. In the case of DCI, examined in three studies with a total of 130 participants (48 in the intervention group and 82 in the control group), the RR was 0.82 with a CI of 0.47 to 1.45 (Figure 3). Despite the moderate het-

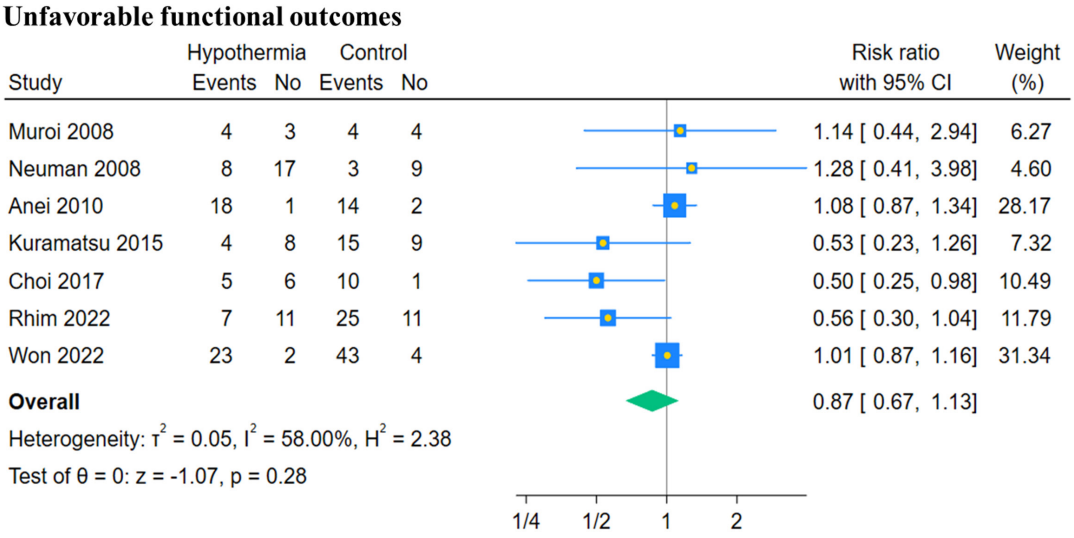

Figure 2. Forest plot of studies comparing unfavorable functional outcomes in the therapeutic hypothermia group with that in the control group. The horizontal bars represent 95% confidence intervals (CIs).

erogeneity among the studies (I^2=39.4%), the results did not reach statistical significance (P=0.50). Regarding hydrocephalus, analyzed in three studies comprising 130 participants (48 in the intervention group and 82 in the control group), the RR stood at 1.14, with a CI of 0.63 to 2.08 and an I^2 of 3.5%, indicating low variability in the study results (Figure 3). However, these findings were not statistically significant (P=0.66).

Finally, for mortality, assessed across five studies including 219 participants (85 in the intervention group and 134 in the control group), the RR was 0.74 with a CI of 0.35 to 1.56 (Figure 3). With an I^2 of 49.0%, indicating moderate heterogeneity, the results showed no significant difference in mortality rates between the groups (P=0.42). These secondary outcome analyses provide a nuanced understanding of the intervention's effects, with only vasospasm demonstrating a significant difference.

Sensitive Analysis

In our comprehensive systematic review and meta-analysis, we evaluated the effectiveness of TH and conducted a sensitivity analysis to determine the influence of different study criteria on TH's functional outcomes (Supplementary Table 3). The analysis encompassed three distinct categories: Firstly, we considered six NRS, deliberately excluding one RCT, which involved a total of 249 patients. The observed risk ratio in this group was 1.00, suggesting that these studies did not significantly deviate from the overall analysis in terms of TH's impact on functional outcomes. Secondly, our focus shifted to more recent research, specifically studies conducted after 2010, comprising 184 patients. Although the risk ratio of 0.69 in this category indicated a potential improvement in outcomes with TH, the CI, ranging from 0.46 to 1.05, did not support statistical significance, as it crossed the threshold of no effect. Lastly, we analyzed five studies that involved the introduction of a shivering control system, covering 199 patients. In this case, the risk ratio stood at 0.75, hinting at possible beneficial outcomes. However, similar to the previous category, the CI (0.52–1.07) was not conclusive enough to firmly establish these results. This sensitivity analysis helped in understanding the consistency and robustness of the observed effects of TH on functional outcomes across various study types and time frames.

DISCUSSION

TH has demonstrated neuroprotective functions in patients who remain unconscious post-cardiac arrest with return of spontaneous circulation [1]. Its effectiveness in reducing secondary brain injury mechanisms like cell edema and inflammation, thereby lowering ICP and brain damage is well documented [4,5]. By reducing body temperature, TH lessens cerebral oxygen demand and metabolism, significantly diminishing secondary brain injury, even under hypoxic conditions [2]. Additionally, its benefits extend to decreasing adenosine triphosphate consumption, inflammation, and seizure incidence, as well as stabilizing the blood-brain barrier, cumula-

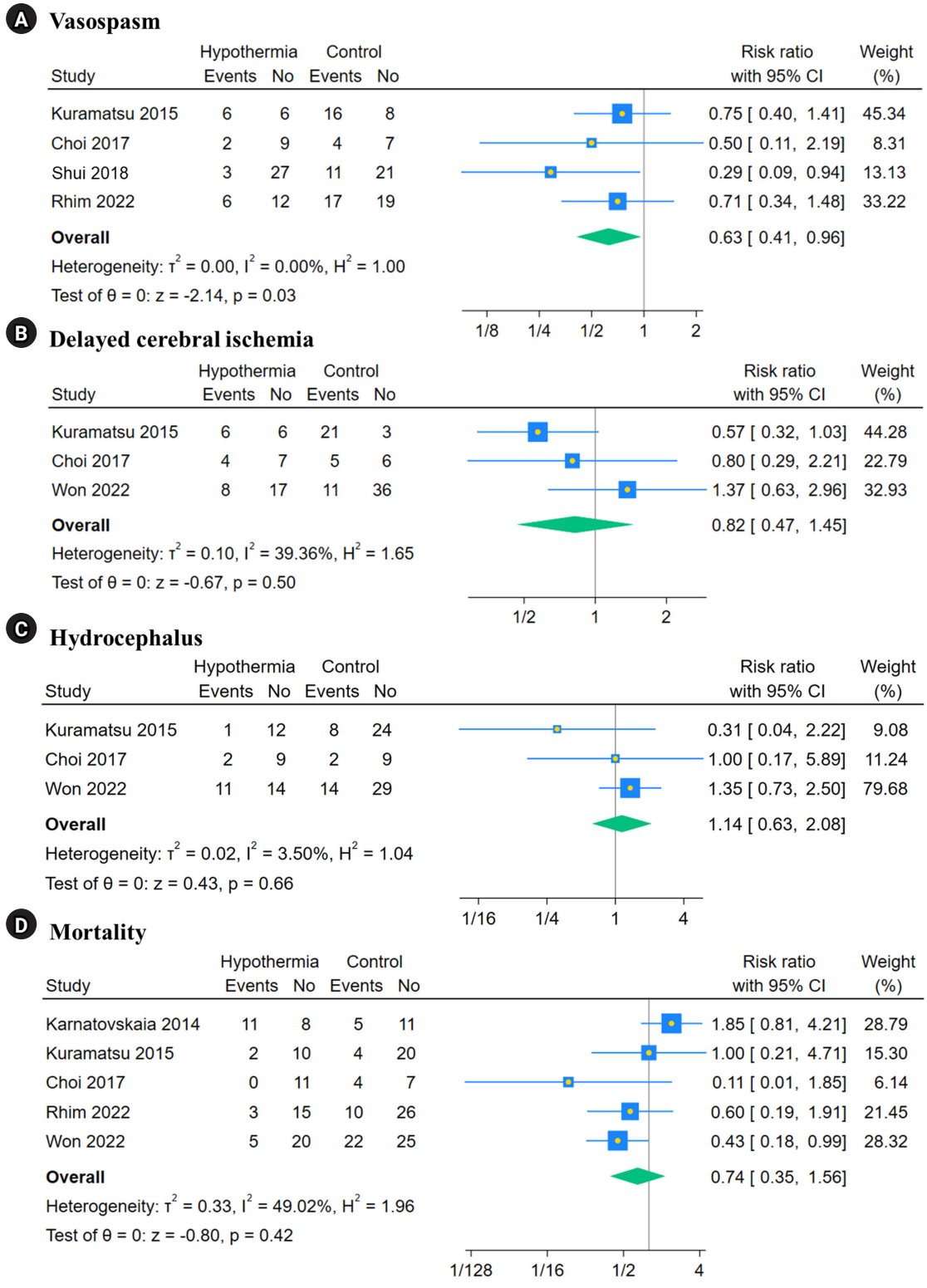

Figure 3. Forest plot of studies comparing the subarachnoid hemorrhage related complication and mortality in the therapeutic hypothermia group with that in the control group. (A) Fours studies reported vasospasm. The meta-analysis of risk ratio reported a statistically lower incidence of vasospasm in patients treated with therapeutic hypothermia. (B) Three studies reported delayed cerebral ischemia. There was no significant effect involving therapeutic hypothermia and delayed cerebral ischemia. (C) Three studies reported hydrocephalus. There was no significant effect involving therapeutic hypothermia and hydrocephalus. (D) Fives studies reported mortality. There was no significant effect involving therapeutic hypothermia and mortality. CI: confidence interval.

tively improving outcomes in neurocritical patients [3].

Despite these foundations, TH's application in TBI and stroke has failed to consistently demonstrate significant efficacy [22-25], except in some cases of ischemic stroke [26]. Nonetheless, it is commonly used as a last resort in treating poor grade SAH, although systematic evidence supporting this practice is lacking. Our systematic review was conducted in light of this gap. While we found that TH does not significantly improve functional outcomes or mortality in SAH, it may reduce the incidence of vasospasm. This finding aligns with previous literature, suggesting a specific area where TH may offer benefits in the management of SAH.

In our investigation of the impact on functional outcomes, seven studies were reviewed [13-21]. Excluding one RCT, the remaining studies exhibited a moderate to high risk of bias in participant selection and confounding factors. Additionally, there was considerable heterogeneity in the hypothermia protocols, including variations in induction time, hypothermia duration, rewarming rate, cooling methods, and the interval from symptom onset to cooling initiation. Some studies included cases with refractory ICP that underwent craniectomy [16,21], while others involved coiling alone [15,20]. However, a common practice across these studies was the application of TH at or below 35 °C after securing aSAH. The sole RCT investigating functional outcomes in aSAH patients initiated TH within 12 hours of symptom onset, maintained it at 34.5 °C for 48 hours, and employed a gradual rewarming rate of 0.5 °C every 12 hours [18]. Nevertheless, the three-month functional outcome did not achieve statistical significance, with a P-value of 0.06. Interestingly, the sole study showing statistical significance in favor of TH applied the intervention for about five days, highlighting a variation in the duration of the TH protocol [20]. This suggests that there is still a need to establish an appropriate protocol for TH.

In a study investigating the effects of TH on vasospasm in patients with aSAH, four papers were reviewed [17-20]. Except for one, none showed statistical significance, but the differences in occurrence rates between the groups suggested potential benefits. Kuramatsu et al. [17] demonstrated a significant reduction in mean middle cerebral artery velocities in the TH group compared to the standard care group using transcranial Doppler. Muroi et al. [13] explained that TH could reduce inflammation by decreasing the secretion of inflammatory cytokines such as interleukin (IL)-6, IL-1β, and tumor necrosis factor-α. Similarly, the studies discussed the potential for a reduction in DCI through TH's neuroprotective properties [17,18,21]. Regarding mortality, although there are reports of an increase in mortality due to adverse events when applied to critically ill patients [27], this analysis indicated a trend towards reduced mortality with TH (RR, 0.74; 95% CI, 0.35–1.56). For SAH-induced hydrocephalus, there is still no significant evidence of effectiveness, and research in this area is insufficient. Thus, the effectiveness of TH in aSAH patients still requires further investigation.

The most significant challenge in maintaining TH effectively is the control of shivering. Since the publication of a document in 2008 introducing "the bedside shivering assessment modulation," the importance of shivering control in TH has gained significant attention [28]. The document notes that when shivering is not controlled, it can actually lead to an increase in resting energy expenditure and oxygen consumption. Five studies implemented a sedation protocol to address shivering control, with three of them suggesting the potential for improved functional outcomes in TH [13,17,18,20]. However, in the remaining study, which focused on patients with severe brain injuries categorized under Hunt & Hess Scale 5 and WFNS scale 5 (Glasgow Coma Scale score <7), both the group that received TH and the group that did not showed extremely poor prognoses [21].

In the past, TH was associated with increased risks of complications such as prolonged sedation, extended mechanical ventilation duration, prolonged intensive care unit stay, hypotension, and infection [2,29,30]. In the nine studies included in this investigation, five of them examined complications associated with TH. While these studies investigated different complications, they collectively did not show a significant difference in the occurrence rates of internal medical complications such as pneumonia, infection, blood pressure abnormalities, arrhythmia, or electrolyte imbalances [16-18,20,21]. One study reported an increase in hospital stay length as a complication of TH [16], but another literature review did not reveal a significant difference [17]. Unlike earlier reports of frequent complications associated with, TH recent advances in bundle management, adjustments based on predictive factors, and the adoption of protocols that maintain the target temperature above 33 °C have led to a reduction in the incidence of complications related to TH [31,32].

According to recent guidelines for the treatment of aSAH, it is mentioned that hypothermia during surgery for patients with Good grade SAH has not been proven effective [10]. These guidelines suggest that TH might only benefit a carefully selected group of patients who have poor grade SAH. Further-

more, the importance of fever control has been highlighted in cases of refractory fever occurring in aSAH patients. However, the effectiveness of TH remains uncertain [10]. It's worth noting that meta-analyses of TH in conditions other than aSAH, such as ICH, TBI, and ischemic stroke, have also failed to demonstrate significant improvements in functional outcomes [6-9]. While there is one meta-analysis examining the efficacy of TH in aSAH, it includes intraoperative TH and normothermia, lacks clear references, and does not conduct a systematic review [33].

Therefore, our study was conducted with a focus on specific eligible criteria to accurately assess the effects of TH. This analysis, focusing on patients with poor-grade SAH treated with TH at or below 35 °C, was conducted with careful attention to study quality, variability in study designs, and the heterogeneity of the included studies. Future research, particularly large-scale RCTs, will be essential in further elucidating the utility of TH. Additionally, exploring the importance of fever control and the potential benefits of normothermia in aSAH management should be topics for future investigation. In our systematic review and meta-analysis, several limitations warrant careful consideration. The included studies demonstrated variability in design, and some had small sample sizes, potentially affecting the robustness of our conclusions. Notable heterogeneity in TH protocols across these studies further complicated the analysis. Additionally, due to inherent complexities and biases in combining RCTs and NRS in a single meta-analysis, we conducted separate analyses for these groups in a sensitivity analysis [34].

However, with only one RCT available, our focus was primarily on NRS. It was observed that the outcomes from the NRS did not significantly differ from those seen in the combined analysis of all studies, suggesting a consistent trend across different study designs. Our funnel plot analysis, guided by the Cochrane Handbook (version 5.1), included seven studies and did not indicate publication bias [34]. Nonetheless, with fewer than 10 studies, there is reduced power to effectively distinguish between chance and real asymmetry, potentially impacting the reliability of this conclusion. These aspects underscore the need for cautious interpretation of our findings and highlight the complexities involved in synthesizing diverse research methodologies.

In the field of neurocritical care, it is often difficult to establish strong recommendations based on systematic reviews or meta-analyses for specific conditions and topics. This challenge stems from a scarcity of randomized clinical trials and a lack of well-organized prospective studies on specific subjects. Therefore, guidelines are challenging to establish for certain conditions, and often the level of evidence remains relatively low. We share the regret that our study also faced difficulties in overcoming these obstacles. However, recent research has synthesized more comprehensive data, verified the effects on vasospasm occurrence, and improved the certainty of the evidence through better analysis. Although our findings align with prior research, our study verified the impact on certain complications and refined the analytical methodology. This improvement contributes positively to the neurocritical care field. Despite the existing limitations, we are hopeful that these incremental advancements will help deliver high-quality clinical guidelines, ultimately improving patient outcomes in critical care.

The results of this systematic review and meta-analysis suggest that the effectiveness of TH in patients with aSAH is primarily observed in its potential to impact vasospasm. However, the current evidence does not provide conclusive insights into the effects of TH on key aspects such as functional outcomes, DCI, hydrocephalus, and mortality. Therefore, further research is needed to comprehensively understand and substantiate the role of TH in the management of aSAH.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/10.4266/acc.2024.00612.

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