Optimal temperature management in aortic arch surgery: A systematic review and network meta-analysis

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Disclaimer

- The main purpose of this journal club is to show how propensity score-based studies are dealt with in network meta-analysis.
- The clinical aspects of the results are not the main focus.

INTRODUCTION

- Different hypothermia regimens alone or combined with selective cerebral perfusion can be used for cerebral protection during surgical interventions involving the aortic arch.
- Historically, cooling of the brain to profoundly hypothermic levels seemed safe.

INTRODUCTION

- However, transitions to warmer hypothermic temperatures in conjunction with antegrade cerebral perfusion has become the trend in the last decades.
- Despite favorable clinical results reported with newer techniques, a variation in hypothermia regimes persists to exist between centers worldwide.

INTRODUCTION

- Several meta analyses have compared different levels of hypothermia in different combinations in a pairwise fashion.
- However, no meta analysis has compared all three levels of hypothermia, deep, moderate and mild.

Objective

- To use a network meta-analysis (NMA) approach to compare the effect of deep hypothermic circulatory arrest (DHCA), moderate hypothermic circulatory arrest (MHCA) and mild hypothermic circulatory arrest (mild HCA) on the operative mortality, postoperative occurrence of stroke and acute kidney renal failure (AKI) after aortic arch surgery.

METHODS

Protocol and registration

- Performed according to the checklist of the Preferred Reporting Items for Systematic Reviews and Meta analysis (PRISMA) extension statement for NMA.
- Registered with PROSPERO (International Prospective Register of Systematic Reviews).
- This study was approved by the institutional review board.

Search strategy and selection criteria

- Biomedical specialist searched databases on February 21, 2022
- Two researchers (D. A. and G.T.) independently reviewed abstracts and full texts based on inclusion/exclusion criteria.
- In case of disagreement, an agreement was negotiated until consensus was reached.
- In case of multiple publications on overlapping study populations, the largest series were included.

Search strategy and selection criteria

Inclusion criteria

- Observational studies (retrospective and prospective),

  RCTs comparing at least two arms.

- That reported outcomes after aortic arch surgery in adults with a sample size ≥10 patients

- Published in English

Search strategy and selection criteria

Exclusion criteria

- Non-original studies (reviews), case reports, animal studies, studies not defining or incomplete reporting of outcome and data.
- Studies reporting on hybrid aortic arch procedures, other than frozen elephant trunk, solely redo cases, type B aortic dissections, articles on exclusively concomitant procedures, mini-sternotomy and all different approaches other than median sternotomy.

Data extraction

- Microsoft Office Excel 2016 (Microsoft Corp)
- Two reviewers (D.A. and G.T.) independently extracted the data and recorded all data with a standardized form.
- All two-arm studies with a within-study comparison of different hypothermia regimens, regardless of cerebral perfusion strategy, were extracted.

Data extraction

- The different levels of hypothermia were classified as following:

  Deep hypothermia (DHCA) : ≤20°C

  Moderate hypothermia (MHCA) : 20.1°C to 25°C

  Mild hypothermia (Mild HCA) : ≥ 25.1°C

- The cutoff of temperature was consistent with the International Aortic Arch Surgery Study Group (IAASSG) consensus guideline.
- Outcomes were considered early outcomes when they occurred within 30 days postoperatively or during the period of initial hospital admission.

Assessment of the quality of individual studies and overall quality of evidence

- Observational studies:

  Newcastle-Ottawa quality assessment scale

- Randomized controlled trial:

  The Cochrane risk of bias tool

Outcome measures

- **The primary outcome:**

  Operative mortality

- **Secondary outcomes:**

  Postoperative incidence of stroke and AKI

Statistical analysis

- Calculated sample-sized weighted pooled baseline patient and procedural characteristics for each hypothermia regimen group.
- Early event risks were pooled using inverse variance weighting
- Random-effects model using the Der Simonian and Laird method to estimate the between-study variance
- Using in R program (version 4.0.5., R Project for Statistical Computing)

Network meta-analysis

- Odds ratios (ORs) were used for the early outcome and were calculated by extracting the raw data from the studies
- NMA was performed using the frequentist method (generic inverse variance method)
- Random effect NMA were performed to make direct and indirect comparisons of two- and three-arm studies comparing different levels of hypothermia

Network meta-analysis

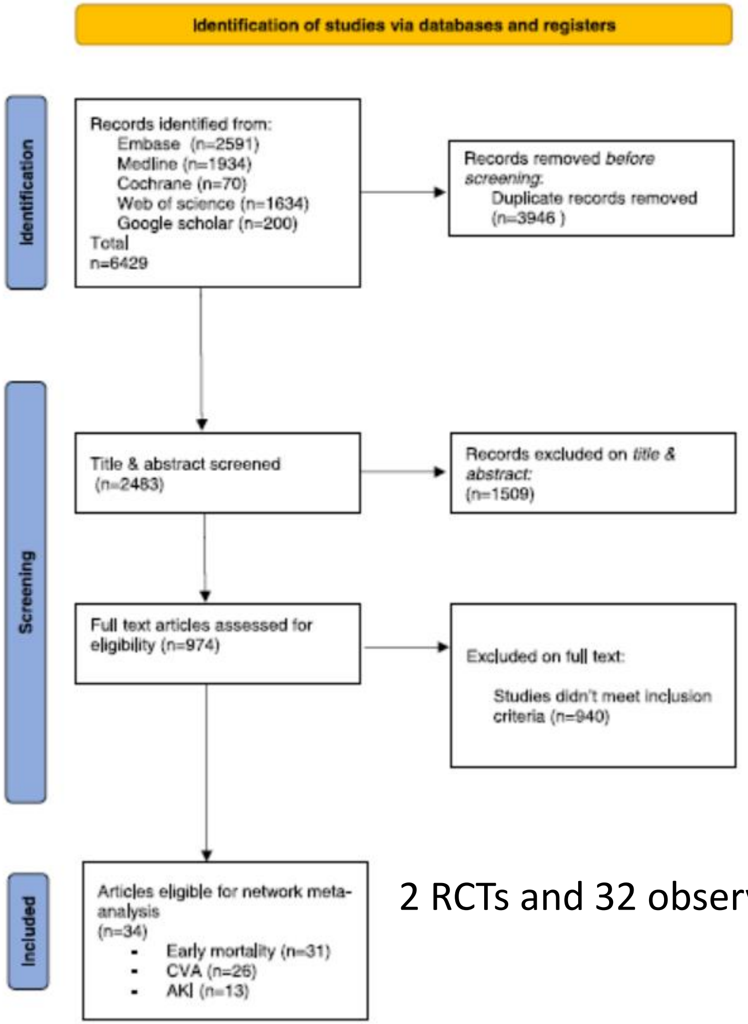
- Inconsistency in NMA was evaluated by conducting conventional pairwise meta-analyses and comparing direct and indirect OR, also called node-splitting
- Heterogeneity was reported as
  - low (I^2 = 0–25%)
  - moderate (I^2 = 26–50%)
  - high (I^2 > 50%)

Sensitivity analyses

- To minimize possible confounding that can be encountered in observational research
- Data from randomized controlled trials (RCTs) and propensity score matched (PSM) studies were analyzed separately

RESULTS

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart of the analysis



2 RCTs and 32 observational (9 PSM)

Table 1. Baseline characteristics (Total 12,370 patients)

Characteristic	DHCA (<20)		MHCA (20–25)		Mild HCA (>25)	
	Pooled estimate	*N*	Pooled estimate	*N*	Pooled estimate	*N*
Age (mean ± SD)	60.4 ± 11.8	26	59.5 ± 12.9	33	60.8 ± 12.4	10
Male	65.9% (30.2–88.0)	26	68.4% (40.0–88.9)	30	68.2% (51.6–81.8)	9
Etiology						
ATAAD	52.8% (0.0–100.0)	23	56.6% (0.0–100.0)	31	67.4% (19.9–100.0)	9
Chronic TAAD	2.7% (0.0–100.0)	24	3.4% (0.0–100.0)	31	0.0% (0.0–0.0)	9
Degenerative	41.5% (0.0–100.0)	23	37.4% (0.0–100.0)	31	32.5% (0.0–80.1)	9
Other	2.7% (0.0–45.7)	22	2.7% (0.0–48.6)	31	0.0% (0.0–0.0)	9
Comorbidities						
Hypertension	72.1% (20.0–88.7)	16	72.6% (21.1–85.1)	21	74.5% (17.7–89.8)	6
Emergency	34.8% (0.0–100.0)	9	42.4% (0.0–100.0)	13	37.7% (23.5–100.0)	5
History of CVA	7.6% (2.3–18.5)	16	7.8% (2.7–13.2)	21	5.0% (0.0–13.3)	6
Marfan	4.2% (0.0–14.3)	11	5.4% (0.0–11.5)	15	4.1% (0.0–10.8)	4
COPD	13.3% (0.0–42.0)	12	15.2% (0.0–37.1)	17	17.2% (0.3–34.3)	6
Prev. cardiac surgery	17.7% (0.0–42.2)	19	20.2% (0.0–43.1)	23	21.0% (3.4–42.8)	5
CAD	14.1% (4.4–36.2)	9	13.7% (0.0–35.9)	15	11.2% (2.4–39.2)	6
DM	9.2% (1.1–32.0)	14	9.2% (2.9–27.8)	18	11.3% (2.9–13.3)	5
Cerebral perfusion						
No cerebral perfusion	25.4% (0.0–100.0)	23	8.5% (0.0–100.0)	30	0.0% (0.0–0.0)	9
Unilateral ACP	28.8% (0.0–100.0)	23	45.5% (0.0–100.0)	30	88.4% (0.0–100.0)	9
Bilateral ACP	5.5% (0.0–100.0)	23	21.4% (0.0–100.0)	30	9.6% (0.0–100.0)	9
RCP	40.2% (0.0–100.0)	23	24.5% (0.0–100.0)	30	2.0% (0.0–100.0)	9

Table 1. Baseline characteristics

Characteristic	DHCA (<20) Pooled estimate	N	MHCA (20–25) Pooled estimate	N	Mild HCA (>25) Pooled estimate	N
Operative details						
Concomitant CABG	12.0% (3.4–36.5)	18	13.3% (2.8–35.0)	25	11.4% (2.7–26.1)	8
Hemiarch replacement	83.1% (0.0–100.0)	20	77.5% (0.0–100.0)	27	79.7% (0.0–100.0)	10
Total arch replacement	15.2% (0.0–100.0)	22	21.4% (0.0–100.0)	30	20.3% (0.0–100.0)	10
Root replacement	25.8% (5.0–88.0)	20	28.6% (2.4–81.4)	26	14.4% (3.2–47.3)	9
AVR	34.8% (5.8–70.2)	14	42.4% (1.9–87.1)	18	59.9% (5.4–75.3)	6
ET	1.9% (0.0–17.3)	24	1.4% (0.0–19.5)	30	2.6% (0.0–28.1)	8
FET	0.0% (0.0–0.0)	21	11.2% (0.0–95.0)	28	25.0% (0.0–82.5)	9
Lowest rectal temp.[a]	18.7 ± 2.2	19	24.0 ± 6.6	23	28.0 ± 1.4	8
Intraoperative outcome						
CPB time (min) (SD)	195.3 (61.6)	25	186.3 (55.8)	32	156.3 (55.0)	10
ACC time (min) (SD)	124.9 (44.8)	22	125.6 (49.9)	28	111.5 (52.6)	7
HCA time (min) (SD)	27.5 (13.9)	21	27.9 (12.8)	25	21.2 (11.9)	8
ACP time (min) (SD)	37.4 (18.7)	6	48.6 (21.8)	10	49.0 (28.1)	4
RCP time (min) (SD)	29.0 (13.0)	1	25.0 (9.7)	1	2.6 (4.3)	1

Note: All values are presented as % (range).

Abbreviations: ACP, antegrade cerebral perfusion; ACC, aortic cross clamp; CABG, coronary artery bypass grafting; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disorder; CPB, cardiopulmonary bypass; CVA, cerebrovascular accident; DHCA, deep hypothermic circulatory arrest; DM, diabetes mellitus; HCA, hypothermic circulatory arrest; ET, elephant trunk; FET, frozen elephant trunk; MHCA, moderate hypothermic circulatory arrest; RCP, retrograde cerebral perfusion; SD, standard deviation.

[a]If no rectal temperature was provided, the mean lowest nasal temperature was used ($n = 7$ for DHCA, $n = 8$ for MHCA, $n = 0$ for mild HCA), presented in degrees Celsius.

Table 2. In-hospital outcomes associated with the use of different temperature strategies

Characteristic	DHCA (<20)		MHCA (20–25)		Mild HCA (>25)	
	Pooled estimate (95% CI)	Number of studies (I^2)	Pooled estimate (95% CI)	Number of studies (I^2)	Pooled estimate (95% CI)	Number of studies (I^2)
Operative mortality	9.9 (7.1–13.7)	25 (88.5%)	8.4 (6.1–11.6)	31 (87.5%)	5.7 (3.4–9.4)	9 (85.1%)
Postoperative stroke	8.5 (5.7–12.4)	24 (90.7%)	5.8 (4.3–7.6)	31 (75.6%)	4.9 (3.2–7.6)	10 (74.2%)
Postoperative AKI	15.3 (8.1–27.1)	14 (97.4%)	13.3 (7.8–24.3)	15 (97.0%)	10.3 (1.5–46.1)	2 (91.0%)

Abbreviations: AKI, acute kidney injury; CI, confidence interval; CVA, cerebrovascular accident; DHCA, deep hypothermic circulatory arrest; HCA, hypothermic circulatory arrest; MHCA, moderate hypothermic circulatory arrest.

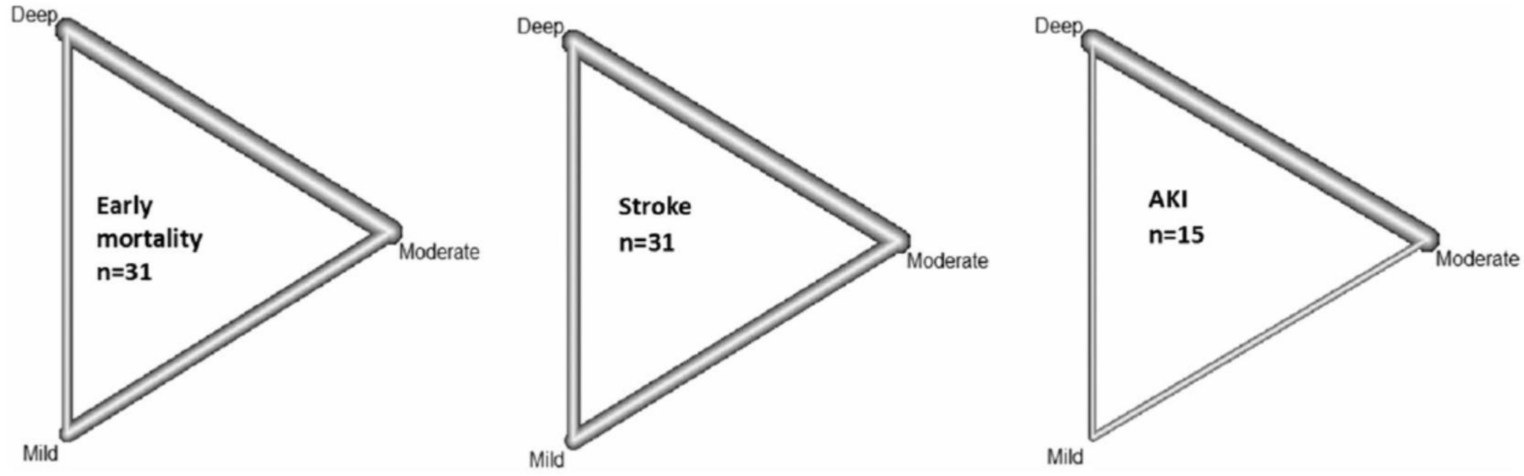


Figure 4. Network graphs for all comparisons of the reported outcomes. The thickness of the beams indicates how commonly a comparison was found in the network analysis, in relation to the other comparisons

Pairwise and network meta-analysis

Operative mortality

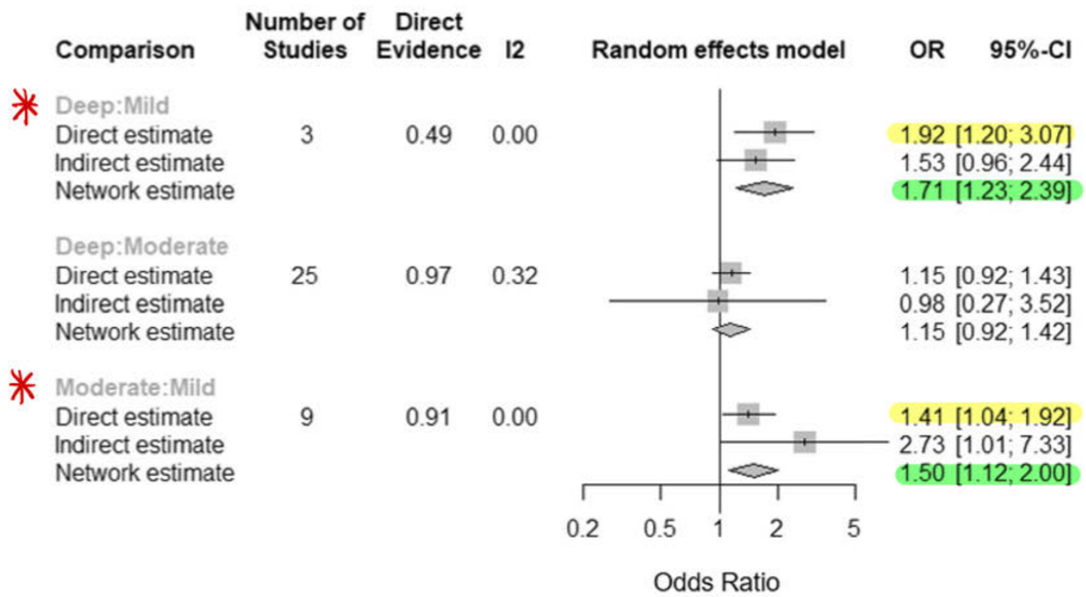


Figure 2. Forest plot of net split results of direct, indirect evidence and network estimates for **operative mortality**

Pairwise and network meta-analysis

Postoperative incidence of stroke

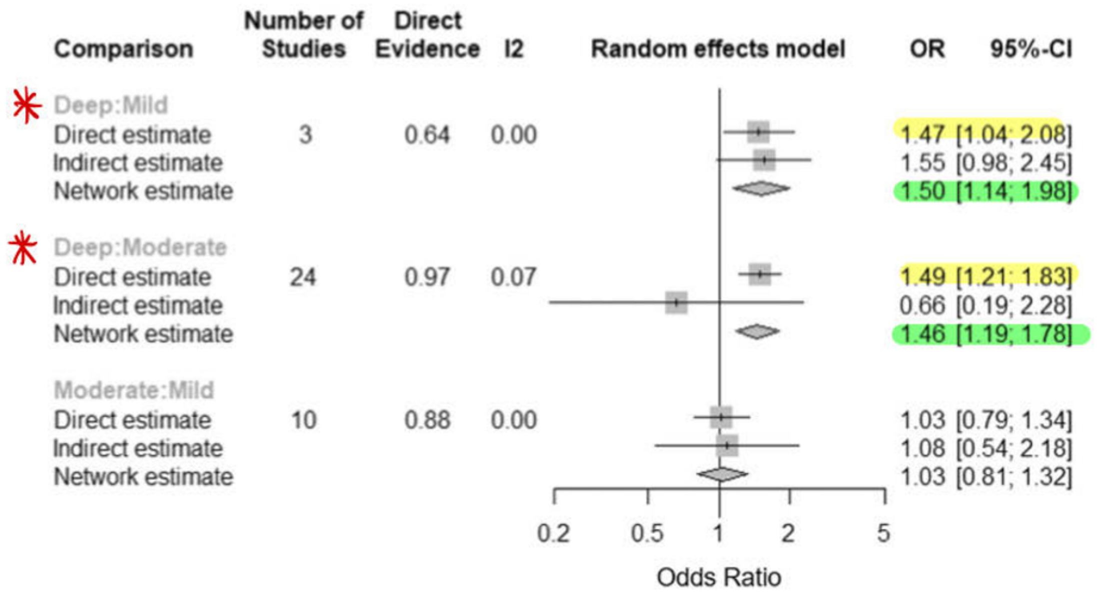


Figure 3. Forest plot of net split results of direct, indirect evidence and network estimates for **the postoperative incidence of stroke.**

Pairwise and network meta-analysis

Postoperative incidence of acute kidney insufficiency

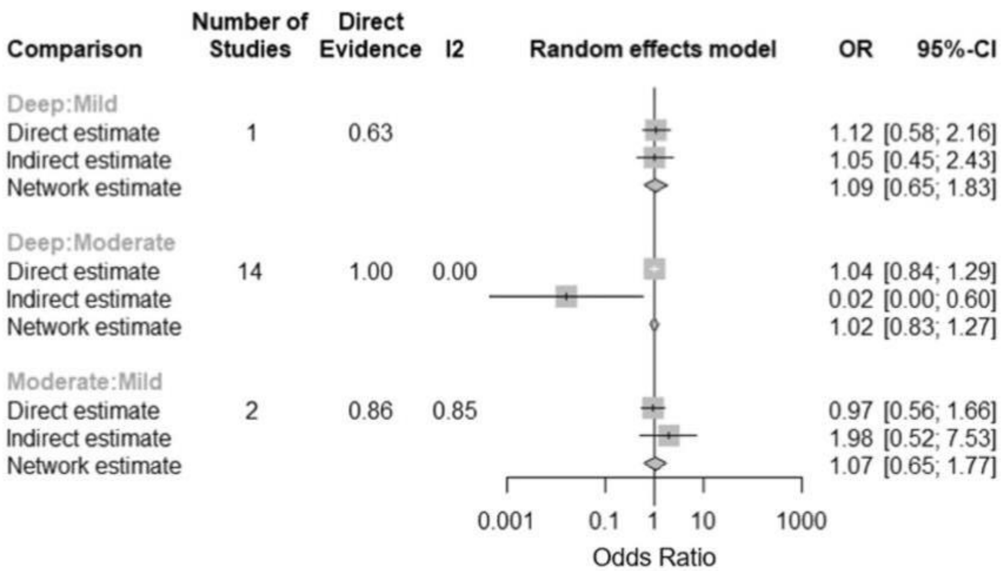


Figure 3. Forest plot of net split results of direct, indirect evidence and network estimates for **the postoperative incidence of acute kidney insufficiency.**

RCTs and PSM studies sensitivity analysis

- Two RCTs and seven PSM studies included 5425 patients.

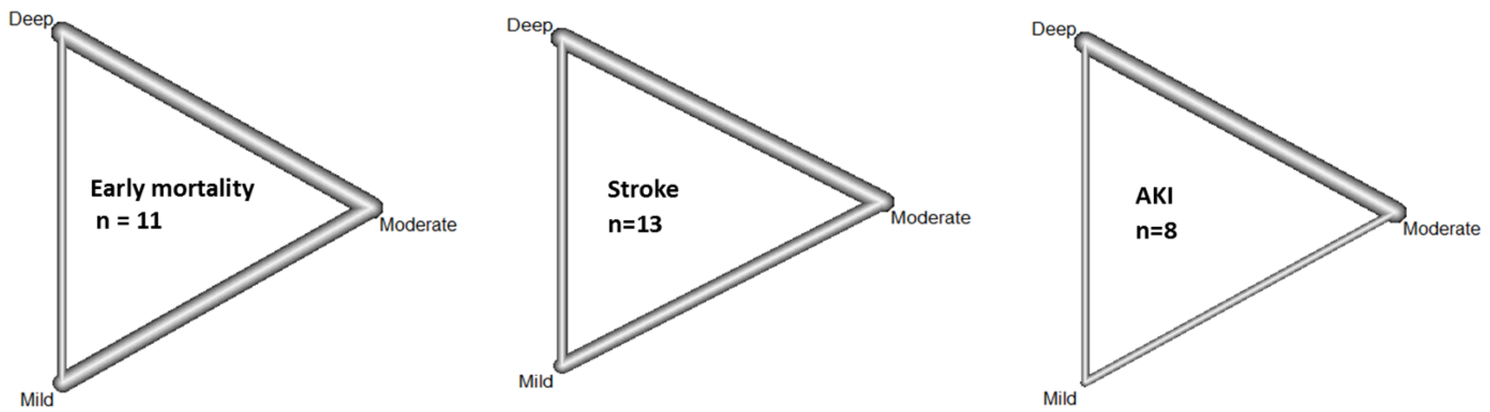


Figure 5. Network graphs for all comparisons of the reported outcomes. The thickness of the beams indicates how commonly a comparison was found in the network analysis, in relation to the other comparisons (randomized controlled trials and propensity score matched studies).

RCTs and PSM studies sensitivity analysis

Operative mortality

Comparison	Number of Studies	Direct Evidence	I2	OR	95%-CI
Deep:Mild					
Direct estimate	1	0.35		1.42	[0.71; 2.84]
Indirect estimate				1.22	[0.73; 2.04]
Network estimate				1.29	[0.85; 1.95]
Deep:Moderate					
Direct estimate	8	0.98	0	0.91	[0.68; 1.22]
Indirect estimate				0.42	[0.06; 2.91]
Network estimate				0.89	[0.67; 1.19]
* Moderate:Mild					
Direct estimate	4	0.97	0	1.39	[1.00; 1.94]
Indirect estimate				4.13	[0.71; 24.05]
Network estimate				1.45	[1.05; 2.00]

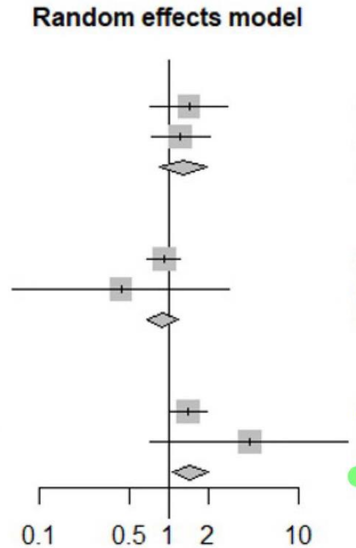


Figure 6. Forest plot of net split results of direct, indirect evidence and network estimates for **operative mortality (randomized controlled trials and propensity score matched studies).**

RCTs and PSM studies sensitivity analysis

Postoperative incidence of stroke

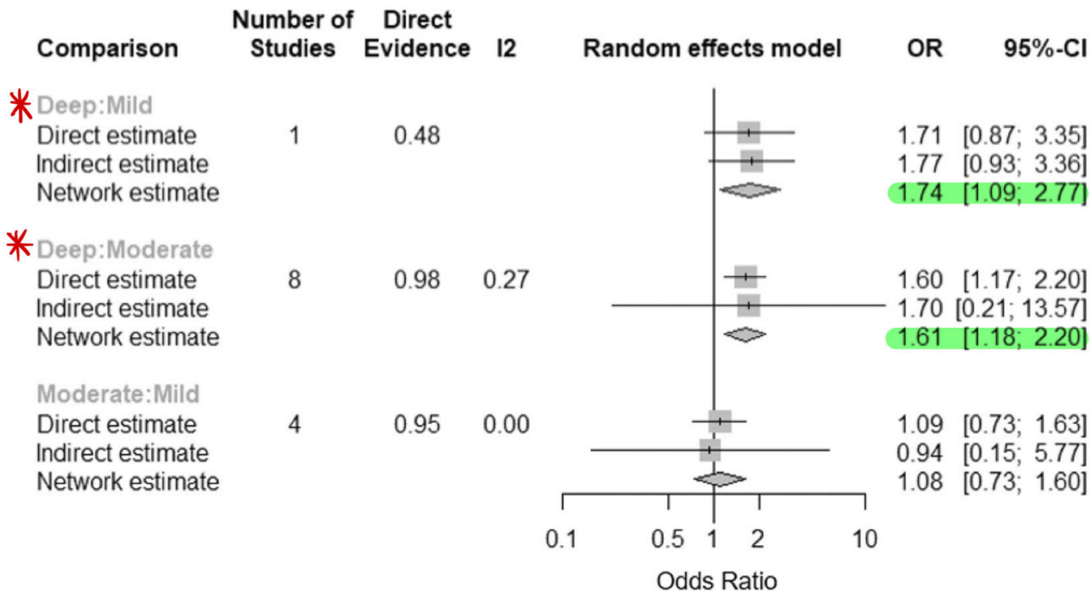


Figure 7. Forest plot of net split results of direct, indirect evidence and network estimates **for the postoperative incidence of stroke (randomized controlled trials and propensity score matched studies).**

RCTs and PSM studies sensitivity analysis

Postoperative incidence of acute kidney insufficiency

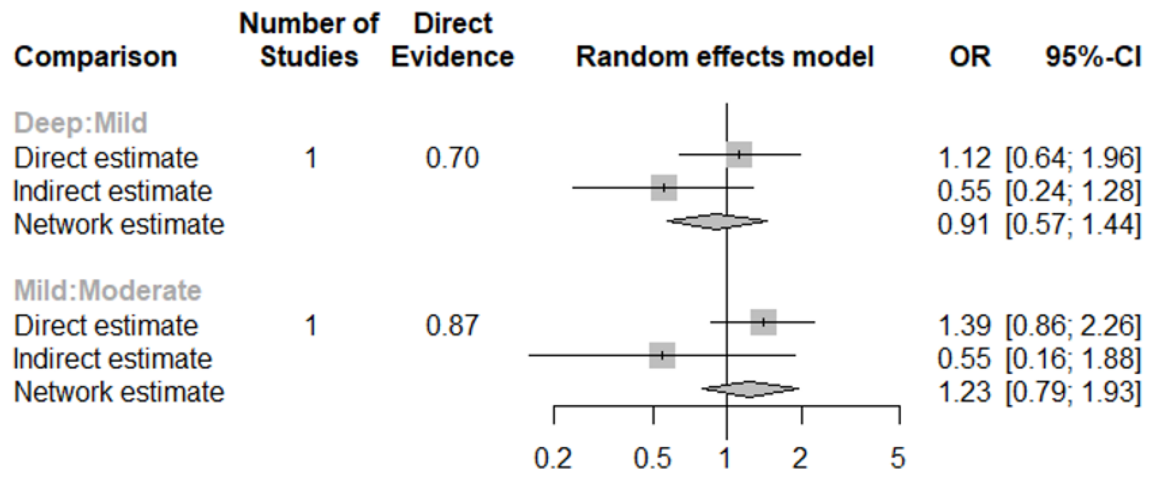


Figure 8. Forest plot of net split results of direct, indirect evidence and network estimates for **the postoperative incidence of acute kidney insufficiency (randomized controlled trials and propensity score matched studies).**

DISCUSSION FROM AUTHOR

- The main finding of this NMA is that the application of moderate and mild hypothermia in combination with selective cerebral perfusion is associated with lower incidence of postoperative stroke, when compared with DHCA alone or in combination with any selective cerebral perfusion strategy.

DISCUSSION FROM AUTHOR

- Sensitivity analysis of solely RCT and PSM studies revealed that DHCA is associated with sustained higher postoperative risk of stroke when compared with MHCA and mild HCA in combination with selective cerebral perfusion.
- There was also a sustained significantly higher risk of operative mortality for MHCA when compared with mild HCA.

DISCUSSION FROM AUTHOR

- Though further differences between DHCA, MHCA and mild HCA for the outcome operative mortality are not holding up.
- Reason behind this result could be underpowered analysis or the adjusted confounding associated with the NMA in unadjusted observational studies.

Strengths and limitations

- **Strengths**
  - Incorporating both types of data allows assessments of larger sample sizes and multiple treatments simultaneously.
  - Most studies included in the current analysis have been published recently, only one study dates from over 30 years ago. This study was not included in the sensitivity analysis.

Strengths and limitations

- **Limitations**
  - Use of observational studies in a meta-analysis. The presence of unmeasured confounders and possible treatment allocation bias cannot be excluded.
  - The randomized evidence is scarce, leading to a relatively large amount of non-randomized studies in NMA.

Strengths and limitations

- **Limitations**
  - There may be variability in surgeon and center expertize, technical variabilities and postoperative protocols.
  - Heterogeneity may arise due to different definitions for stroke and postoperative AKI.

CONCLUSION

- In the present NMA, the risk of operative mortality decreased with the use of mild HCA.
- The use of DHCA was associated with substantial higher risks of postoperative incidence of stroke when compared with moderate-to-mild hypothermia.
- These outcomes were reinforced by the sensitivity analysis of RCTs and PSM studies.

Thank you