

**A.** Important parameters in the therapeutic hypothermia intervention based on the PICO process

| Population                                                                                                                                                                                              | Intervention                                                                                                                                                                                                                                                                                                                                                                                                | Comparison                                                                                                                                                                                                                             | Outcome                                                                                                                                                                                                                                                              |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>• Adult or pediatrics</li> <li>• Number of participants</li> <li>• Closed TBI</li> <li>• GCS of patients at admission</li> <li>• ICP at the admission</li> </ul> | <ul style="list-style-type: none"> <li>• Hypothermia for ICP prophylaxis of high ICP treatment</li> <li>• interval between trauma hypothermia</li> <li>• Cooling rate</li> <li>• Duration of hypothermia</li> <li>• Target temperature</li> <li>• Target ICP</li> <li>• Method of cooling</li> <li>• Use of barbiturate</li> <li>• Rewarming rate</li> <li>• Need for neurosurgical intervention</li> </ul> | <ul style="list-style-type: none"> <li>• Did the normothermia group have any intervention to keep the body temperature at a target temperature, or was the temperature controlled passively</li> <li>• Control temperature?</li> </ul> | <ul style="list-style-type: none"> <li>• Mortality</li> <li>• Unfavorable neurologic outcome</li> <li>• Favorable neurologic outcome</li> <li>• Pneumonia</li> <li>• Bleeding and coagulopathy</li> <li>• Arrhythmia</li> <li>• Electrolyte abnormalities</li> </ul> |

ICP: Intracranial pressure, TBI: traumatic brain injuries

## B. Characteristics of included studies

| Author/published year       | Country | Bias risk assessment and quality checklist                                                                                        | Number and type of included studies | Number of participants (intervention group/control group) | Pediatrics or adults? | GCS of included studies | Type of TBI        | Induction time of hypothermia  | Duration of hypothermia | Methods to apply hypothermia                                                                    | Target temperature (°C) | The fastest rewarming rate | Unfavorable neurologic outcome | Follow up length |
|-----------------------------|---------|-----------------------------------------------------------------------------------------------------------------------------------|-------------------------------------|-----------------------------------------------------------|-----------------------|-------------------------|--------------------|--------------------------------|-------------------------|-------------------------------------------------------------------------------------------------|-------------------------|----------------------------|--------------------------------|------------------|
| Harris et al. (2002) (1)    | USA     | "Assessing the quality of reports of randomized clinical trials: is blinding necessary?" by Jadad et al. (2)                      | 7 RCT                               | 668                                                       | -                     | -                       | -                  | 6 h – mean of 15 h post-injury | ≤ 14 days (mostly 48 h) | -                                                                                               | 32 - 35                 | From 12h – 5 days          | -                              | -                |
| Henderson et al. (2003) (3) | Canada  | assessed studies based on the blinded assessment of the outcome an explanation of their randomization method                      | 8 RCT                               | 748                                                       | -                     | ≤ 9                     | -                  | < 6 h                          | 1-14 days               | -                                                                                               | 32 - 35                 | -                          | GOS ≤ 3                        | 6 months         |
| McIntyre et al. (2003) (4)  | Canada  | allocation concealment and blinding of the outcome assessment were used to assess the methodology                                 | 12 RCT                              | 1069 (543/526)                                            | Adults                | Mean GCS < 8            | -                  | -                              | 1-14 days               | -                                                                                               | 30 – 34.5               | ≤ 1°C/h                    | GOS ≤ 3                        | 3,6,12 months    |
| Alderson et al. (2004) (5)  | UK      | authors used adequacy of allocation concealment and the degree of blinding in the assessment of outcome instead of any checklists | 14 RCT                              | 1094                                                      | Pediatrics and adults | ≤ 8                     | Closed head injury | Within 10 hours after trauma   | 1-4 days                | Cooling blanket, ice, cold gastric lavage, unwarmed ventilator gases, temperature control pads, | 30 – 34.5               | ≤ 0.5°C/2h                 | GOS ≤ 3                        | 3,6,12 months    |

|                            |        |                                                                                                                                                                                                                                                                                                                       |         |                |                       |             |                    |                 |                                    |                                                                       |       |                               |              |                            |
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| Peterson et al. (2008) (6) | USA    | The quality assessment tool was created based on criteria developed by the U.S. Preventive Services Task Force (Harris et al., 2001), the National Health Service Centre for Reviews and Dissemination (U.K.) (Centre for Reviews and Dissemination, 2001), and the Cochrane Collaboration (Higgins and Green, 2006). | 13 RCTs | 1339 (689/650) | adults                | Mean GCS <6 | -                  | Immediately-20h | 1-14 days                          | -                                                                     | 30-35 | $\leq 1^{\circ}\text{C/h}$    | GOS $\leq 3$ | 120 h, 3, 6, 12, 24 months |
| Sydenham et al. (2009) (7) | UK     | The Cochrane Collaboration 2008; Vol. Version 5.0.0 [updated February 2008]                                                                                                                                                                                                                                           | 23 RCT  | 1614           | Pediatrics and adults | $\leq 9$    | closed head injury | 6-48h           | 1-8 days                           | Cooling blankets, Cooling bed, Ice blocks, iced saline stomach lavage | 30-35 | $\leq 1^{\circ}\text{C/3h}$   | GOS $\leq 3$ | 1, 3, 6, 12 months         |
| Fox et al. (2010) (8)      | Canada | Blinding and Allocation concealment                                                                                                                                                                                                                                                                                   | 12 RCT  | 1327 (670/657) | Adult                 | $\leq 8$    | Blunt TBI          | -               | 1-14 days: Short (<48h) long (>48) | -                                                                     | 32-35 | -                             | GOS $\leq 3$ | -                          |
| Harris et al. (2012) (9)   | UK     | Randomized controlled trials were assessed for adequacy of the randomization and allocation                                                                                                                                                                                                                           | 1 RCT   | 25 (12/13)     | Adult                 | $\leq 8$    | -                  | $\leq 48$       | 24 h                               | Head and neck cooling                                                 | 33    | $\leq 0.5^{\circ}\text{C/3h}$ | -            | 1 month                    |

|                             |             |                                                                                              |                                       |                |                       |                                                            |                            |                                 |                                                |                                                                                                                                                                                               |         |           |                                                           |                     |
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|                             |             | concealment process, the potential for selection bias after allocation, and level of masking |                                       |                |                       |                                                            |                            |                                 |                                                |                                                                                                                                                                                               |         |           |                                                           |                     |
| Georgiou et al. (2013) (10) | UK          | GRADE                                                                                        | 18 RCT                                | 1851           | Pediatrics and adults | ≤ 8 (only high and moderate-quality studies were reported) | -                          | -                               | 24-103h                                        | -                                                                                                                                                                                             | 30 - 35 | ≤ 1°C/h   | GOS ≤ 3 in adults<br>PCPC 3-6 in children                 | 3, 6, 12 months     |
| Ma et al. (2013) (11)       | China       | Random allocation and baseline demographic similarity were used for quality assessment       | 6 RCTs                                | 366            | Pediatrics            | Mean GCS <8                                                | -                          | -                               | 1 to >3 days                                   | -                                                                                                                                                                                             | 32-34.7 | ≤ 1°C/h   | -                                                         | -                   |
| Crossley et al. (2014) (12) | UK          | Cochrane Collaboration tool for assessing risk of bias                                       | 20 RCT                                | 1885 (999/886) | Adult                 | -                                                          | Closed head injury         | 2.5 – 20 h                      | Average of 4.5 h on 3 consecutive days to 14 d | Cooling blankets, Application of ice or gastric lavage with ice, cold saline gastric lavage, IV cold crystalloid, gel packs, air cooling, circulating water mattress, Ice pillow, Cooling cap | < 36    | ≤ 0.3°C/h | GOS ≤ 3 or equivalent scoring in Ranchos Los Amigos scale | 3-6 months          |
| Geurts et al. (2014) (13)   | Netherlands | Cochrane Risk of Bias Methods (14)                                                           | 10 clinical trials (out of 23 trials) | 524 (264/260)  | Adults                | -                                                          | -                          | -                               | 1-14 days                                      | Surface cooling                                                                                                                                                                               | 33-35.5 | -         | -                                                         | 3, 6, 12, 24 months |
| Galvin et al. (2015) (15)   | Canada      | Cochrane Collaboration tool for                                                              | 1 (out of 4) RCT                      | 80 (40/40)     | Adults                | ≤ 8                                                        | non-penetrating severe TBI | Immediately after the operation | 4 days                                         | Water-circulating cooling                                                                                                                                                                     | 33 - 35 | -         | GOS ≤ 3                                                   | 12 months           |

|                            |       |                                                                                 |                                                        |                  |                       |                                                       |                     |                                                                                    |                                  |                                                                                                                                                                                                          |         |          |         |                    |
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|                            |       | assessing risk of bias                                                          |                                                        |                  |                       |                                                       |                     |                                                                                    |                                  | blanket, Cooling cap, refrigerated ice bags                                                                                                                                                              |         |          |         |                    |
| Zhang et al. (2015) (16)   | China | Cochrane Reviewer's Handbook 5.1.0                                              | 7 RCTs                                                 | 442 (218/224)    | Pediatrics            | ≤ 15 (9 patients with GCS >8 and the rest had GCS ≤8) | -                   | Less than 8 hours after trauma                                                     | 1-3 days                         | Saline, cooling blankets, ice cap                                                                                                                                                                        | 32-34   | ≤ 1°C/4h | GOS ≤ 3 | 3, 6, 12 months    |
| Zhu et al. (2016) (17)     | China | modified Jadad score, Cochrane Handbook for Systematic Reviews of Interventions | 18 RCTs                                                | 2177 (1122/1055) | Adults                | -                                                     | -                   | Within 24h                                                                         | 24-366 h                         | -                                                                                                                                                                                                        | 32-35   | ≤ 1°C/h  | GOS ≤ 3 | 3 and 6 months     |
| Dunkley e. al. (2017) (18) | UK    | CASP randomized controlled trial checklist or the CASP cohort study checklist   | 8 (6 RCTs/ 2 retrospective quasi-experimental studies) | 689 (493/196)    | Adult                 | ≤ 8                                                   | -                   | -                                                                                  | 2-5 days                         | -                                                                                                                                                                                                        | 33-35   | ≤ 1°C/h  | GOS ≤ 3 | 6, 12, 24 months   |
| Lewis et al. (2017) (19)   | UK    | Cochrane Risk of Bias Tool and GRADE                                            | 37 RCTs                                                | 3110 (1556/1554) | Pediatrics and adults | ≤ 8                                                   | Both open and close | 3 hours after injury – 10 days (Some studies reported immediately after admission) | 1-14 days (until ICP normalizes) | Cooling blanket, Cold IV saline, Crushed ice exposed to the surface, iced saline gastric lavage, cooling cap, cold irrigation of Hartmann's solution onto the surface of the brain, forced air, ice bags | 30 - 35 | ≤ 1°C/h  | GOS ≤ 3 | 1, 3, 6, 12 months |

|                             |           |                                                                                                                      |                   |                  |                         |                 |                    |                                                             |           |                                                                                                                                            |         |                                   |                                          |                         |
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| Zang et al. (2017) (20)     | China     | Cochrane Collaboration's tool for evaluating the risk of bias (14)                                                   | 21 RCTs           | 2275 (1199/1076) | Adult                   | -               | -                  | -                                                           | 1-7 days  | IV refrigerated saline, cooling blanket, wet sheet, gel packs, cold gastric lavage, ice pillow, room temperature air in ventilator cooling | 32-35   | -                                 | GOS $\leq$ 3 or equivalent scoring scale | 3, 6, 12, 24 months     |
| Leng et al. (2018) (21)     | China     | Quality assessment was done based on the similarity between baseline characteristics of groups and random allocation | 7 clinical trials | 1331 (689/642)   | -                       | $\leq 8$        | -                  | 3-10h                                                       | 24-48 h   | -                                                                                                                                          | 32-36   | The fastest rewarming time was 4h | GOS $\leq$ 3                             | 3, 6, and 12 months     |
| Olah et al. (2018) (22)     | Hungary   | Cochrane Handbook (14), The Jadad score (2), level of randomization                                                  | 14 RCTs           | 1786 (896/890)   | adults                  | $\leq 8$        | -                  | -                                                           | 24-336h   | Whole body cooling                                                                                                                         | 32-36   | $\leq 1^{\circ}\text{C/h}$        | -                                        | -                       |
| Watson et al. (2018) (23)   | UK        | Cochrane Collaboration's tool for assessing the risk of bias                                                         | 22 RCTs           | 2346 (1240/1106) | Adults                  | $\leq 8$        | closed head injury | -                                                           | -         | -                                                                                                                                          | <36     | -                                 | -                                        | 3 to >6 months          |
| Chen et al. (2019) (24)     | China     | The Cochrane Collaboration's tool and the Jadad score                                                                | 23 RCT            | 2796 (1448/1348) | Adults                  | $\leq 15$       | -                  | Immediately – 10 days:<br>Early TH (<24h)<br>Late TH (>24h) | 1-14 days | -                                                                                                                                          | 30 - 36 | $\leq 1^{\circ}\text{C/h}$        | GOS $\leq$ 3 or GOS-E $\leq$ 4           | 3, 6, 12, 24, 48 months |
| Meizikri et al. (2019) (25) | Indonesia | GRADE                                                                                                                | 2 RCTs            | 127 (63/64)      | Children and adolescent | Median $\leq 6$ | -                  | < 6h after injury                                           | -         | -                                                                                                                                          | 32-33   | < 1°C/3h                          | -                                        | 3, 6, and 12 months     |

|                              |        |                                                                         |                                 |                  |                       |      |                    |                            |                   |                                                                                                                  |           |         |                                                                         |                                |
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| Huang et al. (2020) (26)     | China  | The Cochrane Risk Assessment Tool (14)                                  | 15 RCTs                         | 2523 (1320/1203) | Adults                | ≤ 8  | -                  | Immediately – 10 days      | 1-14 days         | -                                                                                                                | 32-35     | ≤ 1°C/h | GOS ≤ 3 or GOS-E ≤ 4                                                    | 3, 6, 12, and 24 months        |
| Kim et al. (2020) (27)       | Italy  | Cochrane Handbook for Systematic Reviews of Interventions               | 9 (out of 14 randomized trials) | 1900 (986/914)   | Pediatrics and adults | -    | -                  | -                          | Minimum of 24-72h | Cold saline infusion                                                                                             | 32-35     | -       | GOS ≤ 3, GOS-E ≤ 4, PCPC ≥ 4, and PE-GOS ≥ 5                            | 3,6, 12 months                 |
| Wu et al. (2021) (28)        | China  | Cochrane Collaboration Risk of Bias Tool                                | 6 RCTs                          | 1225 (657/568)   | Adults                | ≤ 8  | -                  | Within 6h after the injury | 1-7 days          | Cooling blanket, nasogastric lavage with iced fluids, IV cooling, room temperature air in the ventilator circuit | 32-35     | ≤ 1°C/h | GOS ≤ 3 GOS-E ≤ 4                                                       | 6 months                       |
| Du et al. (2022) (29)        | China  | Cochrane Handbook of Systematic Evaluation of Interventions (30)        | 8 RCTs                          | 514 (257/257)    | Pediatrics            | ≤ 8  | -                  | 8h After Trauma            | 1-7 days          | Cooling blanket, cooling cap                                                                                     | 32-35     | -       | -                                                                       | -                              |
| Geng et al. (2022) (31)      | China  | Cochrane Review Handbook 5.3                                            | 5 RCTs                          | 421 (206/215)    | Pediatrics            | -    | -                  | -                          | -                 | -                                                                                                                | -         | -       | -                                                                       |                                |
| Utsumi et al. (2023) (32)    | Japan  | Cochrane Collaboration's RCT Risk of bias Tool                          | 6 RCT                           | 448 (220/228)    | Pediatrics            | < 8  | closed head injury | -                          | 1-3 days          | -                                                                                                                | 32 - 34.5 | -       | CPC ≥ 3, GOS ≤ 3, Pediatric CPC ≥ 4, pediatric version of the GOS-E ≤ 4 | 3 months or more               |
| Martyniuk et al. (2024) (33) | Canada | revised Cochrane risk of bias tool for randomized trials (RoB 2), GRADE | 32 RCTs                         | 3909 (2105/1894) | Adults                | ≤ 12 | Blunt TBI          | -                          | 1-14 days         | Cooling cap, cooling neck blanket, water circulating blanket, gastric                                            | 32-35     | -       | GOS ≤ 3 GOS-E ≤ 4                                                       | 1, 3, 6, 12, 24 months-7 years |

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|  |  |  |  |  |  |  |  |  |  | lavage,<br>hypothermia<br>machine with<br>cooling<br>blankets,<br>medical<br>cooling bed,<br>ice bag,<br>chilled fluid<br>irrigation<br>along the<br>subdural<br>catheter,<br>rapid cold<br>infusion,<br>room<br>temperature<br>air in<br>ventilator,<br>gel pads |  |  |  |  |
|--|--|--|--|--|--|--|--|--|--|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|--|--|--|

CASP: Critical Appraisal Skills Program, CPC: Cerebral Performance Category, GCS: Glasgow coma scale, GOS: Glasgow outcome scale, GOS-E: Glasgow outcome scale-extended, GRADE: Grading of Recommendations Assessment, Development, and Evaluation, IV: intravenous, PCPC = Pediatric Cerebral Performance, PE-GOS = Pediatric Extended Glasgow Outcome Scale, PRISMA: The preferred reporting items for systematic reviews and meta-analyses statement, PICU: pediatric intensive care unit, QUOROM: quality of reporting of meta-analyses statement, RCT: Randomized controlled trial, TBI: Traumatic brain injury, TH: therapeutic hypothermia,

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### C. Results of the meta-analysis performed by the included studies

| Author/published year       | Mortality                                                                                                                                                                                                                                                                                                                                                          | Outcome (poor outcome or favorable outcome)                                                                                                                                                                                                                        | Pneumonia                                                                                                                                                            | Other complications of hypothermia assessment?                                                                                                                                                                            |
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| Harris et al. (2002) (1)    | -                                                                                                                                                                                                                                                                                                                                                                  | OR of TH on GOS score: 0.61 (0.26-1.46)                                                                                                                                                                                                                            | OR of pneumonia in TH: 2.05 (95% CI 0.79 – 5.32, p-value 0.14)                                                                                                       | 1) OR for arrhythmia 1.27 (0.38-4.25)<br><br>2) OR for an increase in prothrombin time of the TH group: 0.02 (-0.07 to 0.1)<br><br>3) OR for an increase in partial thromboplastin time of the TH group: 2.22 (1.73-2.71) |
| Henderson et al. (2003) (3) | OR of mortality in TH: 0.81 (0.59 - 1.13)                                                                                                                                                                                                                                                                                                                          | OR of TH on death or severe disability : 0.75 (0.56 – 1.01)                                                                                                                                                                                                        | OR of pneumonia in normothermia: 0.42 (0.25 – 0.7)                                                                                                                   | -                                                                                                                                                                                                                         |
| McIntyre et al. (2003) (4)  | 1) RR of mortality in TH: 0.81 (0.69 – 0.96)<br><br>2) RR for mortality in the TH group for hypothermia >48h: 0.7 (0.56-0.87)                                                                                                                                                                                                                                      | RR of poor neurologic outcome in TH: 0.78 (0.63-0.98)<br><br>2) RR for poor neurologic outcome in the TH group for hypothermia 24h: 0.61 (0.39-0.97)<br><br>3) RR for poor neurologic outcome in the TH group for hypothermia >48h: 0.65 (0.48-89)                 | -                                                                                                                                                                    | -                                                                                                                                                                                                                         |
| Alderson et al. (2004) (5)  | OR for mortality in TH: 0.8 (0.61 - 1.04)                                                                                                                                                                                                                                                                                                                          | OR for death or severe disability: 0.75 (0.56 – 1)                                                                                                                                                                                                                 | OR of pneumonia in TH: 1.95 (1.18 – 3.23)                                                                                                                            | -                                                                                                                                                                                                                         |
| Peterson et al. (2008) (6)  | 1) RR of mortality in the TH group: 0.8 (0.59-1.09)<br><br>2) RR of mortality in TH with hypothermia >48h duration: 0.51 (0.33-0.79)<br><br>3) RR of mortality in TH with hypothermia up to 48h: 1.03 (0.79-1.36)<br><br>4) RR of mortality in the TH group based on the data from studies that didn't use barbiturates as an ICP lowering method: 0.58 (0.4-0.85) | 1) RR of FN in the TH group: 1.25 (0.96-1.62)<br><br>2) RR of FN in TH with hypothermia >48h duration: 1.91 (1.28-2.85)<br><br>3) RR of FN in the TH group based on the data from studies that didn't use barbiturates as an ICP lowering method: 1.79 (1.27-2.52) | 1) RR of pneumonia in the TH group at the 12-month follow-up: 2.37 (1.37-4.10)<br><br>2) RR of pneumonia in the studies that used the barbiturate: 6.45 (2.47-16.85) | RR of arrhythmia in the TH group: 1.07 (0.53-2.18)                                                                                                                                                                        |

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|-----------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|
| Sydenham et al. (2009) (7)  | 1) OR of mortality in the hypothermia group: 0.85 (0.68-1.06)<br><br>2) OR of mortality in hypothermia based on the studies with good allocation concealment methods: 1.11 (0.82-1.51)                                                         | 1) OR of Unfavorable outcome in the hypothermia group at final follow-up: 0.77 (0.62-0.94)<br><br>2) OR of Unfavorable outcome in the hypothermia based on studies with good allocation concealment methods at final follow-up: 0.93 (0.7-1.23) | 1) OR of pneumonia in TH group: 1.35 (0.95-1.91)<br><br>2) OR of pneumonia based on studies with good allocation concealment methods: 0.84 (0.52-1.35)         | -                                                                                                               |
| Fox et al. (8)              | 1) RR of prophylactic TH on mortality in the TH group: 0.73 (0.62–0.85)<br><br>2) RR of short-term prophylactic hypothermia on mortality: 0.98 (0.75-1.3)<br><br>3) RR for long-term prophylactic hypothermia on mortality: 0.62 (0.51 – 0.76) | 1) RR for FN in TH group: 1.52 (1.28–1.80)<br><br>2) RR for FN in short-term hypothermia: 1.31 (0.94 – 1.83)<br><br>3) RR for FN in long-term hypothermia: 1.68 (1.44-1.96)                                                                     | -                                                                                                                                                              | Hypokalemia was the most common electrolyte abnormality and was treated without life-threatening outcomes.      |
| Georgiou et al. (2013) (10) | 1) RR of prophylactic TH on mortality: 0.84 (0.72–0.98)<br><br>2) OR of high-quality studies on the effects of prophylactic TH on mortality: 1.28 (0.89 – 1.83)                                                                                | 1) RR of prophylactic TH on UFN: 0.81 (0.73 – 0.89)<br><br>1) RR of high-quality studies on the effects of prophylactic TH on UFN: 1.07 (0.92-1.24)                                                                                             | -                                                                                                                                                              | -                                                                                                               |
| Ma et al. (2013) (11)       | RR for mortality in the hypothermia group: 1.73 (1.06-2.84)                                                                                                                                                                                    | -                                                                                                                                                                                                                                               | RR for pneumonia in the hypothermia group: 0.9 (0.73-1.12)                                                                                                     | RR for cardiac arrhythmia: 2.57 (1.01-6.54)                                                                     |
| Crossley et al. (2014) (12) | 1) RR of death in the normothermia group: 1.31 (1.13 - 1.52)<br><br>2) RR of mortality in the normothermia group based on the data from the lower risk of bias studies: 1.62 (1.3-2.01)                                                        | 1) RR for poor outcomes in the normothermia group: 1.49 (1.27-1.74)<br><br>2) RR of poor outcome in the normothermia group based on the data from the lower risk of bias studies: 1.67 (1.45-1.92)                                              | 1) RR for pneumonia in the TH group: 0.81 (0.62 -1.05)<br><br>2) RR for pneumonia in the TH group based on the studies with low risk of bias: 0.87 (0.71-1.07) | -                                                                                                               |
| Geurts et al. (2014) (13)   | -                                                                                                                                                                                                                                              | -                                                                                                                                                                                                                                               | -                                                                                                                                                              | The risk of any infection in the TH group was 1.31 (0.95-1.81)                                                  |
| Zhang et al. (2015) (16)    | 1) RR of mortality in the TH group: 1.84 (1.15-2.93)<br><br>2) RR of mortality in the TH group of severe TBI patients (GCS ≤8): 1.75 (1.09-2.81)                                                                                               | 1) RR for FN in the TH group after 3-month follow-up: 0.89 (0.68-1.16)<br><br>2)RR for UFN in the TH after 3-month follow-up: 1.19 (0.8-1.76)                                                                                                   | RR of pneumonia in the TH group: 0.84 (0.63-1.12)                                                                                                              | 1) RR of bleeding in the TH group: 0.94 (0.39-2.26)<br><br>2) RR of arrhythmia in the TH group: 2.6 (1.06-6.41) |

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|                         |                                                                                                                                                                                                                                                                                                                                                                                                                      | 3) RR for FN in the TH group after 6-month follow-up: 0.91 (0.78-1.07)<br><br>2)RR for UFN in the TH after 6-month follow-up: 1.18 (0.88-1.59)                                                                                                                                                                                |                                                             |                                                                                                                                             |
| Zhu et al. (2016) (17)  | 1) RR for mortality in the hypothermia group in the 3-month post-TBI: 0.95 (0.59-1.55)<br><br>2) RR for mortality in the hypothermia group in the 6-month post-TBI: 0.96 (0.76-1.23)<br><br>3) RR for mortality in the hypothermia group for mortality at the final follow-up based on the data from the low-risk-of-bias studies: 1.22 (0.97-1.54)                                                                  | 1) RR for UFN in the hypothermia group in the 3-month post-TBI: 0.79 (0.56-1.12)<br><br>2) RR for UFN in the hypothermia group in the 6-month post-TBI: 0.8 (0.63-1)<br><br>3) RR for mortality in the hypothermia group for UFN at the final follow-up based on the data from the low-risk-of-bias studies: 0.84 (0.62-1.15) | RR for pneumonia in the hypothermia group: 1.51 (1.12-2.03) | 1) RR of cardiac complications in the hypothermia group: 1.75 (1.14-2.7)<br><br>2) RR of bleeding in the hypothermia group: 1.28 (0.4-4.15) |
| Zang et al. (2017) (20) | RR for mortality at the final follow-up in the TH group was 0.78 (0.64-0.96)                                                                                                                                                                                                                                                                                                                                         | The TH group's RR for poor neurologic outcome was 0.71 (0.6-0.84)                                                                                                                                                                                                                                                             | -                                                           | -                                                                                                                                           |
| Leng et al. (2018) (21) | OR of mortality in the hypothermia group: 1.21 (0.93 – 1.57)                                                                                                                                                                                                                                                                                                                                                         | 1) OR of FN in the hypothermia group: 1 (0.8-1.26)<br><br>[the text claims to report RR, but the forest plot reports the OR]                                                                                                                                                                                                  | -                                                           | -                                                                                                                                           |
| Olah et al. (2018) (22) | 1) OR of mortality between two groups: 0.675 (0.517-0.882)<br><br>2) OR of mortality between two groups in 32-33°C hypothermia: 0.705 (0.378-1.317)<br><br>3) OR of mortality between two groups in 33-35°C: 0.627 (0.393-1.001)<br><br>4) OR of mortality between >48h hypothermia and normothermia: 0.534 (0.392-0.729)<br><br>5) OR of mortality between 24-48h hypothermia and normothermia: 0.877 (0.649-1.185) | -                                                                                                                                                                                                                                                                                                                             | -                                                           | -                                                                                                                                           |

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|                           | <p>6) OR of mortality between hypothermia with <math>&lt;0.25^{\circ}\text{C/h}</math> and normothermia: 0.575 (0.369-0.895)</p> <p>7) OR of mortality between hypothermia with <math>&gt;0.25^{\circ}\text{C/h}</math> and normothermia: 0.742 (0.528-1.042)</p> <p>8) OR of mortality between two groups in studies adjusted based on ICP: 0.53 (0.383-0.734)</p> <p>9) OR of mortality in the studies not adjusted based on ICP: 0.849 (0.636-1.133)</p> |                                                                                                                                                                          |                                                      |   |
| Watson et al. (2018) (23) | <p>1) RR of mortality in the TH group: 0.83 (0.73-0.94)</p> <p>2) RR of mortality in the TH group based on the studies with low risk of bias: 1.37 (1.04-1.79)</p> <p>3) RR of mortality in the 3 months follow-up in the TH: 0.73 (0.46-1.17)</p> <p>4) RR of mortality in the <math>&gt;6</math>-month follow-up after the TBI: 0.84 (0.73-0.96)</p>                                                                                                      | <p>1) RR of poor outcome in the TH group: 0.81 (0.75-0.87)</p> <p>2) RR of poor outcome in the TH group based on the studies with low risk of bias: 1.16 (1.02-1.32)</p> | RR of pneumonia in the TH group: 1.5 (1.23-1.83)     | - |
| Chen et al. (2019) (24)   | <p>1) RR for mortality in the TH group: 0.91 (0.80 -1.03)</p> <p>2) RR for mortality in TH use for treatment: 0.66 (0.49 – 0.88)</p> <p>3) RR for mortality when TH is used for prevention: 1.12 (0.93 – 1.36)</p> <p>4) RR for mortality in early TH: 0.83 (0.71-0.96)</p> <p>5) RR for mortality in the control group compared to late TH: 1.12 (0.9-1.4)</p>                                                                                             | RR for UFN: 0.78 (0.67 - 0.91)                                                                                                                                           | RR for pneumonia in the TH group: 1.48 (1.11 – 1.97) | - |

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|                          | 6) RR of mortality in the TH group in studies with a low risk of bias: 1.31 (1.05-1.63)                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                              |   |                                                                                                                                                                                                                 |
| Huang et al. (2020) (26) | RR for mortality in the TH group was 0.94 (0.77-1.14)                                                                                                                                                                                                                                                                                                         | 1) RR of FN outcome in the TH group was: 1.2 (1.01-1.42)<br><br>2) RR for FN outcome at 3-month follow-up: 1 (0.57-1.76)<br><br>3) RR for FN outcome at 6-month follow-up: 1.06 (0.85-1.32)<br><br>4) RR for FN outcome at 12-month follow-up: 1.56 (1.2-2.03)<br><br>5) RR for mortality at 24-month follow-up: 1.79 (1.25-2.56)            | - | -                                                                                                                                                                                                               |
| Kim et al. (2020) (27)   | RR for mortality in the TH group: 1.26 (1.07-1.48)                                                                                                                                                                                                                                                                                                            | -                                                                                                                                                                                                                                                                                                                                            | - | -                                                                                                                                                                                                               |
| Wu et al. (2021) (28)    | 1) RR of prophylactic hypothermia on mortality in the TH at the end of 6 months: 1.11 (0.9-1.37)<br><br>2) RR of prophylactic short-term hypothermia ( $\leq 48$ h) on mortality in the TH at the end of 6 months: 1.04 (0.78-1.39)<br><br>3) RR of prophylactic long-term hypothermia ( $>48$ h) mortality in the TH at the end of 6 months: 1.19 (0.88-1.6) | 1) RR of FN in the prophylactic hypothermia group at the end of 6 months: 1.03 (0.91 -1.16)<br><br>2) RR of FN in the short-term ( $\leq 48$ h) prophylactic hypothermia group at the end of 6 months: 1.1 (0.82-1.47)<br><br>3) RR of FN in the long-term ( $>48$ h) prophylactic hypothermia group at the end of 6 months: 1.01 (0.8-1.28) | - | -                                                                                                                                                                                                               |
| Du et al. (2022) (29)    | RR of TH intervention on mortality: 1.57 (0.96-2.55)                                                                                                                                                                                                                                                                                                          | The mean difference in GOS score was significantly higher in the hypothermia group (p-value: 0.01)                                                                                                                                                                                                                                           | - | RR of incidence of complications: 0.98 (0.82-1.16)                                                                                                                                                              |
| Geng et al. (2022) (31)  | OR of mortality in the hypothermia group: 1.72 (95%CI 0.98-3.02, p-value: 0.04)                                                                                                                                                                                                                                                                               | -                                                                                                                                                                                                                                                                                                                                            | - | 1) OR of adverse outcomes in the hypothermia group: 1.39 (0.86-2.25)<br><br>2) OR of infection in the hypothermia group: 0.79 (0.51-1.23)<br><br>3) OR of arrhythmia in the hypothermia group: 3.10 (0.77-12.5) |

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| Utsumi et al. (2023) (32)    | RR of normothermia on mortality: 1.47 (0.69 – 3.13)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | RR of TH on FN: 0.91 (0.79 – 1.04)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | - | RR for arrhythmia in the TH group: 2.36 (0.74-7.46) |
| Martyniuk et al. (2024) (33) | 1) RR for mortality in the TH group: 0.81 (0.68-0.96)<br><br>2) RR of mortality in the TH group based on the low-risk-of-bias studies: 1.14 (0.81-1.61)<br><br>3) RR of mortality in the TH group based on the data from patients who underwent a neurosurgical intervention: 0.57 (0.27-1.23)<br><br>4) RR of mortality in the TH based on studies with systemic surface cooling: 0.63 (0.53-0.75)<br><br>5) RR of mortality in the TH based on studies with systemic IV or gastric lavage cooling: 1.17 (0.99-1.38)<br><br>6) RR of mortality in the TH based on studies isolated cranial cooling: 0.76 (0.38-1.52) | 1) RR of UFN in the TH group: 0.77 (0.67-0.88)<br><br>2) RR of UFN in the TH group based on the low-risk-of-bias studies: 0.89 (0.7-1.12)<br><br>3) RR of UFN in the TH group based on the data from patients who underwent a neurosurgical intervention: 0.79 (0.56-1.1)<br><br>4) RR of UFN in the TH based on studies with systemic surface cooling: 0.68 (0.59-0.79)<br><br>5) RR of UFN in the TH based on studies with systemic IV or gastric lavage cooling data: 1.17 (0.99-1.38)<br><br>6) RR of UFN in the TH based on studies isolated cranial cooling: 0.44 (0.29-0.67) | - | -                                                   |

GCS: Glasgow Coma Scale, FN: favorable neurological outcome, OR: Odds ratio, RR: Relative risk, TBI: Traumatic brain injury, TH: therapeutic hypothermia, UFN: unfavorable neurological outcome

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