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| Question |
| **Should presence of abnormality on cranial Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) vs. absence be used for predicting poor neurological outcomes in children after cardiac arrest?** |
| **Population:** | Children (<18 years) who achieve a return of spontaneous or mechanical circulation (ROC) after resuscitation from in-hospital cardiac arrest (IHCA) and out-of-hospital (OHCA), from any cause. |
| **Intervention:** | Abnormality on cranial MRI or CT |
| **Comparison:** | No abnormality |
| **Main outcomes:** | Prediction of death or survival with poor neurological outcome: defined as a Pediatric Cerebral Performance Category (PCPC) score of >3, or Vineland Adaptive Behavioural scale-II < 70. PCPC score ranges 1 (normal), 2 (mild disability), 3 (moderate disability), 4 (severe disability), 5 (coma), and 6 (brain death). We will also separately report studies defining poor neurological outcomes with other assessment tools, or as a PCPC score >2, or change in PCPC score from baseline ≤2. |
| **Study DESIGN** | Randomized controlled trials (RCTs) and non-randomized studies (non-randomized controlled trials, interrupted time series, controlled before-and-after studies, cohort studies) were eligible for inclusion. Unpublished studies (e.g., conference abstracts, trial protocols\*) and animal studies were excluded. We selected studies where the sensitivity and false-positive rate (FPR) of the prognostic (index) test are reported and a 2s2 contingency table could be created.  |
| **TIMEFRAME** | All years and all languages were included as long as there was an English abstract; unpublished studies (e.g., conference abstracts, trial protocols) were excluded. Literature search updated to Aug 27th 2024. |

# Assessment

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| ProblemIs the problem a priority? |
| Judgement | Research evidence | Additional considerations |
| ○ No○ Probably no○ Probably yes● Yes○ Varies○ Don't know | Cardiac arrest is uncommon in children; however, it has a low rate of survival and high chance of neurological injury. Prediction of good or poor neurological outcome is a key skill for clinicians to guide appropriate treatment and realistic expectation with parents and legal guardians.  |  |
| Desirable EffectsHow substantial are the desirable anticipated effects? |
| Judgement | Research evidence | Additional considerations |
| ○ Trivial○ Small● Moderate○ Large○ Varies○ Don't know | Head CT was evaluated in three studies and reported the relationship to poor neurological outcome (PCPC >3) in 173 patients. 1-3 The majority of CT imaging was acquired at 24 h or 48 h after the cardiac arrest. Neurological outcome was assessed on discharge from the intensive care unit or hospital in two studies 1,2 and at six months in one.3 The absence of Grey-white matter (GWM) differentiation was reported in one study with a FPR 0% (95%CI 0-12%) and sensitivity 65% for poor outcome prediction. Presence of reversal sign on CT at 24 hours was reported in two studies with a range of FPR of 0% to 36%,and corresponding sensitivity of 20 to 30% for poor outcome prediction.2,3 Presence of effacement of sulci or basal cisterns at 24 hours predicted poor neurological outcome with a low FPR (0-7%; range of 95% CI 0-30%).2,3 Presence of CT lesions, oedema, or intracranial hemorrhage predicted poor neurological outcome with a FPR 7-17%; however, sensitivity ranged 11 to 68%. Clinicians were not blinded to the CT results in any study. CT reported GWM differentiation at 24 hours was a moderately reliable test, but only reported in a single study. All other CT reported tests were unreliable for poor neurological outcome prediction at 24 and 48 hours. MRI imaging was reported in five studies, including 305 patients, to predict poor neurological outcomes. 4-8 Median time from ROC to MRI ranged 3 to 6 days across all studies with inclusion of patients MRI up to 14 days reported in three studies. 5,7,8An Apparent diffusion coefficient (ADC) threshold <650x10-6 mm2/s in ≥10% of brain volume (indicating high ischemic burden), at a median of 4 days after ROC, predicted poor neurological outcome with a sensitivity of 49-52% and FPR 0-6% (95% 1-21%) in 3 studies.4,7,8 One study using ADC thresholds to identify high ischemic burden fulfilled the low FPR <1% with moderate reliability for poor neurological outcome prediction.8Any region of abnormality on restricted diffusion, at a median of 4 days after ROC, predicted poor neurological outcome with a range of FPR 12% to 58% and corresponding sensitivity of 98% to 100%. 7,9 An abnormal MRI by qualitative reporting of presence of hypoxic ischemic injury, predicted a poor neurological outcome at 6 months with a FPR of 19% and sensitivity of 90%.8Three studies reported up to 14 different individual regions of the brain, at 4-6 days post ROC with DWI, T1 and T2 weighted imaging.5,6,9 FPR for outcome prediction was predominately 0-10% but upper limits of the 95% CI ranged widely from 20-50%. Overall, only one study using ADC thresholds fulfilled the low FPR <1% with moderate reliability for poor neurological outcome prediction.  |  |
| Undesirable EffectsHow substantial are the undesirable anticipated effects? |
| Judgement | Research evidence | Additional considerations |
| ○ Large● Moderate○  Small○ Trivial○ Varies○ Don't know | A false positive prediction of a poor outcome and discontinuing treatment based on MRI or CT may lead to inappropriate treatment withdrawal in a patient with a god neurological outcome. The low false positive rate (high specificity) for abnormal MRI on global assessment for predicting poor neurological outcome reduces the chance of false pessimism if an abnormal MRI predicts a poor neurological outcome. FPR <1% was only recording for one study for global assessment of brain injury. Low FPR was identified during regional brain assessment, however only in a small number of cases, with wide confidence limits on the point estimate.  |  |
| Certainty of evidenceWhat is the overall certainty of the evidence of effects? |
| Judgement | Research evidence | Additional considerations |
| ● Very low○ Low○ Moderate○ High○ No included studies | The certainty of evidence from CT & MRI abnormalities are low (downgraded for imprecision, and risk of bias). because of the risk of bias, especially self-fulfilling prophecy and wide confidence intervals around the point estimates. |  |
| ValuesIs there important uncertainty about or variability in how much people value the main outcomes? |
| Judgement | Research evidence | Additional considerations |
| ○ Important uncertainty or variability○  Possibly important uncertainty or variability● Probably no important uncertainty or variability○ No important uncertainty or variability | Neurological outcome is a critical outcome after cardiac arrest (P-COSCA).10 However, tools and definitions to measure poor neurological outcome in our studies were the PCPC >2 and >3, or >1 change in PCPC and the VABS II <70. Change from baseline neurological status may be more important than the neurological functional level, especially in infants and children with pre-existing neurological impairment. We defined poor neurological outcome prediction as imprecise when the false positive rate (FPR) was >1%. However, there is no universal consensus on what the acceptable limits for imprecision should be in prediction for infants and children after cardiac arrest. We defined the reliability of the evidence as reliable if the FPR was <1% and the upper 95% confidence intervals <10%) and moderately reliable if FPR was <1% with without a restriction on width of 95% confidence interval.A low false positive rate means that a low proportion of patients, predicted to have a poor outcome will have a falsely pessimistic prediction (test predicted a poor outcome, but patient went on to have a good outcome). The task force felt that when focused on accuracy of predicting a poor outcome - a low false positive rate (e.g. <1%) is more desirable to avoid falsely pessimistic prediction than a high sensitivity. The cut off of <1% FPR (equivalent to 99% specificity) was chosen as the consequences of false pessimism is substantial. False pessimism may result in discontinuation of life sustaining therapy in a patient who will eventually have a good outcome. Continuing treatment may involve increased resources; however, this may also allow more time for further prognostic evaluation and further additional tests. Reasons for not achieving a very low false positive rate may be non-neurological causes of poor outcome or death, not attributable to the index test assessment.. |  |
| Balance of effectsDoes the balance between desirable and undesirable effects favor the intervention or the comparison? |
| Judgement | Research evidence | Additional considerations |
| ○ Favors the comparison○ Probably favors the comparison○ Does not favor either the intervention or the comparison○ Probably favors the intervention○ Favors the intervention● Varies○ Don't know | The sensitivity of abnormal MRI or CT to predict a poor neurological outcome is moderate to high, most tests had a low FPR 0-10%, but in some cases up to 40% may be falsely categorized and a falsely pessimistic prediction made. Therefore, with the very-low certainty of evidence, we cannot make a treatment recommendation for or against the use of abnormal MRI or CT for predicting poor neurological outcomes as single tests. However, we encourage further research in this area as these modalities appear promising. In the context of multi-modal monitoring, an abnormal MRI showing high ischemic burden on ADC mapping (≥72 hours) or CT scan showing loss of Grey-White Differentiation (at 24 hours) may be utilized as part of multi-modal testing for poor neurological outcome prediction | A CT or MRI scan may be performed for other diagnostic indications (e.g. identify the cause of cardiac arrest) and the information may be combined with other prognostic tests.  |
| Resources requiredHow large are the resource requirements (costs)? |
| Judgement | Research evidence | Additional considerations |
| ○ Large costs○ Moderate costs● Negligible costs and savings○ Moderate savings○ Large savings○ Varies○ Don't know | Specialist equipment and training in interpretation to perform CT & MRI is required. Costs and access to CT & MRI may be variable depending on the health care setting. In some settings imaging may not be available or costs prohibitive. However, no study assessing cost of CT & MRI imaging has been included in our review |  |
| Certainty of evidence of required resourcesWhat is the certainty of the evidence of resource requirements (costs)? |
| Judgement | Research evidence | Additional considerations |
| ○ Very low○ Low○ Moderate○ High● No included studies | We did not identify any studies assessing cost. |  |
| Cost effectivenessDoes the cost-effectiveness of the intervention favor the intervention or the comparison? |
| Judgement | Research evidence | Additional considerations |
| ○ Favors the comparison○ Probably favors the comparison○ Does not favor either the intervention or the comparison○ Probably favors the intervention○ Favors the intervention○ Varies● No included studies | We did not identify any studies addressing cost-effectiveness.  |  |
| EquityWhat would be the impact on health equity? |
| Judgement | Research evidence | Additional considerations |
| ○ Reduced○ Probably reduced○ Probably no impact● Probably increased○ Increased○ Varies○ Don't know | No study assessed the impact on health equity. However, due to the high cost of CT & MRI, there may be health inequity in receiving this investigation and prognostic test. |  |
| AcceptabilityIs the intervention acceptable to key stakeholders? |
| Judgement | Research evidence | Additional considerations |
| ○ No○ Probably no● Probably yes○ Yes○ Varies○ Don't know | We have not identified any study assessing acceptability, but acceptability is likely. |  |
| FeasibilityIs the intervention feasible to implement? |
| Judgement | Research evidence | Additional considerations |
| ○ No○ Probably no○ Probably yes○ Yes○ Varies● Don't know | Although feasibility was not specifically addressed in any of the studies included in this review. However, requires significant resources, personnel and training and this may limit the feasibility in all health care settings. Imaging studies used for neuroprognostication after cardiac arrest cannot be performed at the bedside, and require transportation to a Radiology Department, with additional clinical and safety risks.  |  |

# Summary of judgements

|  | **Judgement** |
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| **Problem** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |
| **Desirable Effects** | Trivial | Small | **Moderate** | Large |  | Varies | Don't know |
| **Undesirable Effects** | Large | **Moderate** | Small | Trivial |  | Varies | Don't know |
| **Certainty of evidence** | **Very low** | Low | Moderate | High |  |  | No included studies |
| **Values** | Important uncertainty or variability | Possibly important uncertainty or variability | **Probably no important uncertainty or variability** | No important uncertainty or variability |  |  |  |
| **Balance of effects** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | **Varies** | Don't know |
| **Resources required** | **Large costs** | Moderate costs | Negligible costs and savings | Moderate savings | Large savings | Varies | Don't know |
| **Certainty of evidence of required resources** | Very low | Low | Moderate | High |  |  | **No included studies** |
| **Cost effectiveness** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | **No included studies** |
| **Equity** | Reduced | Probably reduced | **Probably no impact** | **Probably increased** | Increased | Varies | Don't know |
| **Acceptability** | No | Probably no | **Probably yes** | Yes |  | Varies | Don't know |
| **Feasibility** | No | Probably no | Probably yes | Yes |  | Varies | Don't know |

# Type of recommendation

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| Strong recommendation against the intervention | Conditional recommendation against the intervention | Conditional recommendation for either the intervention or the comparison | Conditional recommendation for the intervention | Strong recommendation for the intervention |
| ○  | ○ | **●** | ○ | ○  |

# Conclusions

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| Recommendation |
| * **We recommend no single imaging test be used alone to predict poor neurological outcome in children after cardiac arrest at any time point (strong recommendation, very-low certainty evidence).**
* **Clinicians should consider using multiple tests in combination for poor neurological outcome prediction (good practice statement).**
* **An abnormal MRI showing high ischemic burden on ADC mapping at 72 hours and beyond after ROC or CT scan showing loss of Grey-White Matter Differentiation within 24 hours after ROC may be considered as part of multi-modal testing to predict poor neurological outcome in children after cardiac arrest (good practice statement).**
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| Justification |
| ● The available scientific evidence had a high risk of bias based on high heterogeneity across studies, small number of studies and small number of patients included in addition to lack of blinding, variation in test assessment and performance, and variability in outcome measurement. Therefore, no meta-analysis was performed. Overall assessment of test performance was based on visual assessment of forest plots.● If only one study was available (with small patient sample size) then a suggestion or recommendation could not be made. Only part of the included studies specifically excluded the presence of residual sedation at the time PLR was assessed. Lack of blinding is a major limitation of PLR, even if WLST based on PLR only has not been documented in any of the studies included in our review. ● The low false positive rate (high specificity) for abnormal MRI on global assessment for predicting poor neurological outcome reduces the chance of false pessimism if an abnormal MRI predicts a poor neurological outcome. FPR <1% was only recording for one study for global assessment of brain injury. Low FPR was identified during regional brain assessment, however only in a small number of cases, with wide confidence limits on the point estimate. ● The sensitivity of abnormal MRI or CT to predict a poor neurological outcome is moderate to high, but up to 40% may be falsely categorized and a falsely pessimistic prediction made. Therefore, with the very-low certainty of evidence, we cannot make a treatment recommendation for or against the use of abnormal MRI or CT for predicting poor neurological outcomes as single tests. However, we encourage further research in this area as these modalities appear promising. ● The precision of MRI and CT is affected by the timing of the investigation and is at risk of pseudonormalization. ● The definition of a presence DWI or cut off values for ADC level on MRI, or GWR on CT was inconsistent in the included studies.● MRI and CT are both expensive tests and require specialist equipment, training, interpretation and most often, patient transport to obtain the information. This may be prohibitive in physiologically unstable patients, or some health care settings..  |

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| Subgroup considerations |
| None |

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| Implementation considerations |
| CT & MRI are expensive tests and requires specialist equipment, training, interpretation, and patient transport to obtain the information. This may be prohibitive in physiologically unstable patients, or some health care settings. |

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| Monitoring and evaluation |
| None |

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| Research priorities |
| The criteria for defining a positive DWI MRI after cardiac arrest need to be standardised. The role of regional areas of brain for predicting outcome, or the use of Magnetic resonance spectroscopy requires further research. |

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