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| Question |
| **Should absence vs. presence of abnormality on cranial MRI be used for predicting good outcome 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:** | Absence of abnormality on cranial MRI |
| **Comparison:** | presence of abnormality on cranial MRI |
| **Main outcomes:** | Prediction of survival with good neurological outcome: defined as a Pediatric Cerebral Performance Category (PCPC) score of 1, 2 or 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 good neurological outcomes with other assessment tools, or as a PCPC score 1 or 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 Unpublished studies (e.g., conference abstracts, trial protocols\*) and animal studies were excluded.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| **TIMEFRAME** | All years and all languages were included as long as there was an English abstract; unpublished studies (e.g., conference abstracts, trial protocols) were excluded.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 Feb 17th, 2022. |

# 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 | MRI imaging was reported in four studies to predict good neurological outcome. Two studies reported presence or absence of abnormalities in multiple regions of the brain in 3 sequences (Diffusion weighted imaging (DWI), T1 and T2) [Fink 2013 31, Fink 2020 185]. Another study presented a composite of presence or absence of 1 (or more) region of abnormality [Kirschen 2021 e719]. Apparent diffusion coefficient (ADC) thresholds cut off values and overall qualitative MRI reporting of evidence of hypoxic ischaemic injury was assessed by one study [Yacoub 2019 103]. In three studies, MRIs were performed between 4 to 6 days and one at two weeks. Three studies ensured the neuroradiologists MRI assessment was blinded to patient clinical status. However, the MRI findings were known by the treating clinicians and neurological outcome assessment was not blinded. [Fink 2013 31, Fink 2020 185, Kirschen 2021 e719].Absence of any region of abnormality on restricted diffusion predicted good neurological outcome with a sensitivity of 88% and corresponding very low FPR 2% [Kirschen 2021 e719]. ADC threshold above >600 x10 power -6 mm2/s in >93% and >650 x10 power -6mm2/s in >89% of brain volume predicted good neurological outcome with a sensitivity of 100% and low FPR (20%) [Yacoub 2019 103]. In the same study, a normal MRI by qualitative reporting of absence of hypoxic ischaemic injury, predicted a good neurological outcome at 6 months with a sensitivity of 81% and FPR of 10% [Yacoub 2019 103].For individual regions of the brain, at 4-6 days post cardiac arrest, DWI MRI sequence had a sensitivity for predicting good neurological outcome ranging 67-100% although associated FPR rates with moderate to high. Absence of lesion in the Lentiform regions on T2 weighted imaging had a sensitivity of 67% and the lowest FPR (7.7%) for any single region of the brain.  |  |
| 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 good outcome and continued treatment based on MRI may lead to treatment in a patient with the outlook of a poor neurological outcome. This is termed false optimism. The low false positive rates for assessment of global injury on MRI (ADC, qualitative reporting of evidence of hypoxic ischaemic injury, or absence of multiple regions of injury) provide a lower risk of false optimism compared to CT imaging.  |  |
| 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 MRI is low. The high sensitivity and low FPR combined with consistency in results across the two studies of global injury provided some certainty. The risk of bias was very high due to risk of selection bias, as only a small subset of patients alive at 4-6 days after cardiac arrest were imaged. Although MRIs were reported by radiologists blinded to patients’ condition and outcome, the initial MRI was used by treating clinicians to decide on treatment management and therefore there is a risk of self-fulfilling prophecy.  | Although the certainty of evidence from MRI was low, the task force identified that the evidence for MRI was more certain that clinical examination, biomarkers, or other imaging modalities.  |
| 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: Topjian, et al Circulation 2020; 142). However, tools and definitions to measure good neurological outcome in our studies were the PCPC 1 to 2 and 1 to 3, or <1 change in PCPC and the VABS II >70. Change from baseline neurodevelopmental status may be more important than the neurodevelopmental level, especially in infants and children with pre-existing neurological impairment. We defined good neurological outcome prediction as imprecise when the false positive rate (FPR) was above 30%. However, there is no universal consensus on what the acceptable limits for imprecision should be in prediction for infants and children after cardiac arrest. **A low false positive rate** means that a low proportion of patients, predicted to have a good outcome will have a ***falsely optimistic prediction*** (test predicted a good outcome, but patient went on to have a bad outcome). The task force felt that when focused on accurate **good** outcome prediction - a low false positive rate (e.g. <30%) is more desirable to avoid falsely optimistic prediction than a high sensitivity. The cut off of 30% FPR (equivalent to 70% specificity) was chosen as the consequences of false optimism were felt by the task force to be less critical than false pessimism. False optimism may result in continued life sustaining therapy in a patient who will eventually have a poor outcome. Also some of the reasons for not achieving very low false positive rate may be non-neurological causes of poor outcome or death, not attributable to the index test assessment. **A high sensitivity** means the majority of patients who have the good outcome tested positive and therefore a low proportion will have a ***falsely pessimistic prediction*** (test predicted a poor outcome, but patient went on to have a good outcome). When considering accurate **poor** outcome prediction, then a high sensitivity (with a corresponding low rate of falsely pessimistic prediction) is more desirable than a low false positive rate. Our cut off threshold for considering precise sensitivity was higher (>95%), as the consequences of false pessimism may be decision to withdrawal life sustaining therapy in a patient who will have a good neurological outcome and therefore greater precision in prognostic accuracy is required.  | The task force identified that the current use of a dichotomised neurological outcome cut off is a limitation for families and patients in considering the range and acceptability of outcomes for individual children after cardiac arrest in children. Our definitions of precision are less precise than the equivalent adults’ recommendations which used the 95% confidence interval margins as their threshold values.For comparison, in the 2021 COSTR, the ALS Task force recommendations for poor outcome prediction in adults comatose after cardiac arrest, the definition of imprecision for a poor test predicting a poor neurological outcome was when the upper limit of 95% confidence intervals (CIs) for false positive rate (FPR) was above 5%. This is equivalent to the sensitivity of a good test predicting a good neurological outcome having the lower 95% confidence interval above 95%. |
| 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 | Considering the moderate to high sensitivity and low false positive rate of using absence of abnormality on MRI as a predictive test 4-6 days or two weeks, the balance probably favours using MRI as a test for **good** neurological outcome prediction.  | An 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. The high sensitivity also indicates that MRI may have a role in predicting poor outcome. However, risk of false pessimism in up to 31% of patients, and low sample size led to a lack of precision.  |
| 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 MRI is required. Costs and access to MRI may be variable depending on the health care setting. In some settings MRI may not be available or costs prohibitive. However, no study assessing cost of 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 specifically assessing costs of performing MRI after cardiac arrest in children. However, the use of specialist personnel, training and equipment may require significant local resources to perform.  |  |
| 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 of MRI after cardiac arrest.  |  |
| 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 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.  |  |
| 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 suggest using normal MRI at 72 hours to 2 weeks after return of circulation for predicting **good** neurological outcome (weak recommendation, low-certainty evidence). |
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| Justification |
| **Overall justification**The low false positive rate (high specificity) for normal MRI on global assessment for predicting good neurological outcome reduces the chance of false optimism if a normal MRI predicts a good neurological outcome. The sensitivity of a normal MRI to predict a good neurological outcome is moderate to high, but up to 30% of may be falsely categorised and a falsely pessimistic prediction made. Therefore, with the low number of studies and patients, high risk of bias in studies, risk of self-fulfilling prophecy, and risk of confounding by selection, we cannot make a recommendation for or against the use of normal or abnormal MRI for predicting poor neurological outcome. The definition of a presence DWI or cut off values for ADC level was inconsistent in the included studies. There is a risk of pseudo normalisation with later timing of MRI. **Detailed justification***Desirable Effects*The low false positive rate (high specificity) for predicting good neurological outcome reduces the chance of false optimism if a normal MRI predicts a good neurological outcome.*Resources required*MRI is an expensive test 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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| Subgroup considerations |
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| Implementation considerations |
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| Monitoring and evaluation |
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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. |