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| Question |
| **Should absence vs. presence of abnormality on cranial CT be used for predicting good neurological 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 CT |
| **Comparison:** | Presence of abnormality on cranial CT |
| **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 Unpublished studies (e.g., conference abstracts, trial protocols\*) and animal studies were excluded.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| **TIMEFRAME** | All years and all languages were included as long as there was an English abstract; unpublished studies (e.g., conference abstracts, trial protocols) were excluded.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 | Head CT was evaluated in three studies and reported the relationship to good neurological outcome (PCPC 1 to 3) in 173 patients [Fink 2014 664, Starling 2015 542, Yang 2019 223]. 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 and six months in one. Reported factors from CT included presence and absence of intracranial haemorrhage, cerebral oedema or ischemia measured by the ‘reversal sign’, grey white matter (GWM) differentiation and sulcal or basal cistern effacement. Two studies described methods of estimating GWM differentiation [Starling 2015 542, Yang 2019 223] and two reported radiologists qualitative reports [Fink 2014 664, Starling 2015 542]. The presence of GWM differentiation on CT at 24 hours, had a sensitivity of 64-100%, and FPR 35-70%. Absence of CT lesions, oedema, or intracranial haemorrhage predicted good neurological outcome with a sensitivity ranging 72-100%; however, a wide range of FPR (14% to 90%) was reported.Absence of effacement of sulci or basal cisterns predicted good neurological outcome with a high sensitivity (93-100%) with a FPR 32-73%.Clinicians were not blinded to the CT results in any study.  |  |
| 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 CT imaging may lead to inappropriate treatment in a patient with a poor neurological outcome. This is termed false optimism. This is possible to occur given the variability of cut offs for sensitivity and specificity (FPR). It remains unclear when CT imaging should exactly be timed after cardiac arrest to increase its sensitivity and specificity. A CT scan involves exposure to radiation which can increase lifetime exposure risk of radiation induced injury.  |  |
| 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 imaging is very low because of the risk of bias, lacking of blinding, especially self-fulfilling prophecy. In addition only selected patients received CT scan as a diagnostic tool and there is a high risk of selection bias. | Differently from other predictors, like those based on clinical examination, imaging is not affected by sedation or paralysis, and it can be potentially assessed blindly.  |
| 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 accuracy of predicting a good outcome - 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. This will involve increased resources and treatment; however, may also allow more time for further prognostic evaluation. Also, 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. A high sensitivity means the majority of patients, who have a good outcome, tested positive and therefore a corresponding low proportion will have a *falsely pessimistic prediction* (test predicted a poor outcome, but patient went on to have a good outcome). When considering the accuracy of predicting a poor outcome (compared to predicting a good outcome), then a low rate of falsely pessimistic predictions is very important. Our cut off threshold for considering precise sensitivity was therefore higher (>95%), as the consequences of inaccurate poor outcome prediction (e.g. false pessimism) may lead to a decision to limit or withdraw life sustaining therapies in a patient who could have a good neurological outcome.  | 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.  |
| 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 high false positive rate of using absence of abnormality on CT imaging as a predictive test at all time points studied, the balance favours not using CT imaging as a test for good neurological outcome prediction.  | A CT 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 moderate to high sensitivity at 24-48 hours indicates that CT imaging may have a role in predicting poor outcome (with a low to moderate level of false pessimism). But due to the low precision and wide range of sensitivity the data does not favour either performing or not performing the test for poor outcome prediction.  |
| 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 cranial CT is required. Costs and access to cranial CT imaging may be variable depending on the health care setting. CT requires exposure to radiation. No study assessing cost of CT imaging has been included in our review; compared to other brain imaging modality such as magnetic resonance imaging, CT requires less acquisition time and less costly.  |  |
| 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 CT imaging 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 CT imaging 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 CT imaging, 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 most often 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 **against** using normal CT at 24-48 hours for predicting **good** neurological outcome (weak recommendation, very-low-certainty evidence).  |
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| Justification |
| The high false positive rate (low specificity) for predicting good neurological outcome may lead to a high rate of false optimism if a normal CT (absence of intracranial haemorrhage, cerebral oedema or ischemia measured by the ‘reversal sign’, grey white matter (GWM) differentiation and sulcal or basal cistern effacement) predicts a good neurological outcome, but the patient proceeds to have a poor neurological outcome. We therefore suggest against using a normal CT as a prognostic test for good outcome.A head CT may be indicated for diagnostic purposes in infants and children following a cardiac arrest to identify causes of cardiac arrest, coma, or intracranial pathology requiring treatment. The sensitivity of a normal CT 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, lack of blinding and risk of self-fulfilling prophecy, and risk of confounding by selection, we cannot make a recommendation for or against the use of abnormal CT for predicting poor neurological outcome.  |

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| Subgroup considerations |
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| Implementation considerations |
| CT required infrastructure, resource and skilled radiologists to perform and interpret imaging. Access to this may be limited or not available in some health care setting.  |

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| Monitoring and evaluation |
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| Research priorities |
| A consistent regional GWR threshold for predicting poor neurological outcome after cardiac arrest should be identified. A standardisation of the methods for GWR calculation is urgently needed. The optimal timing for prognostication using brain CT after cardiac arrest is still unknown. Studies assessing serial brain CT after cardiac arrest are desirable.  |