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| Question | |
| **Should presence of clinical or electrographic seizures, status epilepticus, or myoclonic status epilepticus 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:** | Presence of clinical or electrographic seizures, status epilepticus, or myoclonic status epilepticus within 10 days after cardiac arrest. |
| **Comparison:** | Absence of these features |
| **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). |
| **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 Unpublished studies (e.g., conference abstracts, trial protocols\*) and animal studies were excluded.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| **TIMEFRAME** | All years and all languages were included as long as there was an English abstract; unpublished studies (e.g., conference abstracts, trial protocols) were excluded.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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| Problem Is 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 poor neurological outcome is a key skill for clinicians to guide appropriate treatment and realistic expectation with parents and legal guardians. |  |
| Desirable Effects How substantial are the desirable anticipated effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know | **Presence of clinical or electrographic seizure**  Fourteen studies reported the relationship between presence of clinical and/or electrographic seizures in children post-cardiac arrest and poor neurological outcomes at PICU/hospital discharge, 6 months and 12 month.1-14 These studies included 1165 children, of which 6/12 studies reported using the ACNS criteria.1,3,4,7,11,14  Presence of seizures between 4-6 hours and 24 hours post-ROC were reported in 10 studies and had a FPR of 0-20% and a sensitivity of 2-38% for predicting poor neurological outcome. Three studies had a FPR <1% but with wide 95%CI.4,7,11 At 48 hours and onwards only 3/11 studies reported a FPR for predicting poor outcome of <10%,5,8,11 the majority reported an imprecise FPR 19-50%. Overall presence of seizures was not a reliable prognostic test for poor outcome prediction; although early (≤24hours) had improved accuracy compared to ≥48hours.  **Presence of status epilepticus on EEG**  Presence of status epilepticus was reported in five studies including 299 children. 4,12-15 Poor neurological outcome at PIC/hospital discharge were predicted with a low FPR of 0-5% (upper limit of 95%CI ranged 13-41%) and sensitivity was 9-25%. Presence of status epilepticus had moderate reliability as a prognostic test.  **Presence of myoclonic status epilepticus** **on EEG**  In two studies, including 61 patients, myoclonic status epilepticus was identified in 8 patients. Presence of myoclonic status epilepticus on EEG predicted poor neurological outcomes with a FPR 0% (95% CI 0-34%) and sensitivity of 17-21% at PICU/hospital discharge.2,11 Status myoclonus on EEG had moderate reliability as a prognostic test although there was a very small sample size. |  |
| Undesirable Effects How 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 electrophysiological tests may lead to inappropriate treatment withdrawal in a patient with a good neurological outcome. This is possible to occur given the variability of cut offs for sensitivity and specificity and the potential for confounding from sedation and medication affects of electrophysiological parameters. |  |
| Certainty of evidence What 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 clinical and electrophysiological tests is very low because of the risk of bias, lack of blinding, imprecision and self-fulfilling prophecy. |  |
| Values Is 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).16 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 effects Does 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 | Overall presence of clinical or electrographic seizures was not a reliable prognostic test for poor outcome prediction; although early (≤24hours) had improved accuracy compared to ≥48hours; However, FPR was <1% in only 3/10 studies. Presence of status epilepticus had moderate reliability as a prognostic test with FPR 0-5% in five studies, but precision did not reach the specified FPR <1% cutoff. Status myoclonus on EEG had moderate reliability as a prognostic test although there was a very small sample size in two studies. |  |
| Resources required How 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 | We did not include any specific studies assessing costs of ruling out seziures, status epilepticus or myoclonic status epilepticus on EEG for neuroprognostication. However, specific equipment and skills are required for performing continuous EEG monitoring in critically ill children and these may not be available in resource-limited settings. |  |
| Certainty of evidence of required resources What 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 continuous or intermittent electroencephalography and/or ruling out seizures. |  |
| Cost effectiveness Does 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. |  |
| Equity What 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 | The specific equipment and skills needed to obtain EEG recordings in critically ill children post cardiac arrest may not be available everywhere and every time. This can create a problem in terms of equity. |  |
| Acceptability Is 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. |  |
| Feasibility Is the intervention feasible to implement? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know | Feasibility was not specifically addressed in any of the studies included in this review. Evaluating seizures and status epilepticus on a continuous critical care EEG recording for prognostication purposes requires specific equipment for recording continuous EEG and the expertise to interpret the tracing. This may not be feasible everywhere or during all times of the day. |  |

# 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**  **(Clinical/ electrographic seizure)** | **Conditional recommendation for either the intervention or the comparison**  **(myoclonic status epilepticus)** | **Conditional recommendation for the intervention**  **(Status epilepticus)** | Strong recommendation for the intervention |
| ○ | **●** | **●** | **●** | ○ |

# Conclusions

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| Recommendation |
| * **We recommend that no single electrophysiology test be used in isolation 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).** * **The presence of status epilepticus between 24-72 hours after ROC had moderate reliability and may be considered as part of multi-modal testing to predict poor neurological outcome in children after cardiac arrest (good practice statement).** * **We suggest against using the following EEG features for predicting poor neurological outcome: presence of clinical or electrographic seizures, at any time point (weak recommendation, very-low-certainty evidence).** * **There was insufficient evidence to make a recommendation for or against the use of presence of myoclonic status epilepticus, to predict poor neurological outcome in children after cardiac arrest at any time point.** |
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| Justification |
| **Overall justification**  Overall presence of clinical or electrographic seizures was not a reliable prognostic test for poor outcome prediction; although early (≤24hours) had improved accuracy compared to ≥48hours; However, FRP was <1% in only 3/10 studies. We therefore suggest not using this test as for prediction of poor neurological outcome.  Presence of status epilepticus had moderate reliability as a prognostic test with FPR 0-5% in five studies, but precision did not reach our <1% FPR cutoff. This test may therefore be useful as part of multi-modal testing but should not be used in isolation.  Status myoclonus on EEG had moderate reliability as a prognostic test although there was a very small sample size in two studies. We could therefore not make a suggestion for or against its use due to insufficient evidence.  **Detailed justification**  *Certainty of evidence*  None of the studies adjusted for the confounding effect of sedation or targeted temperature management on the absence of seizures  *Resources required*  Performance and interpretation of continuous EEG in the pediatric critical care environment requires resources.  *Equity*  Resources required for continuous EEG monitoring and interpretation may not be available in resource-limited settings.  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.  In addition to providing prognostic information, electrophysiology monitoring may allow identification of reversible events e.g. seizures. Treatment of seizures may prevent additional secondary injury following a hypoxic-ischemic insult. The role of electrophysiology monitoring was not assessed for this purpose.  If only one study was available (with small patient sample size) then a suggestion or recommendation could not be made.  There was limited or no context of when tests were undertaken in relation to concurrent pharmacological exposure, sedation and ongoing treatment (e.g., TTM) in patients following cardiac arrest.  American Clinical Neurophysiology Society (ACNS) definitions for seizures and EEG indices were followed in some studies. EEG and SSEP prognostic criteria require clear and reproducible definitions and require validation in the pediatric ICU environment. |

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| Subgroup considerations |
| None |

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| Implementation considerations |
| Performance and interpretation of continuous EEG in the pediatric critical care environment requires resources and these may not be uniformly available even in resource-rich settings. |

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| Monitoring and evaluation |
| None |

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| Research priorities |
| Electrophysiology tests for prognostication after cardiac arrest appear promising but more research is required in infants and children.  More research is required on type of monitoring, intermittent or continuous EEG, use of reduced channel monitoring, quantitative EEG systems, duration and timing of prognostic assessment.  Validation of ACNS or other international definitions of EEG indices within the pediatric ICU environment for infants and children after cardiac arrest.  Further work on multi-modal prognostication, timing, definitions of testing, accurate outcome timing and definition.  We encourage wider research and consultation with patients, children, parents, guardians and caregivers, health care professionals and members of the wider society on understanding survivorship after pediatric cardiac arrest to inform correct definitions and framework of good neurological outcome for prediction research. Status epilepticus represents increased seizure burden in comparison to individual seizures. Evaluation of association between seizure burden during the first 72 hours post cardiac arrest and neurodevelopmental outcomes is needed.  Future studies should also more carefully adjust for the confounding effect of medications, targeted temperature management and other critical care interventions. |

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