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| Question |
| **Should blood based biomarker measurement 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:** | Blood Lactate, pH and other blood-based biomarkers (eg S100b, NSE, NfL, GFAP)  |
| **Comparison:** | none |
| **Main outcomes:** | Prediction of 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 good 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 Unpublished studies (e.g., conference abstracts, trial protocols\*) and animal studies were excluded.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| **TIMEFRAME** | All years and all languages were included as long as there was an English abstract; unpublished studies (e.g., conference abstracts, trial protocols) were excluded.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 common and has a very high mortality, with neurologic injury as the most common cause of death. The majority of these deaths occur as a result of withdrawal of life-sustaining treatment (WLST) based on prediction of poor neurological outcome. Prediction of 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 | **Lactate**Lactate was evaluated in 6 studies.(1-6). Only two studies identified a FPR <1% for poor outcome prediction. The first used a lactate threshold >28.8 mmols/L at <1 hour (6) with a corresponding sensitivity of 11%. The second, used failure of lactate clearance to <2mmol/L by 48 hours with a sensitivity of 23%. (1) All other tests with a lactate level >2mmols at 6-12, 24 and 48 hours had a reported FPR of 14-84%. (1, 3-5) A lactate >5mmol/L at <1 hour or 24 hours had a FPR of 34% and 11% respectively. (2) Lactate was not a reliable prognostic test.**pH**pH was evaluated in 4 studies. (1, 4-6) pH thresholds were <6.6, <7.0, <7.3, and >7.5 at resuscitation and within 1 hour, 6-12 hours and 24 hours of return of circulation. Extremes of pH <6.6 and >7.5 had a FPR for poor outcome prediction of <5% but very low <14% sensitivity. Blood pH of <7.0 measured 6-12 hours from ROC also had a FPR of 3-4% and a low sensitivity of 3-14% for predicting poor neurological outcome. (4, 5) pH was not a reliable prognostic test. **Neuronal biomarkers**Three study reported NSE and S100b in 156 children (6-8). Cut off values were calculated and reported to classify low FPR for poor neurological outcome. Values were calculated at <1, 6-12, 24, 48 and 72 hours. Wide (10+ fold) variation in cutoff values were reported. At 24 hours s100b levels of 0.128 µg/L (8), 2.0 µg/L (7) and 2.24 µg/L (6) were reported to predict a poor neurological outcome with a FPR of 0% (95% CI 0-20%) and a sensitivity of 29-38%. Similarly, NSE level of both 53.1 µg/L (8), 56 µg/L (7) and 132.7 µg/L (6) predicted a poor neurological outcome with a FPR of 0% (95% CI 0-20%) and a sensitivity of 19-26%. MBP was assessed in one study at 24 and 48 hours with cut off threshold of 5.83 µg/L predicting poor neurological outcome with low FPR 0% (95%CI 0-20%). NSE, S100b and MBP all fulfilled reliable test criteria but with wide range of cutoff thresholds in the individual studies.Only one study reported UCH-L1, NfL, Tau and GFAP biomarker prediction of poor neurological outcome at 24, 48 and 72 hours.(9) Cut off threshold values were calculated to produce an optimal FPR of 4-5% (95%CI 1 to 15%) and corresponding sensitivity of 12-61%.  |  |
| 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 based on lactate, pH of blood biomarker levels above the cut off level may lead to and premature withdrawal of life sustaining therapy in a patient who would have a good neurological outcome. This is likely to occur given the variability of cut offs for sensitivity and specificity and the potential for confounding from non-neurological causes of a raised lactate.  |  |
| 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 lactate and pH is very low (down graded for study design, risk of bias, inconsistency, indirectness, and imprecision). Risk of bias is high especially self-fulfilling prophecy and non-specific nature of lactate and acidosis metabolism. Other blood-based biomarkers are more specific for neurological injury; however the certainty of evidence is low (downgraded for risk of bias and publication bias) due to the wide variability in the cut off values demonstrating imprecision in the use of this test and potential for other studies, not reporting dichotomous results to have been excluded.  |  |
| 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 | Lactate and pH were non-specific markers of hypoxic-ischemia following cardiac arrest. Extreme values (very high lactate, very low pH) have a low FPR in the included studies, but frequent outliers and very low sensitivity were reported. Four studies identified cut-offs across a range of blood-based biomarkers (S100b, NSE, MBP, UCH-L1, NfL, Tau and GFAP) that are known to represent brain injury and are associated with poor neurological outcome with a low FPR. However, sensitivity was low and the wide range of reported cut off thresholds preclude any accurate description of clinical utility. Furthermore, these tests require specialized laboratory equipment and are not widely available, even though they only require the patient's blood. |  |
| 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 | Lactate and pH is measured on blood gas analysers and is easily accessible in most settings. However, other blood-based biomarkers require specialist equipment and are currently not available in many health care settings. However, no study evaluated cost in our study. |  |
| 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 blood-based biomarkers for prognostication after cardiac arrest.  |  |
| 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 | A problem of inequity is possible, since assessment of biomarkers implies resources that cannot be universally available. |  |
| 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 | Feasibility was not specifically addressed in any of the studies included in this review. Although may not be available in resource limited settings.  |  |

# 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 that no single blood-based biomarker examination 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).**
* **We suggest against using lactate and pH after return of circulation (ROC), for predicting poor neurological outcome in children after cardiac arrest at any time point (weak recommendation, very-low-certainty evidence).**
* **There is insufficient evidence to make a recommendation for or against the use of other blood-based biomarkers (e.g. S100beta, Neuron Specific Enolase, Neurofilament Light Chain (NfL) etc.) after ROC for predicting poor neurological outcome in children after cardiac arrest at any time point.**
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| Justification |
| ● The Task Force considered the use of single biomarker tests in predicting a poor neurological outcome. ● The available 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.● Included studies were observational studies and randomized controlled trials, but not primarily designed to test prognosis of blood biomarkers. ● Lactate and pH were non-specific markers of hypoxic-ischaemia following cardiac arrest. Extreme values (very high lactate, very low pH) have a low FPR in the included studies, but frequent outliers and very low sensitivity were reported. ● Four studies identified cut-offs across a range of blood-based biomarkers (S100b, NSE, MBP, UCH-L1, NfL, Tau and GFAP) that are known to represent brain injury and are associated with poor neurological outcome with a low FPR. However, sensitivity was low and the wide range of reported cut off thresholds preclude any accurate description of clinical utility. Furthermore, these tests require specialized laboratory equipment and are not widely available, even though they only require the patient's blood. ● No studies reported any assessment of the confounding influence of medication. None of the included studies specifically excluded the presence of residual sedation at the time clinical examination was assessed.● Lack of blinding is a major limitation of biomarker tests, even if the withdrawal of life-sustaining therapy based on test results has not been documented in any of the studies included in our review. No studies included blinding of test results from treating clinicians and only one study had blinded outcome assessment. |

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| Subgroup considerations |
| none |

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| Implementation considerations |
| Lactate levels and lactate clearance is widely used to guide therapy, thus only relevant implementation considerations are for settings without access to this biomarker and interpreting in context of whole patient because of the many potential confounders.Until blood-based biomarkers become more widely used (i.e., more indications with higher certainty of evidence), this test will likely be used for research purposes primarily. The field is growing quickly and equipment is becoming more accessible so that the clinician may adopt this test in the future. |
| Research priorities |
| ● This is a relatively new field of research and holds considerable promise. There are a range of potential candidate biomarkers more specific for neurological injury (e.g. NSE, s100b, NFL, GFAP, Tau, UCH-L1) that should be explored. ● Economic cost evaluation and cost-effectiveness studies are required as biomarker testing can be expensive. ● Further research is required on multi-modal prognostication, timing, definitions of testing, accurate outcome timing and outcome 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 neurological outcome for prediction research. |

# References Summary

1. De La Llana RA, Le Marsney R, Gibbons K, Anderson B, Haisz E, Johnson K, et al. Merging two hospitals: The effects on pediatric extracorporeal cardiopulmonary resuscitation outcomes. Journal of Pediatric Intensive Care. 2021;10(3):202-9.

2. Lopez-Herce J, del Castillo J, Matamoros M, Canadas S, Rodriguez-Calvo A, Cecchetti C, et al. Post return of spontaneous circulation factors associated with mortality in pediatric in-hospital cardiac arrest: a prospective multicenter multinational observational study. Critical care (London, England). 2014;18(6):607.

3. Meert KL, Guerguerian AM, Barbaro R, Slomine BS, Christensen JR, Berger J, et al. Extracorporeal Cardiopulmonary Resuscitation: One-Year Survival and Neurobehavioral Outcome among Infants and Children with In-Hospital Cardiac Arrest\*. Critical Care Medicine. 2019;47(3):393-402.

4. Moler FW, Silverstein FS, Holubkov R, Slomine BS, Christensen JR, Nadkarni VM, et al. Therapeutic Hypothermia after In-Hospital Cardiac Arrest in Children. New England Journal of Medicine. 2017;376(4):318-29.

5. Moler FW, Silverstein FS, Holubkov R, Slomine BS, Christensen JR, Nadkarni VM, et al. Therapeutic hypothermia after out-of-hospital cardiac arrest in children. New England Journal of Medicine. 2015;372(20):1898-908.

6. Kramer P, Miera O, Berger F, Schmitt K. Prognostic value of serum biomarkers of cerebral injury in classifying neurological outcome after paediatric resuscitation. Resuscitation. 2018;122:113-20.

7. Bangshoj J, Liebetrau B, Wiberg S, Gjedsted J, Kjaergaard J, Hassager C, et al. The Value of the Biomarkers Neuron-Specific Enolase and S100 Calcium-Binding Protein for Prediction of Mortality in Children Resuscitated After Cardiac Arrest. Pediatric Cardiology. 2022;43(7):1659-65.

8. Fink EL, Berger RP, Clark RSB, Watson RS, Angus DC, Richichi R, et al. Serum biomarkers of brain injury to classify outcome after pediatric Cardiac Arrest\*. Critical Care Medicine. 2014;42(3):664-74.

9. Fink EL, Kochanek PM, Panigrahy A, Beers SR, Berger RP, Bayir H, et al. Association of Blood-Based Brain Injury Biomarker Concentrations with Outcomes after Pediatric Cardiac Arrest. JAMA Network Open. 2022;5:E2230518.

10. Topjian AA, Scholefield BR, Pinto NP, Fink EL, Buysse CMP, Haywood K, et al. P-COSCA (Pediatric Core Outcome Set for Cardiac Arrest) in Children: An Advisory Statement From the International Liaison Committee on Resuscitation. Resuscitation. 2021;162:351-64.