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| Question | |
| **GFAP, serum tau protein, and NFL for prediction of poor neurological outcome in adults with cardiac arrest** | |
| **Population:** | Adults who are comatose after resuscitation from cardiac arrest (either in-hospital or out-of-hospital), regardless of target temperature management. |
| **Intervention:** | Blood levels of biomarkers (GFAP, serum tau protein, NFL), assessed within one week after cardiac arrest. |
| **Comparison:** | *None.* |
| **Main outcomes:** | Prediction of poor neurological outcome defined as Cerebral Performance Categories (CPC) 3-5 or modified Rankin Score (mRS) 4-6 at hospital discharge/1 month or later. |
| **STUDY DESIGN:** | Prognostic accuracy studies where the 2 x 2 contingency table (i.e., the number of true/false negatives and positives for prediction of poor outcome) was reported, or where those variables could be calculated from reported data. are eligible for inclusion. Unpublished studies, reviews, case reports, case series, studies including less than 10 patients, letters, editorials, conference abstracts, and studies published in abstract form were excluded. |
| **TIMEFRAME:** | In 2015, an ILCOR evidence review identified four categories of predictors of neurological outcome after cardiac arrest, namely clinical examination, biomarkers, electrophysiology and imaging. In the last four years, several studies have been published and new predictors have been identified, therefore the topic needs an update.  The most recent search of the previous systematic reviews on neuroprognostication was launched on May 31, 2013. We searched studies published from January 1, 2013 onwards. |

# 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 common and has a very high mortality, with neurologic injury as the most common cause of death. The vast majority of these deaths occur as a result of withdrawal of life-sustaining treatment (WLST) based on prediction of poor neurological outcome. Prognostication is of utmost importance because futile treatments for unsalvageable patients can be avoided and realistic expectations can be given to relatives. |  |
| Desirable Effects How substantial are the desirable anticipated effects? | | |
| Judgement | Research evidence | Additional considerations |
| ● Trivial ○ Small  ○ Moderate ○ Large ○ Varies ○ Don't know | **Glial fibrillary acid protein (GFAP)**  In one study [Helwig 2017 68, 100 pts] ***GFAP with a cut-off of 0.08 μg/L at 48±12h*** predicted poor neurological outcome at 1 month with 100% specificity and 21.3% sensitivity (low certainty of evidence).  **Serum Tau Protein**  In one study [Mattson 2017 665, 667 pts] ***Serum Tau Protein with a cut-off ranging from 72.7 to 874.5 ng/L at 24-72h*** predicted poor neurological outcome at 6 months with 100% specificity and a sensitivity ranging from 4% to 42% (very low certainty of evidence).  **Serum Neurofilament Light Chain (NFL)**  In one study [Moseby-Knappe 2019 64, 717 pts] ***Serum Neurofilament Light Chain with a cut-off ranging from 1539 to 12317 pg/mL at 24-72h*** predicted poor neurological outcome at 6 months with 100% specificity and sensitivity ranging from 53.1% to 65% (moderate certainty of evidence).  In one study [Rana 2013 1322, 61 pts] ***Serum Neurofilament Light Chain with a cut-off ranging from 252 to 405 pg/mL from day 1 to day 7*** predicted poor neurological outcome (CPC 4-5) at 6 months with 100% specificity and sensitivity ranging from 55.6% to 94.4% (very low certainty of evidence). | Among the three biomarkers we included here, NFL showed the highest sensitivity with 100% specificity. |
| 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 occurring in patients having serum levels of a given biomarker above the cut-off identified as the one for predicting poor neurological outcome with 100% specificity may lead to treatment restrictions in patients destined to a good recovery. This is not likely to occur with the biomarkers included in this list, since their investigation is still in the explorative phase and none of them has been adopted as a criterion for WLST. | None of these biomarkers are currently widely available for clinical use. |
| 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 for GFAP, serum tau protein, and NFL is very low because of the very limited number of studies. | Differently from other predictors, like those based on clinical examination, biomarkers are not affected by sedation or paralysis, and can be assessed blindly.  A specific advantage of NFL is the fact of originating only in neurons. Both its sensitivity and specificity are high. However, the range of thresholds for 100% specificity is wide. |
| 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 | Neurologic outcome is generally accepted as a critical outcome after cardiac arrest. However, CPC from 3 to 5 (severe neurological disability, persistent vegetative state, or death) as a threshold for defining poor neurological outcome is not universally accepted. In a minority of prognostication studies in literature, a threshold of CPC 4-5 is used instead.  We defined prediction as imprecise when the upper limit of 95% confidence intervals (CIs) for false positive rate (FPR) was above 5%. However, there is no universal consensus on what the acceptable limits for imprecision should be. A recent survey (Steinberg 2019 190) among 640 medical providers showed that 56% felt an acceptable FPR for withdrawal of life sustaining treatment from patients who might otherwise have recovered was ≤0.1%, and that 59% of them felt that an acceptable FPRs threshold for continuing life sustaining treatment in patients with unrecognized unrecoverable injury was ≤1%. |  |
| Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Favours the comparison ● Probably favours the comparison ● Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know | Considering the little evidence supporting their use, the balance of effects suggests against using these biomarkers, or not favouring either option. Outside the context of studies, these biomarkers are not currently widely available and there are too few studies to support their use. |  |
| 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 | The costs of biomarkers’ assessment are higher when compared with those of clinical examination. No study assessing savings from prognostication based on GFAP, serum tau protein, or NFL has been included in our review. |  |
| 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 GFAP, serum tau protein, or NFL for prognostication after cardiac arrest. |  |
| 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 of these biomarkers. |  |
| 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 | A problem of inequity is possible, since assessment of biomarkers implies resources that could not be universally available. |  |
| 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. Assessment of biomarkers requires resources that may not be universally available. More specifically, GFAP, serum tau protein, and NFL have been assessed in highly specialised centres for research purposes and are not routinely available for clinical use in most hospitals. |  |

# 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 serum levels of GFAP, serum tau protein, or NFL for predicting poor neurological outcome of adults who are comatose after cardiac arrest (weak recommendation, very low-certainty evidence).** |
| Justification |
| Although these biomarkers, and in particular NFL, appear to be promising for prognostication after cardiac arrest, supporting evidence is limited to very few studies. Consistent thresholds for 100% specificity need to be identified before any of these biomarkers can be recommended for prognostication in the clinical setting.  These biomarker tests are not widely available. The methods used for measuring these biomarkers need to be more widely available, standardised, and studied. |
| Subgroup considerations |
| None |
| Implementation considerations |

Techniques and equipment for measuring biomarkers may vary among centres.

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| Monitoring and evaluation |
| These tests are currently not widely available. |
| Research priorities |
| Further studies on GFAP, serum tau protein, and NFL are needed to confirm their predictive value after cardiac arrest, to assess their reproducibility, and to identify consistent thresholds for 100% specificity. |