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| QUESTION | |
| **GFAP, serum tau protein, and NFL for prediction of good neurological outcome in adults after 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 72 hours after cardiac arrest. |
| **COMPARISON:** | *None.* |
| **MAIN OUTCOMES:** | Prediction of good neurological outcome defined as Cerebral Performance Categories (CPC) 1-2 at 6 or 12 months after cardiac arrest |
| **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 good 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 Unpublished studies, reviews, case reports, case series, studies including less than 10 patients, letters, editorials, conference abstracts, and studies published in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:** | An ILCOR review from 2013 and an update from 2020 presented the evidence of predictors of poor neurological outcome after cardiac arrest. More recently, several studies identifying predictors of good neurological outcome after cardiac arrest have been published, therefore an ILCOR evidence review for predictors of good neurological outcome after cardiac arrest is necessary. The most recent search of this systematic review evidence update on neuroprognostication was conducted in May 2022. |

# 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 | Neurologic injury is the most common cause of death in patients with post cardiac arrest syndrome. The vast majority of these deaths occur as a result of withdrawal of life-sustaining treatment (WLST) based on prediction of poor neurological outcome. Neurological prognostication after cardiac arrest is of utmost importance to avoid futile treatments for unsalvageable patients but also to minimize the risk of falsely pessimistic prediction and self-fulfilling prophecy. Identifying patients with a likely good outcome based on prognostication results could facilitate the continuation of care in some unconscious patients. |  |
| 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)**  GFAP was investigated in two observational studies [Moseby-Knappe 2021, Humaloja 2021].  **24h:** One study [Moseby-Knappe 2021] used the normal value for GFAp (<22 pg/mL) at 24h to predict good outcome after cardiac arrest and reported **specificity of 97% and sensitivity of 41%.**  **48h:** One study [Moseby-Knappe 2021] used the normal value for GFAp (<22 pg/mL) at 48h to predict good outcome after cardiac arrest and reported specificity **of 97% and sensitivity of 35%.** One study [Humaloja 2021] determined the cut-off to predict good neurological outcome with **100% and 95% specificities (210 and 439 pg/mL, respectively) with sensitivities of 43% and 75% respectively**.  **72h:** One study [Moseby-Knappe 2021] used the normal value for GFAp (<22 pg/mL) at 72h to predict good outcome after cardiac arrest and reported **specificity of 95% and sensitivity of 44%.** One study [Humaloja 2021] determined the cut-off to predict good neurological outcome with **100% and 95% specificities (187 and 359 pg/mL, respectively) with sensitivities of 44% and 73%, respectively**.  **Serum Tau Protein**  Serum Tau was investigated in two observational studies [Moseby-Knappe 2021, Humaloja 2021]  **24h:** One study [Moseby-Knappe 2021] used the normal value for Tau-protein (<1.55 pg/mL) at 24h to predict good outcome after cardiac arrest and reported **specificity of 94% and sensitivity of 28**%.  **48h:** One study [Moseby-Knappe 2021] used the normal value for Tau-protein (<1.55 pg/mL) at 48h to predict good outcome after cardiac arrest and reported **specificity of 95% and sensitivity of 41%.** One study [Humaloja 2021] determined the cut-off to predict good neurological outcome with **95% specificity (3.28 pg/mL) with sensitivity of 53%.**  **72h:** One study [Moseby-Knappe 2021] used the normal value for Tau-protein (<1.55 pg/mL) at 72h to predict good outcome after cardiac arrest and reported specificity of 93% and sensitivity of 52%. One study [Humaloja 2021] determined the cut-off to predict good neurological outcome **with 100% and 95% specificities (2.10 and 3.37 pg/mL, respectively) with sensitivities of 21% and 52%,** respectively.  **Serum Neurofilament Light Chain (NFL)**  **24 h**: Serum NfL was investigated in three observational studies [Moseby-Knappe 2021, Wihersaari 2021, WIhersaari 2022] at 24 h. Two studies [Wihersaari 2021, Wihersaari 2022] determined the NfL cut-off to predict good outcome with **100% specificity (12.5 and 30 pg/mL) with sensitivity ranging between 12–79%.** One study [Wihersaari 2022] determined the cut-off to predict good outcome with **95% specificity (21.5 pg/mL) with sensitivity of 37%.** One study [Moseby-Knappe, 2021]used the normal value for NfL (55 pg/mL) as the cut-off, and it predicted good outcome with **specificity of 95% and sensitivity of 65%.**  **48h**: Serum NfL was investigated in three observational studies [Moseby-Knappe 2021, Wihersaari 2021, WIhersaari 2022] at 48h. Two studies [Wihersaari 2021, Wihersaari 2022] determined the NfL cut-off to predict good outcome with **100% specificity (8 and 30 pg/mL) with sensitivity ranging between 6–74**%. One study [Wihersaari 2022] determined the cut-off to predict good outcome with **95% specificity (29 pg/mL) with sensitivity of 39%.** One study [Moseby-Knappe, 2021] used the normal value for NfL (55 pg/mL) as the cut-off, and it predicted good outcome with specificity of **96% and sensitivity of 54%.**  **72h**: Serum Nfl was investigated in two observational studies [Moseby-Knappe 2021, Wihersaari 2021] at 72h. One study [Wihersaari, 2021] determined the cut-off to predict good outcome **with 100% specificity (27 pg/mL) with corresponding sensitivity of 67%.** One study [Moseby-Knappe, 2021] used the normal value for NfL (55 pg/mL) as the cut-off, and it predicted good outcome with **specificity of 97% and sensitivity of 51%.**  **Ubiquitin carboxy-terminal hydrolase-L1 (UCH-L1**)  Serum UCH-L1 was investigated in one observational study [Moseby-Knappe 2021]. They used the normal value of UHC-L1 (<327 pg/mL) at **24, 48 and 72 hours** after cardiac arrest as cut-off and it predicted good neurological outcome with **specificities of 85%, 82%, and 70%,** respectively with corresponding sensitivities of 64%, 74%, and 88%, respectively. | NfL is investigated in three studies, whereas both GFAP and tau protein are investigated in two studies. UHC-L1 is only investigated in one study.  Cut-off values, specificities and sensitivities for GFAp, tau, and NfL are varying between the studies. |
| Undesirable Effects How substantial are the undesirable anticipated effects? | | |
| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
| ○ Large ○ Moderate ○ Small ● Trivial ○Varies  ○Don't know | Falsely positive prediction occurring in patients having serum levels of a given biomarker below the identified cut-off with 100% specificity are not likely to occur with the biomarkers included, 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, NFL, and UHC-L1 is very low because of the very limited number of studies and varying cut-offs reported between 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. 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 | It is common to define CPC scores 1–2 as good neurological outcome after cardiac arrest. One found study [Streiberger, 2017] used CPC scores 1–3 as the definition for good neurological recovery. There is limited data available regarding whether some people value a CPC 1-3 in the same way as a CPC 1-2. |  |
| 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 small amount of evidence supporting their use, the balance of effects suggests against using these biomarkers, or not favouring either option. Outside of 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 biomarker assessment are higher when compared with those of clinical examination. No study assessing savings from prognostication based on GFAP, serum tau protein, or NFL was identified 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, NFL, or UHC-L1 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, NFL, UHC-L1 have been assessed from thawed samples that were previously frozen in highly specialised centres for research purposes and are not currently 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 glial fibrillary acidic protein, serum tau protein, or neurofilament light chain in clinical practice for predicting favorable neurological outcome in adults who are comatose after cardiac arrest (weak recommendation, very low- certainty evidence). |
| Justification |
| The cut-offs used for predicting good outcome with the these biomarkers vary to a great degree making it difficult to provide recommendations. |
| Subgroup considerations |
| Most studies have been conducted in OHCA with a cardiac cause of the arrest. |
| Implementation considerations |

All studies conducted thus far have been done in specialised centres with the biomarker assessed outside clinical practise. No study has used a commercially available assay that would facilitate biomarker assessment in clinical practice.

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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. |

References:

Moseby-Knappe M, Mattsson-Carlgren N, Stammet P, Backman S, Blennow K, Dankiewicz J, Friberg H, Hassager C, Horn J, Kjaergaard J, Lilja G, Rylander C, Ullen S, Unden J, Westhall E, Wise MP, Zetterberg H, Nielsen N, Cronberg T (2021) Serum markers of brain injury can predict good neurological outcome after out-of-hospital cardiac arrest. Intensive Care Med 47:984–994

Wihersaari L, Ashton NJ, Reinikainen M, Jakkula P, Pettila V, Hastbacka J, Tiainen M, Loisa P, Friberg H, Cronberg T, Blennow K, Zetterberg H, Skrif- vars MB, Comacare Study G (2021) Neurofilament light as an outcome predictor after cardiac arrest: a post hoc analysis of the COMACARE trial. Intensive Care Med 47:39–48

Wihersaari L, Reinikainen M, Furlan R, et al. Neurofilament light compared to neuron-specific enolase as a predictor of unfavorable outcome after out-of-hospital cardiac arrest, Resuscitation174:1–8

Humaloja J, Lahde M, Ashton N J, et al. GFAp and tau protein as predictors of neurological outcome after out-of-hospital cardiac arrest: A post hoc analysis of the COMACARE trial, Resuscitation 170: 141–149