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| Question | |
| **Grey matter/white matter ratio (GWR) on brain computed tomography (CT) for prediction of poor neurological outcome in adults with cardiac arrest**  **(Subsection of Prognostication ETD)** | |
| **Population:** | Adults who are comatose after resuscitation from cardiac arrest (either in-hospital or out-of-hospital), regardless of target temperature management. |
| **Intervention:** | Grey matter/white matter ratio (GWR) on brain computed tomography (CT)), 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 Unpublished studies, reviews, case reports, case series, studies including less than 10 patients, letters, editorials, conference abstracts, and studies published in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 | Grey matter to white matter ratio (GWR) is the ratio between the densities (measured in Hounsfield units) of the grey matter and the white matter on brain CT. In the normal brain, the grey matter has a higher density than the white matter. Occurrence of brain oedema reduces GWR.  The sites and methods for GWR calculation, and the GWR thresholds were inconsistent across studies.  **GWR-AVERAGE (GWR-AVG)**  GWR-AVG was investigated in seven observational studies [Jeon 2017 118; Kim 2013 57; Kim 2014 1121; Kim 2018 33; Lee 2017 1628; Wang 2018 599; Youn 2017 120].  In four studies [Jeon 2017 118, 39 pts; Kim 2013 57, 51 pts; Kim 2014 1121, 91 pts; Kim 2018 33, 174 pts] GWR-AVG ≤1.23 within 6h from ROSC predicted poor neurological outcome from hospital discharge to 6 months with 100% specificity and sensitivity ranging from 13.3% to 83.8% (certainty of evidence from low to very-low).  In one study [Lee 2017 1628, 67 pts] GWR-AVG ≤1.13 at 124.5±59.9 min from ROSC predicted poor neurological outcome at 1 month with 85% specificity and 29.8% sensitivity (very-low certainty of evidence).  In one study [Youn 2017 120, 240 pts] GWR-AVG ≤1.077 within 24h from ROSC predicted poor neurological outcome at hospital discharge with 100% specificity and 15.6% sensitivity (very-low certainty of evidence).  In one study [Wang 2018 599, 58 pts] GWR-AVG ≤1.14 within 72h from ROSC predicted poor neurological outcome at hospital discharge with 100% specificity and 38.1% sensitivity (very-low certainty of evidence).  **GWR-Basal Ganglia (GWR-BG)**  GWR-BG was investigated in four observational studies [Kim 2013 57; Scarpino 2018 114; Scarpino 2019 115; Wang 2018 599].  In one study [Kim 2013 57, 51 pts] GWR-BG ≤1.12 within 1h from ROSC predicted poor neurological outcome at hospital discharge with 100% specificity and 3.3% sensitivity (very-low certainty of evidence).  In two studies [Scarpino 2018 114, 183 pts; Scarpino 2019 115, 346 pts] GWR-BG ≤1.21 within 24h from ROSC predicted poor neurological outcome at 6 months with 100% specificity and sensitivity ranging from 41.8% to 42.1% (certainty of evidence from moderate to very low).  In one study [Wang 2018 599, 58 pts] GWR-BG ≤1.12 within 72h from ROSC predicted poor neurological outcome at hospital discharge with 100% specificity and 28.6% sensitivity (very-low certainty of evidence).  **GWR Putamen/Corpus Callosum (P/CC)**  GWR-P/CC was investigated in three observational studies [Lee 2013 1387; Lee 2018 37; Jeon 2017, 21].  In two studies [Lee 2013 1387, 186 pts; Jeon 2017 21, 39 pts] GWR-P/CC ≤1.17 within 6h from ROSC predicted poor neurological outcome from hospital discharge to 6 months with 100% specificity and sensitivity ranging from 31.3% to 52.9% (very-low certainty of evidence).  In one study [Lee 2018 37, 258 pts] GWR-P/CC ≤0.91 within 24h from ROSC predicted poor neurological outcome at 6 months with 100% specificity and 1.7% sensitivity (very-low certainty of evidence).  **GWR-Simplified (GWR-SI: Putamen/Posterior limb of internal capsule).**  GWR-SI was investigated in one observational study [Wang 2018 1599].  In one study [Wang 2018 1599, 58 pts] GWR-SI ≤1.1 within 72h from ROSC predicted poor neurological outcome at hospital discharge with 100% sensitivity and 28.6% sensitivity (very-low certainty of evidence).  **GWR Caudate Nucleus/Posterior limb of internal capsule (CN/PIC)**  GWR-CN/PIC was investigated in two observational studies [Lee 2013, 186 pts; Jeon 2017, 39 pts].  In two studies [Lee 2013 1387, 186 pts; Jeon 2017 21, 39 pts] GWR-CN/PIC ≤1.15 within 6h from ROSC predicted poor neurological outcome from hospital discharge to 6 months with 100% specificity and sensitivity ranging from 19.8% to 40.6% (very-low certainty of evidence).  **GWR cerebrum**  GWR-cerebrum was investigated in two observational studies [Kim 2013 (a) 57; Wang 2018 1599].  In one study [Kim 2013 57, 51 pts] GWR-cerebrum ≤1.12 within 1h from ROSC predicted poor neurological outcome at hospital discharge with 100% specificity and 20% sensitivity (very-low certainty of evidence).  In one study [Wang 2018 599, 58 pts] GWR-cerebrum ≤1.09 within 72h from ROSC predicted poor neurological outcome at hospital discharge with 100% specificity and 28.6% sensitivity (very-low certainty of evidence).  **GWR Thalamus/Corpus Callosum (GWR-T/CC)**  GWR-T/CC was investigated in one observational study [Jeon 2017 118, 39 pts].  In this study GWR-T/CC ≤1.13 at median time of 90 (IQR 52–150) min predicted poor neurological outcome at 6 months with 100% specificity and 50% sensitivity (very-low certainty of evidence).  **GWR Caudate nucleus /Corpus callosum (GWR-CN/CC)**  GWR-CN/CC was investigated in one observational study [Jeon 2017 118, 39 pts].  In this study GWR-CN/CC ≤1.15 at median time of 90 (IQR 52–150) min predicted poor neurological outcome at 6 months with 100% specificity and 46.9% sensitivity (very-low certainty of evidence).  **GWR in cardiac vs. non-cardiac etiology**  In one study including CA with cardiac aetiology [Lee 2015 46, 283 pts] GWR-AVR ≤1.13 at 50 (IQR 26-107) min from ROSC predicted poor neurological outcome at hospital discharge with 100% specificity and 3.5% sensitivity (very-low certainty of evidence).  In one study including CA with non-cardiac aetiology [Lee 2016 1583, 164 pts] GWR-AVR ≤1.22 at 67 (IQR 29-115) min from ROSC predicted poor neurological outcome at hospital discharge with 100% specificity and 28.3% sensitivity (very-low certainty of evidence).  In one study including CA with cardiac aetiology [Lee 2015 46, 283 pts] GWR-BG ≤1.11 at 50 (IQR 26-107) min from ROSC predicted poor neurological outcome at hospital discharge with 100% specificity and 3.5% sensitivity (very-low certainty of evidence).  In one study including CA with non-cardiac aetiology [Lee 2016 1583, 164 pts] GWR-BG ≤1.17 at 67 (IQR 29-115) min from ROSC predicted poor neurological outcome at hospital discharge with 100% specificity and 26.2% sensitivity (very-low certainty of evidence).  In one study including CA with cardiac aetiology [Lee 2015 46, 283 pts] GWR-P/CC ≤1.107 at 50 (IQR 26-107) min from ROSC predicted poor neurological outcome at hospital discharge with 100% specificity and 5.6% sensitivity (very-low certainty of evidence).  In one study including CA with non-cardiac aetiology [Lee 2016 1583, 164 pts] GWR-P/CC ≤1.2 at 67 (IQR 29-115) min from ROSC predicted poor neurological outcome at hospital discharge with 100% specificity and 43.4% sensitivity (very-low certainty of evidence).  In one study including CA with cardiac aetiology [Lee 2015 46, 283 pts;] GWR-SI ≤1.06 at 50 (IQR 26-107) min from ROSC predicted poor neurological outcome at hospital discharge with 100% sensitivity and 3.5% sensitivity (very-low certainty of evidence).  In one study including CA with non-cardiac aetiology [Lee 2016 1583, 164 pts] GWR-SI ≤1.12 at 67 (IQR 29-115) min from ROSC predicted poor neurological outcome at hospital discharge with 100% sensitivity and 9.7% sensitivity (very-low certainty of evidence).  In one study including CA with cardiac aetiology [Lee 2015 46, 283 pts] GWR-CN/PIC ≤1.094 at 50 (26-107) min from ROSC predicted poor neurological outcome at hospital discharge with 100% specificity and 3.5% sensitivity (very-low certainty of evidence).  In one study including CA with non-cardiac aetiology [Lee 2016 1583, 164 pts] GWR-CN/PIC ≤1.138 at 67 (29-115) min from ROSC predicted poor neurological outcome at hospital discharge with 100% specificity and 20% sensitivity (very-low certainty of evidence).  In one study including CA with cardiac aetiology [Lee 2015 46, 283 pts] GWR-cerebrum ≤1.15 at 50 (26-107) min from ROSC predicted poor neurological outcome at hospital discharge with 100% specificity and 4.2% sensitivity (very-low certainty of evidence).  In one study including CA with non-cardiac aetiology [Lee 2016 1583, 164 pts] GWR-cerebrum ≤1.2 at 67 (29-115) min from ROSC predicted poor neurological outcome at hospital discharge with 100% specificity and 11% sensitivity (very-low certainty of evidence). |  |
| 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 based on GWR levels above the cut-off chosen for predicting poor neurological outcome may lead to treatment restrictions in patients destined to a good recovery. An additional risk is represented by the wide variability of cut-offs for 100% specificity across studies. |  |
| 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 GWR is very low because of the risk of bias, especially self-fulfilling prophecy and selection bias. In some studies, brain CT was performed in about half of the potentially includible patients, because brain CT was not performed within the expected time window, or results of brain CT were discarded because of poor image quality or artefacts.  A source of confounding for GWR is represented by the different available methods and sites of measurement. | 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.  There is no consensus on what are the normal levels for GWR. |
| 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 | GWR has a potential for predicting poor outcome after cardiac arrest and several studies identified thresholds for predicting poor outcome with 100% specificity. However, there was a high heterogeneity in both the methods used to calculate GWR across studies and the thresholds associated with 100% specificity. |  |
| 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 imaging assessment are higher when compared with those of clinical examination. In addition, measurement of GWR requires additional calculations and skills. No study assessing savings from prognostication based on imaging 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 imaging 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. |  |
| 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 prognostic assessment using imaging implies resources and skills that may 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. Imagingstudies used for neuroprognostication after cardiac arrest cannot be performed at the bedside, and require transportation in 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 using grey matter/white matter (GWR) ratio on brain CT for predicting neurological outcome of adults who are comatose after cardiac arrest (weak recommendation, very-low-certainty evidence). However, no GWR threshold for 100% specificity can be recommended.** |
| Justification |
| A severe brain oedema in patients who are unconscious after cardiac arrest predicts poor outcome with high specificity. GWR allows a quantitative evaluation of brain oedema. However, there is a wide heterogeneity of measurement techniques (sites and calculation methods) for GWR. This may partly explain the wide variability of thresholds for 100% specificity across the studies we included. The evidence supporting GWR has very low certainty. |

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| Subgroup considerations |
| None |
| Implementation considerations |

Prognostication based on imaging requires technology and skills that may not be universally available.

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| Monitoring and evaluation |
| |  | | --- | | Research priorities | | A consistent 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. |   None |