Appendix B

Advanced Life Support – 2026 Evidence Updates

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2026 Evidence Update

ALS 3511 (Part 1) – Prognostication EEG SSEP

Worksheet author(s): Claudio Sandroni, Sonia D'Arrigo
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Task Force: ALS
Date Submitted to SAC rep for peer review and approval: September 10, 2025
SAC rep: Erik Lavonas

PICOST / Research Question:
Population: Adults who are comatose after resuscitation from cardiac arrest (either in-hospital or out-of-hospital), regardless of target temperature.
Interventions: index test based on electrophysiology: short-latency somatosensory evoked potentials (SSEP)
Comparison: none.
Outcomes: poor neurological outcome, defined as Cerebral Performance Categories (CPC) 3-5 or Glasgow Outcome Scale (GOS) 1-3, or modified Rankin Score (mRS) 4-6 at hospital discharge/1 month or later.
Study designs: Prognostic accuracy studies where the 2x2 contingency table (ie, 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 Unpublished studies, reviews, case reports, case series, studies including fewer than 10 patients, letters, editorials, conference abstracts, and studies published in abstract form were excluded.

Year of last full review: 2020

Current ILCOR Consensus on Science and Treatment Recommendation for this PICOST: COSTR 2024
We recommend that neuroprognostication always be undertaken by using a multimodal approach because no single test has sufficient specificity to eliminate false positives (strong recommendation, very low-certainty evidence).

We suggest using a bilaterally absent N20 wave of SSEP in combination with other indices to predict poor outcome in adult patients who are comatose after cardiac arrest (weak recommendation, very low–certainty evidence).

Database searched: PubMed. The references of full-text articles were screened for additional studies.

Time Frame: (existing PICOST) – April 2024 (prior EvUp) to Aug 2025
Date Search Completed: Aug 31, 2025
Search Results (Number of articles identified, and number identified as relevant): 25/2

Summary of Evidence Update:

Two studies **(Czimmeck 2025, Scarpino 2025)** evaluated **low SSEP amplitude** and its threshold for predicting poor neurological outcome. In one study (Scarpino 2025) in 65 patients, a bilaterally absent N20 wave **within 6 h after ROSC** predicted poor outcome with 100[89-100]% specificity and 67[48-82]% sensitivity.
Adding three additional criteria (low-amplitude [<1.2 μV] or prolonged [>10 milliseconds] N20 wave, absence of the N70 (middle-latency) SSEP wave) increased sensitivity to 93[79-99]% without reducing specificity. In the other study (Czimmeck 2025), in 116 patients an absent or low-amplitude (**<0.5 μV)** N20 wave **on day 3** predicted poor neurological outcome at hospital discharge with **100 [96-100]% specificity** and **56 [46-65]% sensitivity.**

Relevant Guidelines or Systematic Reviews: none

RCTs: none

Nonrandomized Trials, Observational Studies published

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Cortical somatosensory evoked potentials (SSEPs) amplitude				
Czimmeck et al. 2025	**Study Type:** retrospective, single-centre observational study. One hundred fifty-two patients were included in the study. SSEP amplitude was tested on 116 patients.	**Inclusion Criteria:** OHCA and IHCA patients with serum NFL testing within 24–96 h after CA. **Exclusion criteria:** N/A	The SSEP accuracy was not the primary endpoint of the study. **1° endpoint:** to evaluate NFL as a biomarker for neuroprognostication after CA in clinical routine. **2° endpoint:** to compare NFL to established prognostication methods. **Results: SSEP amplitude <0.5 µV at day 3** predicted poor neurological outcome (CPC 4-5) at hospital discharge with **100 [96-100]% specificity** and **56 [46-65]% sensitivity.**	The study identified a low-amplitude N20 SSEP wave as a highly specific predictor of poor neurological outcome, in line with previous studies (e.g., Scarpino, 2021). The amplitude threshold was <0.5 µV and includes an absent N20.
Scarpino et al. 2025	**Study Type:** Prospective single-center study. Six-five patients were included in the study. SSEP amplitude was tested in all patients.	**Inclusion Criteria:** Consecutive comatose adult patients (GCS<8) who received the first multimodal prognostic evaluation within 6 hours after CA, as well as the NSE dosage within 12 hours after CA.	**1° endpoint:** the accuracy of short- and middle-latency SSEPs recorded within 6 hours of ROSC in predicting both poor (CPC 3–5) and good (CPC 1–2) neurological outcomes at hospital discharge. **2° endpoint:** to evaluate the prognostic accuracy of other ERC-ESICM predictors. **Results:** **A bilaterally absent N20** wave **within 6 hours** from	This preliminary study indicates that an absent N20 SSEP wave predicts poor outcome with 100% specificity and high sensitivity as early as 6 hours after ROSC. Additional criteria based on the quantitative analysis of the N20 wave or on the absence of the middle-latency SSEP wave increase the SSEP sensitivity while maintaining 100%

		<u>Exclusion criteria:</u> traumatic or neurological causes of CA, pre-existing neurological disability, regain of consciousness or death before neurophysiological tests.	ROSC predicted poor outcome with 100[89-100]% specificity and 67[48-82]% sensitivity. Adding **low-amplitude (<1.2 µV),** prolonged (>10 milliseconds) N20 wave and the absence of the N70 (middle-latency) SSEP wave increased the sensitivity to 93[79-99]% without compromising specificity. SSEPs outperformed all other predictors for poor outcome prediction at the study time point.	specificity for poor outcome prediction. However, confirmation from larger and multicentre studies is necessary.

Reviewer Comments: ***(including whether this PICOST should have a systematic or scoping review*****)**

Two articles show that a low-amplitude N20 wave predicts poor outcome after cardiac arrest with 100% specificity. Results are in line with previous studies from the same author groups (Endisch, 2015, Scarpino, 2021). In a single-centre study, SSEPs analysed quantitatively within 6 hours after ROSC and combined with middle-latency SSEP outperformed all other predictors for poor outcome prediction at that early time point, but results need validation in larger cohorts.

The measuring methods and the thresholds of the N20 amplitude are not consistent in the literature, as shown by the previous 2022 and 2024 ILCOR Evidence Updates.

The task force is planning an updated systematic review of all modalities of neuroprognostication in the near future.

Note on the interpretation of test results

Neuroprognostic tests used in patients who are comatose after resuscitation from cardiac arrest measure the severity of brain injury. An abnormal response from these tests may be classified as "positive," and a normal response as "negative," or vice versa, depending on the prognostic perspective taken. Usually, as in this evidence review, a positive result of these tests indicates that the outcome of that patient will be poor. If this occurs, the prediction is correct, and the test result is a true positive. Conversely, if the outcome is good, the positive test result is a false positive. In this context, the false-positive rate (FPR) of a test is the proportion of patients with good outcome who are assigned a falsely pessimistic prediction. In other words, the FPR is the number of false positives divided by the total number of patients with a good outcome. FPR is also the complement of specificity, i.e., 100% − specificity. Therefore, a test with 100% specificity has 0% FPR. Ideally, all neuroprognostic tests predicting poor outcome should yield 100% specificity. While neuroprognostic tests predicting outcome should also ideally offer a reasonably high sensitivity when "negative" (in this case indicating that the outcome of the patient will be good), this is less important than their having a high specificity (low FPR), since the latter minimizes the risk of incorrectly predicting (and acting upon) a poor prognosis in a potentially viable patient.

In most neuroprognostic studies, as in prognostic studies in general, the treating team is aware of the results of the prognostic tests under investigation. Consequently, these results may affect their treating decisions, leading to a self-fulfilling prophecy bias that may overestimate the specificity of prognostic tests in predicting poor outcome. This bias contributes to the low certainty of the evidence of most neuroprognostic studies after cardiac arrest. For that reason, the ILCOR 2020 Consensus for this PICOST is that The decision to limit treatment of comatose post–cardiac arrest patients should never rely on a single prognostication element. The consensus of the task force was that in patients who remain comatose in the absence of confounders (eg, sedative drugs), a multimodal approach should be used, with all supplementary tests considered in the context of the clinical examination.

For further details on the methodology and interpretation of prognostic tests see Geocadin RG, Callaway CW, Fink EL, Golan E, Greer DM, Ko NU, Lang E, Licht DJ, Marino BS, McNair ND, Peberdy MA, Perman SM, Sims DB, Soar J, Sandroni C; American Heart Association Emergency Cardiovascular Care Committee. Standards for Studies of Neurological Prognostication in Comatose Survivors of Cardiac Arrest: A Scientific Statement From the American Heart Association. Circulation. 2019 Aug 27;140(9):e517-e542.).

Reference list:

Czimmeck C, Resuscitation 2025 Aug:213:110650. https://pubmed.ncbi.nlm.nih.gov/40409670/
Endisch C, Neurology 2015, 20: 1752-60. https://pubmed.ncbi.nlm.nih.gov/26491086/
Scarpino M, Resuscitation 2021; 163: 162-71. https://pubmed.ncbi.nlm.nih.gov/33819501/
Scarpino M, Resuscitation 2025 Sep 4:110801. https://pubmed.ncbi.nlm.nih.gov/40914341/

2026 Evidence Update

ALS 3511 (Part 2) – Prognostication EEG

Worksheet author(s): Claudio Sandroni, Sonia D'Arrigo
External Collaborator (data extraction and management): Sofia Cacciola
Task Force: ALS
Date Submitted to SAC rep for peer review and approval: September 10, 2025
SAC rep: Eric Lavonas

PICOST / Research Question:
Population: Adults who are comatose after resuscitation from cardiac arrest (either in-hospital or out-of-hospital), regardless of target temperature.
Interventions: index test based on electrophysiology: electroencephalogram (EEG)
Comparison: none.
Outcomes: poor neurological outcome, defined as Cerebral Performance Categories (CPC) 3-5 or Glasgow Outcome Scale (GOS) 1-3, or modified Rankin Score (mRS) 4-6 at hospital discharge/1 month or later.
Study designs: Prognostic accuracy studies where the 2x2 contingency table (ie, 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 fewer than 10 patients, letters, editorials, conference abstracts, and studies published in abstract form were excluded.

Year of last full review: 2020

Current ILCOR Consensus on Science and Treatment Recommendation for this PICOST:
We recommend that neuroprognostication always be undertaken by using a multimodal approach because no single test has sufficient specificity to eliminate false positives (strong recommendation, very low-certainty evidence).
We suggest using "highly malignant" EEG patterns to predict poor outcome in adult patients who are comatose and who are off sedation after cardiac arrest (weak recommendation, very low-certainty evidence).
We suggest against EEG background reactivity alone to predict poor outcome in adult patients who are comatose after cardiac arrest (weak recommendation, very low-certainty evidence).

Database searched: PubMed. The references of full-text articles were screened for additional studies.

Time Frame: (existing PICOST) –April 2024 (prior EvUp) to Aug 2025
Time Frame: (new PICOST) – at the discretion of the Task Force (please specify)
Date Search Completed: Aug 31, 2025
Search Results (Number of articles identified, and number identified as relevant): 25/5

Summary of Evidence Update:
Five studies evaluated the **presence of "highly malignant" patterns on EEG** in 1409 patients (Admiraal 2025, Benghanem 2025, Czimmeck 2025, Scarpino 2025, Shivji 2025) between the early phase (within 6 or 12-24h) and 14 days after ROSC.

In one study (Scarpino 2025) in 65 patients, the early presence (within 6 h after ROSC) of "highly malignant" patterns (suppression and burst suppression) predicted poor neurological outcome at discharge with 78 [66-87]% and 100 [93-100]% specificity and 67 [53-78]% and 33 [22-46]% sensitivity, respectively.

In one study (Admiraal 2025) in 191 patients investigated the prognostic performance of "synchronous EEG patterns" within 24 h in addition to the late EEG predictors (>24 h) recommended in the European post-resuscitation guidelines. The presence of **synchronous EEG patterns** (suppression with GPDs, BS with identical or " epileptiform bursts) on early cEEG at **12-24h after ROSC** predicted poor neurological outcome at 6 months with 30 [23-37]% sensitivity and 100 [97-100]% specificity. **Late EEG predictors** (BS with heterogeneous bursts and suppression without discharges) **at 24-36 h, 36-48 h and 48-72 h** predicted poor neurological outcome at 6 months with 100 [96-100]% specificity and 42 [35-50]%, 29 [23-37]% and 34 [26-44]% sensitivity, respectively.
In one study (Shivji 2025) in 81 patients the presence of "highly malignant" patterns on EEG **at 2-14 days** after ROSC predicted poor neurological outcome at 3-6 months with 73 [62-82]% sensitivity and 100 [94-100]% specificity.
In one study (Benghanem 2025) in 966 patients, the presence of "highly malignant" EEG patterns **at 48-72 h** after ROSC predicted poor neurological outcome at 3-6 months with 100 [99-100]% specificity and 34 [31-37]% sensitivity.
In another study (Czimmeck 2025) in 106 patients, the presence of "highly malignant" patterns on EEG **at 4 days after ROSC** predicted poor neurological outcome at hospital discharge with 51 [41-61]% sensitivity and 100% specificity.

Only one study (Shivji 2025) in 81 patients evaluated the additional value of the **absence of reactivity on EEG** at 2-14 days, showing that it predicted poor neurological outcome at 3-6 months with 89 [80-95]% specificity and 86 [76-92]% sensitivity. FPR was about 10%.

In all studies, "highly malignant" EEG patterns were suppression (with or without superimposed discharges) or burst-suppression, defined according to the American Clinical Neurophysiology Society (ACNS) terminology (Hirsch LJ et al., 2012, 2021). Further details are provided in the note at the end of this document.

Relevant Guidelines or Systematic Reviews: none

RCT: none

Nonrandomized Trials, Observational Studies published Apr 30, 2024 to Aug 31, 2025

Study Acronym; Author; Year Published	**Study Type/Design; Study Size (N)**	**Patient Population**	**Primary Endpoint and Results (include P value; OR or RR; & 95% CI)**	**Summary/Conclusion Comment(s)**
"Highly Malignant" Patterns				
Admiraal et al. 2025	**Study Type:** retrospective observational substudy of the TTM2-trial. One hundred and ninety-one patients were included in the study. cEEG was performed on all patients.	**Inclusion Criteria:** OHCA of a presumed cardiac or unknown cause, sustained ROSC, unconsciousness defined as not being able to obey verbal commands after sustained ROSC.	**1° endpoint:** to investigate the prognostic performance of "synchronous EEG patterns" within 24 h in addition to the late EEG predictors (>24 h) recommended in the European post-resuscitation guidelines. **2° endpoint:** to investigate the added value of assessing consecutive time-epochs of	Suppression and burst-suppression ("highly malignant patterns") assessed on continuous EEG monitoring predicted poor neurological outcome at 6 months with 100% specificity and moderate sensitivity.

		Exclusion criteria: unwitnessed cardiac arrest with an initial rhythm of asystole, temperature on admission <30°C, on ECMO prior to ROSC, obvious or suspected pregnancy, intracranial bleeding, severe COPD with long-term home oxygen therapy.	the cEEG-recording, thus gradually collecting prognostic cEEG information during the first 72 h for prediction of poor outcome. **Results:** **synchronous EEG patterns present at 12-24 h (early)** (suppression with GPDs, BS with identical or highly epileptiform bursts) predicted poor neurological outcome at 6 months with 30 [23-37]% sensitivity and 100 [97-100]% specificity. **Late EEG predictors at 24-36 h, 36-48 h and 48-72 h** (BS with heterogeneous bursts and suppression without discharges) predicted poor neurological outcome at 6 months with **100% specificity and 42 [35-50]%, 29 [23-37]% and 34 [26-44]% sensitivity,** respectively.	The study suggests that 'synchronous' patterns (suppression with periodical discharges, burst-suppression with identical or epileptiform bursts) predict poor outcome early (at 12-24h after ROSC), while 'non-synchronous patterns' (suppression without discharges and burst-suppression with heterogeneous bursts) predict poor outcome later (24-72h after ROSC).
Benghanem et al. 2025	**Study Type:** prospective, bicentric study. Ninety hundred sixty-six patients were included in the study. EEG was performed on all patients.	**Inclusion Criteria:** comatose adult patients who had at least a serum NSE measurement at 48 hours and an EEG ≥ 24 hours after CA. **Exclusion criteria:** N/A	The EEG accuracy was not the primary endpoint of the study. **1° endpoint:** neurological recovery at 3 months. **2° endpoint:** to examine the relationship between markers of brain injury (NSE and EEG patterns) obtained in early post-resuscitation period and the subsequent degree of neurological recovery. **Results:** **"Highly malignant" EEG at 2.2 (1.8-3) days** predicted poor neurological outcome at 3 months with **100% specificity and 34 [31-37]% sensitivity.**	"Highly malignant" EEG at 36-72 h predicted poor neurological outcome at 3 months with 100% specificity and moderate sensitivity.
Czimmeck et al. 2025	**Study Type:**	**Inclusion Criteria:**	The EEG accuracy was not the primary endpoint of the study.	"Highly malignant" EEG at day

	retrospective, monocentric observational study. One-hundred and fifty-two patients were included in the study. EEG was performed on 106 patients.	OHCA and IHCA patients with serum NFL testing within 24–96 h after CA. **Exclusion criteria:** N/A	**1° endpoint:** to evaluate NFL as a biomarker for neuroprognostication after CA in clinical routine. **2° endpoint:** to compare NFL to established pr ognostication methods. **Results:** **"Highly malignant" EEG at day 4** predicted poor neurological outcome at hospital discharge with **100% specificity and 51 [41-61]% sensitivity.**	4 predicted poor neurological outcome at hospital discharge with 100% specificity and moderate sensitivity.
Scarpino et al. 2025	**Study Type:** Prospective single-centre study. Sixty-five patients were included in the study. EEG was performed in all patients.	**Inclusion Criteria:** Consecutive comatose adult patients (GCS<8) who received the first multimodal pr ognostic evaluation within 6 hours after CA, as well as the NSE dosage within 12 hours after CA. **Exclusion criteria:** traumatic or neurological causes of CA, pre-existing neurological disabil ity, regain of consciousness or death before neurophysiological tests.	EEG accuracy was not the primary endpoint of the study. **1° endpoint:** the accuracy of short- and middle-latency SSEPs recorded within 6 hours of ROSC in predicting both poor (CPC 3–5) and good (CPC 1–2) neurological outcomes at hospital discharge. **2° endpoint:** to evaluate the prognostic accuracy of other ERC-ESICM predictors early after CA. **Results:** **Suppression and burst suppression on EEG ("early malignant" patterns) within 6 h after ROSC** predicted poor neurological outcome at discharge with 78 [66-87]% and 100 [93-100]% specificity and 67 [53-78]% and 33 [22-46]% sensitivity, respectively.	"Highly malignant" EEG within 6 h after ROSC predicted poor neurological outcome at hospital discharge. Specificity was high for burst-suppression, but lower for suppression at this early time point.
Shivji et al. 2025	**Study Type:** retrospective, monocentric study. Eighty-one patients were included in the study. EEG was performed on all patients.	**Inclusion Criteria:** age $\geq$ 18 years, coma due to cardiac arrest. **Exclusion criteria:** N/A	**1° endpoint:** to retrospectively evaluate the patterns seen on EEG in patients with post-anoxic coma following cardiac arrest and their relationship to outcome. **Results:**	"Highly malignant" EEG at 2-14 days predicted poor neurological outcome at 3-6 months with 100% specificity and 73% sensitivity.

			"Highly malignant" EEG at 2-14 days predicted poor neurological outcome at 3-6 months with **100 [94-100]% specificity and 73 [62-82]% sensitivity.**	
Absence of reactivity on EEG				
Shivji et al. 2025	**Study Type:** retrospective, monocentric study. Eighty-one patients were included in the study. EEG was performed on all patients.	**Inclusion Criteria:** age ≥ 18 years, coma due to cardiac arrest. **Exclusion criteria:** N/A	**1° endpoint:** to retrospectively evaluate the patterns seen on EEG in patients with post-anoxic coma following cardiac arrest and their relationship to outcome. **Results:** **Unreactive EEG at 2-14 days** predicted poor neurological outcome at 3-6 months with **89 [80-95]% specificity and 86 [76-92]% sensitivity.** FPR was about 10%.	Unreactive EEG at 2-14 days predicted poor neurological outcome at 3-6 months with 89% specificity and 86% sensitivity.

Reviewer Comments: *(including whether this PICOST should have a systematic or scoping review*)
All five studies included in this review confirmed that "highly malignant" EEG patterns (suppression and burst suppression) recorded early (within 6 h) and after 24h predict poor outcome with 100% specificity after cardiac arrest, in line with the current ILCOR recommendation. Two studies (Admiraal 2025 and Scarpino 2025) suggest that "highly malignant" patterns with a synchronous component may accurately predict poor outcome before 24h. However, this study was conducted by experienced electrophysiologists who analysed continuous EEG records, and it deserves confirmation from further studies. One study (Shivij, 2025) confirmed that an unreactive EEG background does not reach 100% specificity for predicting poor outcome after cardiac arrest. The task force is planning an updated systematic review on all modalities for neuroprognostication in the near future.

Note: definition of "highly malignant" EEG patterns, EEG reactivity, early EEG predictors
In all studies included in this Evidence Update, "highly malignant" patterns included suppression or burst-suppression, defined according to the Standardized Critical Care EEG Terminology of the American Clinical Neurophysiology Society's (ACNS). The ACNS terminology was published in 2012 and 2021 (Hirsch LJ et al, J Clin Neurophysiol 30(1): 1-27; https://pubmed.ncbi.nlm.nih.gov/23377439/ Hirsch LJ et al., J Clin Neurophysiol 2021 Jan 1;38(1):1-29; https://pubmed.ncbi.nlm.nih.gov/33475321/). Based on the ACNS terminology, suppression occurs when the background voltage in the entire record is below 10 µV, and burst suppression occurs when >50% of the record consists of suppression, alternated with bursts. This definition was consistent with that used in the ILCOR 2024 CoSTR.
EEG background reactivity is defined by ACNS as "change in cerebral EEG activity to intense auditory and/or noxious stimuli. This may include change in amplitude or frequency, including attenuation of activity".
Early EEG predictors, including synchronuous patterns such as identical burst-suppression, evaluated in Admiraal et al. 2025 had the highest sensitivity at time-points before 24 h after CA and thereafter sensitivity declined

confirming previous studies (Ruijter BJ, Tjepkema-Cloostermans MC, Tromp SC, et al. Early electroencephalography for outcome prediction of postanoxic coma:
a prospective cohort study. Ann Neurol 2019;86(2):203–14; Hofmeijer J, Tjepkema-Cloostermans MC, Van Putten MJAM. Burstsuppression with identical bursts: a distinct EEG pattern with poor outcome in postanoxic coma. Clin Neurophysiol 2014;125
(5):947–54).
Guidelines recommended late EEG predictors, including non-identical/heterogenous burst-suppression and suppression, showed a relatively stable sensitivity between 24 and 72 h after CA, in line with
previous studys (Westhall E, Rossetti AO, van Rootselaar AF, et al. Standardized EEG interpretation accurately predicts prognosis after cardiac arrest.Neurology 2016;86(16):1482–90).
Searching for both early and late EEG predictors is a novel strategy which identified even more patients with poor outcome and performed best between 24 and 36 h after CA. Since EEG patterns are often transient, assessment of an individual time-window was less informative compared to continuously evaluating the EEG. When using this combined strategy and gradually adding EEG information from before 12 h up to 36 h after CA (requiring cEEG) sensitivity significantly increased and half of all patients with long-term poor outcome could be identified.

Note on the interpretation of test results
Neuroprognostic tests used in patients who are comatose after resuscitation from cardiac arrest measure the severity of brain injury. An abnormal response from these tests may be classified as “positive,” and a normal response as “negative,” or vice versa, depending on the prognostic perspective taken. Usually, as in this evidence review, a positive result of these tests indicates that the outcome of that patient will be poor. If this occurs, the prediction is correct, and the test result is a true positive. Conversely, if the outcome is good, the positive test result is a false positive. In this context, the false-positive rate (FPR) of a test is the proportion of patients with good outcome who are assigned a falsely pessimistic prediction. In other words, the FPR is the number of false positives divided by the total number of patients with a good outcome. FPR is also the complement of specificity, i.e., 100% − specificity. Therefore, a test with 100% specificity has 0% FPR. Ideally, all neuroprognostic tests predicting poor outcome should yield 100% specificity. While neuroprognostic tests predicting outcome should also ideally offer a reasonably high sensitivity when “negative” (in this case indicating that the outcome of the patient will be good), this is less important than their having a high specificity (low FPR), since the latter minimizes the risk of incorrectly predicting (and acting upon) a poor prognosis in a potentially viable patient.
In most neuroprognostic studies, as in prognostic studies in general, the treating team is aware of the results of the prognostic tests under investigation. Consequently, these results may affect their treating decisions, leading to a self-fulfilling prophecy bias that may overestimate the specificity of prognostic tests in predicting poor outcome. This bias contributes to the low certainty of the evidence of most neuroprognostic studies after cardiac arrest. For that reason, the ILCOR 2020 Consensus for this PICOST is that the decision to limit treatment of comatose post–cardiac arrest patients should never rely on a single prognostication element. The consensus of the task force was that in patients who remain comatose in the absence of confounders (eg, sedative drugs), a multimodal approach should be used, with all supplementary tests considered in the context of the clinical examination.
For further details on the methodology and interpretation of prognostic tests see Geocadin RG, Callaway CW, Fink EL, Golan E, Greer DM, Ko NU, Lang E, Licht DJ, Marino BS, McNair ND, Peberdy MA, Perman SM, Sims DB, Soar J, Sandroni C; American Heart Association Emergency Cardiovascular Care Committee. Standards for Studies of Neurological Prognostication in Comatose Survivors of Cardiac Arrest: A Scientific Statement From the American Heart Association. Circulation. 2019 Aug 27;140(9):e517-e542.).

Reference list: ***(List by ILCOR ref standard (last name first author, year of publication, first page number) and insert hyperlink to all articles identified as relevant (if available on PubMed)***

Admiraal M, Resuscitation 2025 Aug 7:215:110762. https://pubmed.ncbi.nlm.nih.gov/40783100/
Benghanem S, Resuscitation 2025 Aug 6:110757. https://pubmed.ncbi.nlm.nih.gov/40780697/
Czimmeck C, Resuscitation 2025 Aug:213:110650. https://pubmed.ncbi.nlm.nih.gov/40409670/

Shivji Z, Brain Sci 2024 Dec 17;14(12):1264. https://pubmed.ncbi.nlm.nih.gov/39766463/
Scarpino M, Resuscitation 2025 Sep 4:110801. https://pubmed.ncbi.nlm.nih.gov/40914341/

2026 Evidence Update

ALS 3513 – Prognostication Clinical Examination

Worksheet author(s): Claudio Sandroni, Sonia D'Arrigo
External Collaborator (data extraction and management): Sofia Cacciola
Task Force: ALS
Date Submitted to SAC rep for peer review and approval: September 10, 2025
SAC rep: Eric Lavonas

PICOST / Research Question:
Population: Adults who are comatose after resuscitation from cardiac arrest (either in-hospital or out-of-hospital), regardless of target temperature.
Interventions: index tests based on clinical examination
Comparison: none.
Outcomes: poor neurological outcome, defined as **Cerebral Performance Categories (CPC) 3-5** or Glasgow Outcome Scale (GOS) 1-3, or modified Rankin Score (mRS) 4-6 at hospital discharge/1 month or later.
Study designs: Prognostic accuracy studies where the 2x2 contingency table (ie, 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 fewer than 10 patients, letters, editorials, conference abstracts, and studies published in abstract form were excluded.

Year of last full review: 2020

Current ILCOR Consensus on Science and Treatment Recommendation for this PICOST: COSTR 2024
We recommend that neuroprognostication always be undertaken by using a multimodal approach because no single test has sufficient specificity to eliminate false positives (strong recommendation, very low-certainty evidence).
We suggest using PLR at 72 hours or more after ROSC for predicting neurological outcome of adults who are comatose after cardiac arrest (weak recommendation, very low-certainty evidence).
We suggest using quantitative pupillometry at 72 hours or more after ROSC for predicting neurological outcome of adults who are comatose after cardiac arrest (weak recommendation, low-certainty evidence).
We suggest using bilateral absence of corneal reflex at 72 hours or more after ROSC for predicting poor neurological outcome in adults who are comatose after cardiac arrest (weak recommendation, very low-certainty evidence).
We suggest using presence of myoclonus or status myoclonus within 7 days after ROSC, in combination with other tests, for predicting poor neurological outcome in adults who are comatose after cardiac arrest (weak recommendation, very low-certainty evidence). We also suggest recording EEG in the presence of myoclonic jerks to detect any associated epileptiform activity (weak recommendation, very low-certainty evidence).

Database searched: PubMed. The references of full-text articles were screened for additional studies.

Time Frame: (existing PICOST) –April 2024 (last EvUp) to Aug 2025
Date Search Completed: Aug 31, 2025
Search Results (Number of articles identified and number identified as relevant): 25/4

Summary of Evidence Update:
This update identified **4 relevant studies** that were not included in the 2024 ILCOR evidence update.

Regarding **clinical examination**, three studies (Bae 2025, Beekman 2025, Scarpino 2025) assessed the absence of **standard pupillary light reflex (PLR) immediately after ROSC or within 6 h** as a predictor of poor neurological

outcome at hospital discharge, showing a specificity ranging from **82 [68-91]%** to **100 [93-100]%** and sensitivity ranging from **44 [31-59]%** to **88 [77-94]%.**
None of the included studies were designed to investigate PLR as the primary endpoint of the study.

Automated pupillometry showed greater specificity for predicting poor neurological outcomes compared to standard PLR. Only one study (Nyholm 2024) in 710 patients performed an external validation. The proposed thresholds for neurological pupil index (NPi) and quantitative pupillary light reflex (qPLR) were ≤2 and <4%, respectively. An **NPi ≤2 measured at admission and 48 h** predicted poor neurological outcome at 3 months with **100 [99-100]% specificity** and **10 [8-13]% and 9 [7-12]% sensitivity**, respectively. **A qPLR <4% measured at admission and 48 h** predicted poor neurological outcome at 3 months with **95 [93-96]% and 99.7 [98.6-100]% specificity** and **31 [27-34]% and 21 [17-24]% sensitivity,** respectively.

Corneal reflex (CR) was evaluated in one study (Bae 2025), where CR accuracy was not the primary endpoint. The **absence of CR measured immediately after ROSC** predicted poor neurological outcome at hospital discharge with **46 [31-62]% specificity** and **92 [78-98]% sensitivity.**

One study (Scarpino 2025) evaluated the accuracy of status myoclonus in 65 patients, showing that its presence within 6 h after ROSC predicted poor neurological outcome at hospital discharge with 100 [93-100]% specificity and 21 [12-33]% sensitivity.

Relevant Guidelines or Systematic Reviews: none

RCT: none

Nonrandomized Trials, Observational Studies

Study Acronym; Author; Year Published	**Study Type/Design; Study Size (N)**	**Patient Population**	**Primary Endpoint and Results (include P value; OR or RR; & 95% CI)**	**Summary/Conclusion Comment(s)**
Pupillary Light Reflex (PLR)				
Bae et al. 2025	**Study Type:** retrospective study of prospectively collected data. Fifty-one patients were included in the study. PLR was measured in all patients.	**Inclusion Criteria:** adult CA survivors treated with TTM and underwent brain CT within 2 h and brain MRI within 3 days of ROSC. **Exclusion criteria:** brain edema due to acute intracerebral hemorrhage and previous strokes, acquired CT images technically unsuitable for fusion with MRI, patients with a	The PLR accuracy was not the primary endpoint of the study. **1° endpoint:** validate the prognostic value of the GWR measured by MRI-based CT structures compared to conventional measures in adult patients after cardiac arrest. **Results:** the **absence of PLR measured immediately after ROSC** predicted poor neurological outcome at	The absence of PLR immediately after ROSC predicted poor neurological outcome at hospital discharge with 82% specificity and 44% sensitivity.

		pre-cardiac arrest CPC score of 3 or 4.	hospital discharge with **82 [68-91]% specificity** and **44 [31-59]% sensitivity**.	
Beekman et al. 2025	**Study Type:** retrospective, single-center study. Three hundred eighty-two patients were included in the study. PLR was measured in all patients.	**Inclusion Criteria:** OHCA, age ≥ 18 years, sustained ROSC, and admission to an ICU following ROSC. **Exclusion criteria:** missing pupil size data, inconsistent pupil size documentation, bilateral surgical pupils.	The PLR accuracy was not the primary endpoint of the study. **1° endpoint:** brain death/death based on neurologic criteria. **2° endpoint:** the association between pupil size and reactivity immediately following ROSC and neurological outcome and mortality at hospital discharge. **Results:** the **absence of PLR measured immediately after ROSC** predicted poor neurological outcome at hospital discharge with **94 [91-96]% specificity** and **60 [55-65]% sensitivity**.	The absence of visually-assessed (non-quantitative) PLR immediately after ROSC predicted poor neurological outcome at hospital discharge with 94% specificity and 60% sensitivity.
Scarpino et al. 2025	**Study Type:** Prospective single-centre study. Sixty-five patients were included in the study. PLR was performed in all patients.	**Inclusion Criteria:** Consecutive comatose adult patients (GCS<8) who received the first multimodal prognostic evaluation within 6 hours after CA, as well as the NSE dosage within 12 hours after CA. **Exclusion criteria:** traumatic or neurological causes of CA, pre-existing neurological disability, regain of consciousness or death before neurophysiological tests.	The PLR accuracy was not the primary endpoint of the study. **1° endpoint:** the accuracy of short- and middle-latency SSEPs recorded within 6 hours of ROSC in predicting both poor (CPC 3–5) and good (CPC 1–2) neurological outcomes at hospital discharge. **2° endpoint:** to evaluate the prognostic accuracy of other ERC-ESICM predictors. **Results:** the **absence of PLR within 6 h after ROSC** predicted poor neurological outcome at hospital discharge with **100 [93-100]% specificity** and **88 [72-96]% sensitivity**.	The absence of PLR within 6h after ROSC predicted poor neurological outcome at hospital discharge with 100% specificity and 88% sensitivity.
Corneal Reflex (CR)				

Bae et al. 2025	**Study Type:** retrospective study of prospectively collected data Fifty-one patients were included in the study. PLR was measured in all patients.	**Inclusion Criteria:** adult CA survivors treated with TTM and underwent brain CT within 2 h and brain MRI within 3 days of return of ROSC. **Exclusion criteria:** brain edema due to acute intracerebral hemorrhage and previous strokes, acquired CT images technically unsuitable for fusion with MRI, patients with a pre-cardiac arrest CPC score of 3 or 4.	The CR accuracy was not the primary endpoint of the study. **1° endpoint:** to validate the prognostic value of the GWR measured by MRI-based CT structures compared to conventional measures in adult patients after cardiac arrest. **Results:** the **absence of CR measured immediately after ROSC** predicted poor neurological outcome at hospital discharge with **46 [31-62]% specificity** and **92 [78-98]% sensitivity**.	The absence of CR immediately after ROSC predicted poor neurological outcome at hospital discharge with 46% specificity and 92% sensitivity.
Pupillometry: Neurological Pupil index (NPi)				
Nyholm et al. 2024	**Study Type:** prospective, multi- center prognostic sub-study within the Blood Pressure and Oxygenation Targets after Cardiac Arrest (BOX) trial. Seven hundred and ten patients were included in the study. NPi was measured in all patients included.	**Inclusion Criteria:** Age ≥18 years, OHCA of presumed cardiac cause, sustained ROSC, GCS <8 after sustained ROSC. **Exclusion criteria:** conscious patients, IHCA, OHCA of presumed non-cardiac cause, suspected or confirmed acute intracranial bleeding or acute stroke, unwitnessed asystole, DNR order, known pre-arrest CPC 3 or 4.	**1° endpoint:** to perform an external validation with a similar methodology of the previous studies proposing pupillometry thresholds of qPLR <4% and NPi ≤2, shown to predict unfavorable outcomes from admission to 72 h with 0% FPR in comatose OHCA survivors. **Results:** **Npi ≤2 measured at admission and 48 h** predicted poor neurological outcome at 3 months with **100 [99-100]% specificity** and **10 [8-13]% and 9 [7-12]% sensitivity**, respectively.	An NPi value ≤2 at admission and 48 h after ROSC predicted a poor neurological outcome at 3 months with 100% specificity but very low sensitivity.
Pupillomentry: Quantitative Pupillary Light Reflex (qPLR)				
Nyholm et al. 2024	**Study Type:** prospective, multi- center prognostic sub-study within the Blood Pressure and Oxygenation	**Inclusion Criteria:** Age ≥18 years, OHCA of presumed cardiac cause, sustained ROSC, GCS < 8 after sustained ROSC. **Exclusion criteria:**	**1° endpoint:** to perform an external validation with a similar methodology of the previous studies proposing pupillometry thresholds of qPLR <4% and NPi ≤2, shown to predict	A qPLR <4% at admission and 48 h after ROSC predicted a poor neurological outcome at 3 months with 95% and 99.7% specificity, respectively.

	Targets after Cardiac Arrest (BOX) trial. Seven hundred and ten patients were included in the study. qPLR was measured in all patients included at admission and in 543 patients at 48 h.	conscious patients, IHCA, OHCA of presumed non-cardiac cause, suspected or confirmed acute intracranial bleeding or acute stroke, unwitnessed asystole, Do Not Resuscitate-order, known pre-arrest CPC 3 or 4.	unfavorable outcomes from admission to 72 h with 0% FPR in comatose OHCA survivors. **Results:** **qPLR <4% measured at admission and 48 h** predicted poor neurological outcome at 3 months with **95 [93-96]% and 99.7 [98.6-100]% specificity** and **31 [27-34]% and 21 [17-24]% sensitivity,** respectively.	The sensitivity was low at both time points.
Status myoclonus				
Scarpino et al. 2025	**Study Type:** Prospective single-center study. Six-five patients were included in the study.	**Inclusion Criteria:** Consecutive comatose adult patients (GCS<8) who received the first multimodal prognostic evaluation within 6 hours after CA, as well as the NSE dosage within 12 hours after CA. **Exclusion criteria:** traumatic or neurological causes of CA, pre-existing neurological disability, regain of consciousness or death before neurophysiological tests.	The accuracy of status myoclonus was not the study's primary endpoint. **1° endpoint:** the accuracy of short- and middle-latency SSEPs recorded within 6 hours of ROSC in predicting both poor (CPC 3–5) and good (CPC 1–2) neurological outcomes at hospital discharge. **2° endpoint:** to evaluate the prognostic accuracy of other ERC-ESICM predictors. **Results:** The presence of status myoclonus within 6h after ROSC predicted poor neurological outcome at hospital discharge with 100 [93-100]% specificity and 21 [12-33]%	The presence of status myoclonus within 6 h after ROSC predicted poor neurological outcomes with 100% specificity and 21% sensitivity.

Reviewer Comments: *(including whether this PICOST should have a systematic or scoping review*)
The fours studies included in this evidence update largely confirmed the results of both the ILCOR 2024 evidence update and the 2020 systematic review. The only study assessing corneal reflex (CR) showed that CR has low specificity for predicting poor outcome immediately after cardiac arrest. However, this early timing is not recommended by the current guidelines.
Four studies assessed pupillary light reflex (PLR) immediately or within 6 h after ROSC. Results showed that specificity was highest (100%), with low sensitivity, for the pupillometry-assessed NPi index, followed by the pupillometry-assessed qPLR index (95% specificity) and visually assessed, non-quantitative PLR (94% specificity). Unlike pupillometry-based indices, visual PLR assessment is operator-dependent. The ability of quantitative pupillometry to yield 100% specificity from day 1 after cardiac arrest is in line with previous multicentre studies (Oddo et al, 2018).

The task force is planning an updated systematic review on all modalities for neuroprognostication in the near future

Note on the interpretation of test results

Neuroprognostic tests used in patients who are comatose after resuscitation from cardiac arrest measure the severity of brain injury. An abnormal response from these tests may be classified as "positive," and a normal response as "negative," or vice versa, depending on the prognostic perspective taken. Usually, as in this evidence review, a positive result of these tests indicates that the outcome of that patient will be poor. If this occurs, the prediction is correct, and the test result is a true positive. Conversely, if the outcome is good, the positive test result is a false positive. In this context, the false-positive rate (FPR) of a test is the proportion of patients with good outcome who are assigned a falsely pessimistic prediction. In other words, the FPR is the number of false positives divided by the total number of patients with a good outcome. FPR is also the complement of specificity, i.e., 100% − specificity. Therefore, a test with 100% specificity has 0% FPR. Ideally, all neuroprognostic tests predicting poor outcome should yield 100% specificity. While neuroprognostic tests predicting outcome should also ideally offer a reasonably high sensitivity when "negative" (in this case indicating that the outcome of the patient will be good), this is less important than their having a high specificity (low FPR), since the latter minimizes the risk of incorrectly predicting (and acting upon) a poor prognosis in a potentially viable patient.

In most neuroprognostic studies, as in prognostic studies in general, the treating team is aware of the results of the prognostic tests under investigation. Consequently, these results may affect their treating decisions, leading to a self-fulfilling prophecy bias that may overestimate the specificity of prognostic tests in predicting poor outcome. This bias contributes to the low certainty of the evidence of most neuroprognostic studies after cardiac arrest. For that reason, the ILCOR 2020 Consensus for this PICOST is that The decision to limit treatment of comatose post–cardiac arrest patients should never rely on a single prognostication element. The consensus of the task force was that in patients who remain comatose in the absence of confounders (eg, sedative drugs), a multimodal approach should be used, with all supplementary tests considered in the context of the clinical examination.

For further details on the methodology and interpretation of prognostic tests see Geocadin RG, Callaway CW, Fink EL, Golan E, Greer DM, Ko NU, Lang E, Licht DJ, Marino BS, McNair ND, Peberdy MA, Perman SM, Sims DB, Soar J, Sandroni C; American Heart Association Emergency Cardiovascular Care Committee. Standards for Studies of Neurological Prognostication in Comatose Survivors of Cardiac Arrest: A Scientific Statement From the American Heart Association. Circulation. 2019 Aug 27;140(9):e517-e542.).

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2026 Evidence Update

ALS 3512 (Part 1) – Prognostication Biomarkers NfL

Worksheet author(s): Claudio Sandroni, Sonia D'Arrigo
External Collaborator (data extraction and management): Sofia Cacciola
Task Force: ALS
Date Submitted to SAC rep for peer review and approval: September 10, 2025
SAC rep: Eric Lavonas

PICOST / Research Question:
Population: Adults who are comatose after resuscitation from cardiac arrest (either in-hospital or out-of-hospital), regardless of target temperature.
Interventions: index test based on biomarkers: **neurofilament light chain (NfL)**
Comparison: none.
Outcomes: poor neurological outcome, defined as Cerebral Performance Categories (CPC) 3-5 or Glasgow Outcome Scale (GOS) 1-3, or modified Rankin Score (mRS) 4-6 at hospital discharge/1 month or later.
Study designs: Prognostic accuracy studies where the 2x2 contingency table (ie, 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 fewer than 10 patients, letters, editorials, conference abstracts, and studies published in abstract form were excluded.

Year of last full review: 2020

Current ILCOR Consensus on Science and Treatment Recommendation for this PICOST:
We suggest against using serum levels of glial fibrillary acidic protein, serum tau protein, or neurofilament light chain for predicting poor neurological outcome of adults who are comatose after cardiac arrest (weak recommendation, very low-certainty evidence).

Database searched: PubMed. The references of full-text articles were screened for additional studies.

Time Frame: (existing PICOST) –Apr 2024 (last EvUp) to Aug 2025
Date Search Completed: Aug 31, 2025
Search Results (Number of articles identified, and number identified as relevant): 24/3

Summary of Evidence Update:
Three studies evaluated the ability of blood levels of NfL measured between 24h and 72h after ROSC to predict poor neurological outcome in comatose patients after CA (Ayasse 2025, Czimmeck 2025, Meyer 2025). Two studies (Ayasse 2025, Meyer 2025), which included a total of 590 patients, investigated NfL at 24 hours **after ROSC**. In these studies, NfL levels of 1121 pg/mL and 5811 pg/mL predicted poor neurological outcome at 3 and 12 months, respectively, with a specificity of 100% (95% CIs 93-100% and 99-100%, respectively). The corresponding sensitivities were 14[7-26]% and 41[37-45]%, respectively.

The study from Ayasse et al (Ayasse 2025) also investigated NfL **48 hours after ROSC** in 48 patients. In that study, NfL levels of 1324 pg/mL predicted poor neurological outcome at 3 months with a specificity of 100 [91-100]%, and sensitivity of 56 [41-70]%. The same study (Ayasse 2025) investigated NfL **72h after ROSC** in 35 patients. In that study, NfL levels of 510 pg/mL predicted poor neurological outcome at 3 months with a specificity of 100 [88-100]%, respectively, and 74 [56-87]% sensitivity.

The study by Ayasse et al. also reported the optimal threshold, defined as the one that balances optimised sensitivity with a specificity greater than 90%. Optimised sensitivity was not defined in the study. These thresholds were 250 pg/mL, 383 pg/mL, and 406 pg/mL at 24h, 48h, and 72h, respectively. The corresponding specificities were 90[75-90]%, 94[82-98]%, and 92[76-98]%, respectively.

One study (Czimmeck, 2025) in 152 patients investigated NfL **at 1-4 days after ROSC**. NfL levels more than 2000 pg/mL predicted poor neurological outcome at hospital discharge with 100 [97-100]% specificity and 53 [45-61]% sensitivity.

Relevant Guidelines or Systematic Reviews: none

RCT: none

Nonrandomized Trials, Observational Studies published Apr 30, 2024 to Aug 31, 2025

Study Acronym; Author; Year Published	**Study Type/Design; Study Size (N)**	**Patient Population**	**Primary Endpoint and Results (include P value; OR or RR; & 95% CI)**	**Summary/Conclusion Comment(s)**
Ayasse et al. 2025	**Study Type:** prospective, monocentric study. Sixty-seven patients were included in the study. NfL was measured in all patients.	**Inclusion Criteria:** GCS<8 at ICU admission after an IHCA or OHCA and who had at least one serum NfL level measurement at 24, 48 and/or 72 h after ROSC. **Exclusion criteria:** age < 18 years, established brain death.	**1° endpoint:** to evaluate the prognostic value of NfL measured at 24, 48 and 72 h after CA for predicting unfavorable and favorable neurological outcome. **2° endpoint:** to assess the prognostic value of NfL trends over time for predicting outcomes; to compare the prognostic accuracy of NFL and NSE. **Results: NfL > 1121 pg/mL at 24 h, NfL >1324 pg/mL at 48 h and NfL >510 pg/mL at 72 h** after CA predicted poor neurological outcome at 3 months with **100% specificity** and **14 [7-25]%, 56 [41-70]% and 74 [56-87]% sensitivity, respectively**.	NfL levels >1121 ng/mL at 24h, >1324 pg/mL at 48h and >510 pg/mL at 72h predicted poor neurological outcome with high specificity (100%) and moderate sensitivity (56% and 74%, respectively). Confidence intervals were wide, due to the small study sample. Unlike NSE, the NfL value trend between 24h and 72h did not predict functional outcome. The authors used the Lumipulse G600 chemiluminescent enzyme immunoassay (CLEIA) by Fujirebio to measure NFL. This assay has been utilised in clinical

			An NfL increase was not associated with neurological outcomes (AUC 0.50), whereas an increase of NSE measured between 24 and 72 h predicted poor outcome with an AUC of 0.92.	studies involving patients with multiple sclerosis, demonstrating str ong agreement with the SIMOA platform. Validat ed reference ranges for routine clinical use are still lacking. The assay is not explicitly labelled as diagnostic, suggesting it is still in the research or pre-clinical validation phase. NSE was measured using the Cobas® immunochemiluminescent El ecsys assay.
Czimme ck et al. 2025	**Study Type:** retrospective, monocentric observational study. One-hundred and fifty-two patients were included in the study. NfL was measured in all patients.	**Inclusion Criteria:** OHCA and IHCA patients with serum NfL testing within 24–96 h after CA. **Exclusion criteria:** N/A	**1° endpoint:** to evaluate NfL as a biomarker for neuroprognostication afte r CA. **2° endpoint:** to compare NfL to established pr ognostication methods. **Results:** **NfL >2000 pg/mL at Days 1-4** after CA predicted poor neurological outcome (CPC 4-5) at hospital discharge with **100 [97-100] % specificity** and **53 [45-61] % sensitivity**.	NfL levels above 2000 pg/mL at Days 1-4 after CA predicted poor neurological outcome (CPC 4-5) at hospital discharge with 100% specificity and moderate sensitivity. The NfL threshol d was pre-defined. The authors used the Quanterix SIMOA assay for measuring NfL. This assay is for research use only. The timing of NfL measurement was only reported as a range. The use of a 4-5 CPC threshold instead of 3-5 CPC for defining poor neurological outcome prevents a direct comparison with the outcome of other studies.
Meyer et al. 2025	**Study Type:** Sub-study of the prospective randomise d controlled BOX trial (Blood Pressure and Oxygenation targets in post-resuscitation care).	**Inclusion Criteria:** Adult OHCA with p resumed cardiac cause of the arrest, and coma at admission. **Exclusion criteria:** N/A	**1° endpoint:** to validate the NfL cut-offs previously suggested by Moseby-Knappe et al. 2019 for predicting poor functional outcome (1232 pg/ ml at 24h and 1539 pg/ml at 48h after CA).	The assay used by the authors (MSD ELISA QuickPlex) differed from the Quanterix SIMOA assay used by Moseby-Knappe et al. This may have contributed to differences in accuracy of the cut-offs used in the

	Six thousand and thirty-eight patients were included in the analysis. 523 were included at 24 h. NfL was measured in all patients, at least once at 24 or 48h.		**<u>Results:</u>** At 24 h, a cut-off of 1232 pg/mL had a specificity of 98 [96-99]%, for prediction of poor neurologic outcome. False-positive results occurred in 7 patients (1.4%). In a sensitivity analysis, the **NfL cut-off levels at 24 h** after CA, **corresponding to a specificity of 100%, 99% and 98%** for predicting poor neurological outcome at 1 year were **5811 pg/mL, 4372 pg/mL and 1966 pg/mL** respectively. Sensitivity ranged from 41% to 66%.	two studies. Both QuickPlex and SIMOA assays are for research use only. The authors measured NfL at 48h as well. However, 311/638 patients (49%) were awake at 48h. For this reason, we included only accuracy data at 24h. The authors reported AUROCs of 0.96 (0.94–0.98) in the subpopulation of patients who did not awake by 48 h (n=300), but did not report the relevant contingency table.

Reviewer Comments: *(including whether this PICOST should have a systematic or scoping review*)

There is considerable heterogeneity in the methodologies employed for neurofilament light chain (NfL) quantification across studies, ranging from ELISA to ultra-sensitive platforms such as SIMOA (Single Molecule Array). This heterogeneity might have led to significant variation in NfL measured levels, thereby preventing direct comparisons between studies.

One of the three included studies assessed NfL over a wide temporal range, from days 1 to 4 after CA. The authors of that study evaluated the ability of NfL to predict a CPC 4-5, therefore including awakening with severe neurological disability (CPC 3) among good functional outcomes. This prevents a direct comparison with the vast majority of neuroprognostic studies, which use a CPC 3-5 threshold. From the accuracy standpoint, using a CPC 4-5 instead of a CPC 3-5 threshold for defining poor outcome is likely to increase the NfL threshold for poor outcome prediction and reduce measured sensitivity, all other things being equal.

Limited evidence suggests that NfL and NSE have distinct kinetic profiles. NfL levels show a sustained increase following HIBI, possibly reflecting axonal degeneration over time, whereas NSE levels decrease more rapidly than NfL.

The task force is planning an updated systematic review on all modalities for neuroprognostication in the near future.

Note on the interpretation of test results

Neuroprognostic tests used in patients who are comatose after resuscitation from cardiac arrest measure the severity of brain injury. An abnormal response from these tests may be classified as “positive,” and a normal response as “negative,” or vice versa, depending on the prognostic perspective taken. Usually, as in this evidence review, a positive result of these tests indicates that the outcome of that patient will be poor. If this occurs, the prediction is correct, and the test result is a true positive. Conversely, if the outcome is good, the positive test result is a false positive. In this context, the false-positive rate (FPR) of a test is the proportion of patients with good outcome who are assigned a falsely pessimistic prediction. In other words, the FPR is the number of false positives divided by the total number of patients with a good outcome. FPR is also the complement of specificity, i.e., 100% − specificity. Therefore, a test with 100% specificity has 0% FPR. Ideally, all neuroprognostic tests predicting poor outcome should yield 100% specificity. While neuroprognostic tests predicting outcome should

also ideally offer a reasonably high sensitivity when “negative” (in this case indicating that the outcome of the patient will be good), this is less important than their having a high specificity (low FPR), since the latter minimizes the risk of incorrectly predicting (and acting upon) a poor prognosis in a potentially viable patient.
In most neuroprognostic studies, as in prognostic studies in general, the treating team is aware of the results of the prognostic tests under investigation. Consequently, these results may affect their treating decisions, leading to a self-fulfilling prophecy bias that may overestimate the specificity of prognostic tests in predicting poor outcome. This bias contributes to the low certainty of the evidence of most neuroprognostic studies after cardiac arrest. For that reason, the ILCOR 2024 Consensus for this PICOST is that the decision to limit treatment of comatose post–cardiac arrest patients should never rely on a single prognostication element. The consensus of the task force was that in patients who remain comatose in the absence of confounders (eg, sedative drugs), a multimodal approach should be used, with all supplementary tests considered in the context of the clinical examination.

Notes on the interpretation of biomarkers
Unlike the results of other neuroprognostic tests (e.g., clinical examination), biomarker blood levels are continuous rather than dichotomous (categorical) variables. Results are dichotomised to calculate the sensitivity and specificity of these biomarkers by establishing a threshold that divides positive from negative results. Consequently, test sensitivity and specificity depend on the threshold chosen: a high threshold increases the specificity of the test and decreases the sensitivity, and vice versa.
The kinetics of NfL after cardiac arrest are only incompletely known but are likely different from those of NSE. An important source of confounding for NfL is the presence of different assays, which can yield varying results across measurement methods. Moreover, all studies included in this and previous Evidence Updates employed NfL assays that are for research use only.
An important advantage of biomarkers is that – unlike other outcome predictors after cardiac arrest – they can be easily assessed in a blinded fashion, therefore reducing the risk of a self-fulfilling prophecy bias.
For further details on the methodology and interpretation of prognostic tests see Geocadin RG, Callaway CW, Fink EL, Golan E, Greer DM, Ko NU, Lang E, Licht DJ, Marino BS, McNair ND, Peberdy MA, Perman SM, Sims DB, Soar J, Sandroni C; American Heart Association Emergency Cardiovascular Care Committee. Standards for Studies of Neurological Prognostication in Comatose Survivors of Cardiac Arrest: A Scientific Statement From the American Heart Association. Circulation. 2019 Aug 27;140(9):e517-e542.).

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Meyer MAS, Crit Care 2025 Aug 6;29(1):348. https://pubmed.ncbi.nlm.nih.gov/40770665/

2026 Evidence Update

ALS 3512 (Part 2) – Prognostication Biomarkers NSE

Worksheet author(s): Claudio Sandroni, Sonia D'Arrigo
External Collaborator (data extraction and management): Sofia Cacciola
Task Force: ALS
Date Submitted to SAC rep for peer review and approval: September 10, 2025
SAC rep: Eric Lavonas

PICOST / Research Question:
Population: Adults who are comatose after resuscitation from cardiac arrest (either in-hospital or out-of-hospital), regardless of target temperature.
Interventions: index test based on biomarkers: **neuron-specific enolase (NSE)**
Comparison: none.
Outcomes: poor neurological outcome, defined as Cerebral Performance Categories (CPC) 3-5 or Glasgow Outcome Scale (GOS) 1-3, or modified Rankin Score (mRS) 4-6 at hospital discharge/1 month or later.
Study designs: Prognostic accuracy studies where the 2x2 contingency table (ie, 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 fewer than 10 patients, letters, editorials, conference abstracts, and studies published in abstract form were excluded.

Year of last full review: 2020

Current ILCOR Consensus on Science and Treatment Recommendation for this PICOST:
We suggest using NSE within 72 hours after ROSC, in combination with other tests, for predicting neurological outcome of adults who are comatose after cardiac arrest (weak recommendation, very low-certainty evidence).

Database searched: PubMed. The references of full-text articles were screened for additional studies.

Time Frame: (existing PICOST) –Apr 2024 (last EvUp) to Aug 2025
Date Search Completed: Aug 31, 2025
Search Results (Number of articles identified, and number identified as relevant): 25/3

Summary of Evidence Update:
This update identified **3 relevant studies** that were not included in the 2024 ILCOR evidence update (Benghanem 2025, Czimmeck 2025, Scarpino 2025).

One study (Scarpino 2025) in 65 patients evaluated the ability of NSE measured within 12 h after ROSC, showing that an NSE higher than **60 mcg/L** predicted poor neurological outcome at hospital discharge with 100 [93-100]% specificity and 67 [54-78]% sensitivity. Two studies evaluated the ability of **NSE** blood levels **at 48-72 h after ROSC** to predict poor neurological outcome in comatose patients after CA (Benghanem 2025, Czimmeck 2025). One study (Benghanem 2025) in 966 patients investigated **NSE at 48 h after ROSC**, showing that **NSE levels >60 mcg/L** predicted poor neurological outcome at 3 months with 98 [97-99] % specificity and 52 [49-55] % sensitivity. The other study (Czimmeck 2025) in 114 patients showed that **NSE levels >90 mcg/L at 48-72 h** after CA predicted poor neurological outcome at hospital discharge with **100[96-100] % specificity** and **56 [46-65] % sensitivity**.

Relevant Guidelines or Systematic Reviews: none

RCT: none

Nonrandomized Trials, Observational Studies

Study Acronym; Author; Year Published	**Study Type/Design; Study Size (N)**	**Patient Population**	**Primary Endpoint and Results (include P value; OR or RR; & 95% CI)**	**Summary/Conclusion Comment(s)**
Benghanem et al. 2025	**Study Type:** cohort study analysing two prospective registries. Nine hundred sixty-six patients were included in the study. NSE was measured in all patients.	**Inclusion Criteria:** comatose adult patients who had at least a serum NSE measurement at 48 hours and an EEG ≥ 24 hours after CA. **Exclusion criteria:** N/A	**1° endpoint:** to examine the relationship between markers of brain injury (NSE and EEG patterns) obtained in early post-resuscitation period and the subsequent degree of neurological recovery. **Results:** **NSE >60 mcg/L at 48 h** after CA predicted poor neurological outcome at 3 months with **98 [97-99] % specificity** and **52 [49-55] % sensitivity**.	NSE >60 mcg/L at 48 h after CA predicted poor neurological outcome at 3 months with high specificity and moderate sensitivity.
Czimmeck et al. 2025	**Study Type:** retrospective, single-centre observational study. One-hundred and fifty-two patients were included. NSE was measured in 114 patients.	**Inclusion Criteria:** adult out-of-hospital (OHCA) and in-hospital-CA (IHCA) patients with serum NFL testing within 24–96 h after CA **Exclusion criteria:** N/A	The NSE accuracy was not the primary endpoint of the study. **1° endpoint:** to evaluate NfL as a biomarker for neuroprognostication after CA in clinical routine. **2° endpoint:** to compare NFL to established prognostication methods. **Results:** **NSE >90 mcg/L at 48-72 h** after CA predicted poor neurological outcome at hospital discharge with **100 [96-100] % specificity** and **56 [46-65] % sensitivity**.	NSE >90 mcg/L at 48-72 h after CA predicted poor neurological outcome (**CPC 4-5**) at hospital discharge with 100% specificity and moderate sensitivity.
Scarpino et al. 2025	**Study Type:**	**Inclusion Criteria:**	The NSE accuracy was not the primary endpoint of the study.	NSE >60 mcg/L within 12 h after CA predicted

	Prospective single-centre study. Sixty-five patients were included in the study. NSE was measured in all patients.	Consecutive comatose adult patients (GCS<8) who received the first multimodal pro gnostic evaluation within 6 hours after CA, as well as the NSE dosage within 12 hours after CA. **Exclusion criteria:** traumatic or neurological causes of CA, pre-existing neurological disability, regain of consciousness or death before neurophysiological tests.	**1° endpoint:** the accuracy of short- and middle-latency SSEPs recorded within 6 hours of ROSC in predicting both poor (CPC 3–5) and good (CPC 1–2) neurological outcomes at hospital discharge. **2° endpoint:** to evaluate the prognostic accuracy of other ERC-ESICM predictors. **Results:** NSE > **60 mcg/L within 12 h** after ROSC predicted poor neurological outcome at hospital discharge with 100 [93-100]% specificity and 67 [54-78]% sensitivity.	poor neurological outcome at hospital discharge with high specificity and moderate sensitivity.

Reviewer Comments: *(including whether this PICOST should have a systematic or scoping review*)
We included only three studies in this evidence update, all confirmed that high NSE levels predict poor outcome with high specificity not only at 48 or 72h after ROSC, but also within 12 h. Two studies confirmed the 60 mcg/L threshold recommended by the European Resuscitation Council in 2021. The other study found a 90 mcg/L threshold for 100% specificity, but the definition of good functional outcome included severe neurological disability (CPC 3), which may have affected the NSE threshold.
The task force is planning an updated systematic review on all modalities for neuroprognostication in the near future.

Note on the interpretation of test results
Neuroprognostic tests used in patients who are comatose after resuscitation from cardiac arrest measure the severity of brain injury. An abnormal response from these tests may be classified as "positive," and a normal response as "negative," or vice versa, depending on the prognostic perspective taken. Usually, as in this evidence review, a positive result of these tests indicates that the outcome of that patient will be poor. If this occurs, the prediction is correct, and the test result is a true positive. Conversely, if the outcome is good, the positive test result is a false positive. In this context, the false-positive rate (FPR) of a test is the proportion of patients with good outcome who are assigned a falsely pessimistic prediction. In other words, the FPR is the number of false positives divided by the total number of patients with a good outcome. FPR is also the complement of specificity, i.e., 100% − specificity. Therefore, a test with 100% specificity has 0% FPR. Ideally, all neuroprognostic tests predicting poor outcome should yield 100% specificity. While neuroprognostic tests predicting outcome should also ideally offer a reasonably high sensitivity when "negative" (in this case indicating that the outcome of the patient will be good), this is less important than their having a high specificity (low FPR), since the latter minimizes the risk of incorrectly predicting (and acting upon) a poor prognosis in a potentially viable patient.
In most neuroprognostic studies, as in prognostic studies in general, the treating team is aware of the results of the prognostic tests under investigation. Consequently, these results may affect their treating decisions, leading to a self-fulfilling prophecy bias that may overestimate the specificity of prognostic tests in predicting poor outcome.

This bias contributes to the low certainty of the evidence of most neuroprognostic studies after cardiac arrest. For that reason, the ILCOR 2020 Consensus for this PICOST is that the decision to limit treatment of comatose post–cardiac arrest patients should never rely on a single prognostication element. The consensus of the task force was that in patients who remain comatose in the absence of confounders (eg, sedative drugs), a multimodal approach should be used, with all supplementary tests considered in the context of the clinical examination.

Notes on the interpretation of biomarkers

Unlike the results of other neuroprognostic tests (e.g., clinical examination), biomarker blood levels are continuous rather than dichotomous (categorical) variables. Results are dichotomized to calculate the sensitivity and specificity of these biomarkers by establishing a threshold that divides positive from negative results. Consequently, test sensitivity and specificity depend on the threshold chosen: a high threshold increases the specificity of the test and decreases the sensitivity, and vice versa.

Biomarkers are released with different latency and speed following acute brain injury. Although the kinetics of NSE after cardiac arrest is incompletely known, studies have shown that NSE blood levels increase up to 72h in patients with unfavourable outcome and tend to decrease in patients with favourable outcome (Martìnez-Losas P Rev Esp Cardiol (Engl Ed) 73(2): 123-130. https://www.ncbi.nlm.nih.gov/pubmed/30857978). Ryczek R, Kardiol Pol. 2021;79(5):546-553. https://pubmed.ncbi.nlm.nih.gov/34125928/)

NSE is released from red blood cells following haemolysis and from neuroendocrine tumours. Both these conditions may, therefore, cause falsely pessimistic predictions in patients resuscitated from cardiac arrest (Czimmeck C, Resuscitation 2023 Nov; 192:109964. https://pubmed.ncbi.nlm.nih.gov/37683997/). A final source of confounding for biomarkers is the presence of different assays, which may create different results across measuring methods (Rundgren M, BMC Research Notes 2014, 7:726. http://www.ncbi.nlm.nih.gov/pubmed/25319200).

An important advantage of biomarkers is that – unlike other outcome predictors after cardiac arrest – they can be easily assessed in a blinded fashion, reducing the risk of a self-fulfilling prophecy bias.

For further details on the methodology and interpretation of prognostic tests see Geocadin RG, Callaway CW, Fink EL, Golan E, Greer DM, Ko NU, Lang E, Licht DJ, Marino BS, McNair ND, Peberdy MA, Perman SM, Sims DB, Soar J, Sandroni C; American Heart Association Emergency Cardiovascular Care Committee. Standards for Studies of Neurological Prognostication in Comatose Survivors of Cardiac Arrest: A Scientific Statement From the American Heart Association. Circulation. 2019 Aug 27;140(9):e517-e542.).

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Benghanem S, Resuscitation 2025 Aug 6:110757. https://pubmed.ncbi.nlm.nih.gov/40780697/

Czimmeck C, Resuscitation 2025 Aug:213:110650. https://pubmed.ncbi.nlm.nih.gov/40409670/

Scarpino M, Resuscitation 2025 Sep 4:110801. https://pubmed.ncbi.nlm.nih.gov/40914341/

2026 Evidence Update

ALS 3510 (Part 1) – Prognostication Brain CT

Worksheet author(s): Claudio Sandroni, Sonia D'Arrigo
External Collaborator (data extraction and management): Sofia Cacciola
Task Force: ALS
Date Submitted to SAC rep for peer review and approval: September 10, 2025
SAC rep: Eric Lavonas

PICOST / Research Question:
Population: Adults who are comatose after resuscitation from cardiac arrest (either in-hospital or out-of-hospital), regardless of target temperature.
Intervention: **brain computed tomography (CT)**
Comparison: none
Outcomes: poor neurological outcome, defined as Cerebral Performance Categories (CPC) 3-5 or Glasgow Outcome Scale (GOS) 1-3, or modified Rankin Score (mRS) 4-6 at hospital discharge/1 month or later.
Study designs: Prognostic accuracy studies where the 2x2 contingency table (ie, 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 fewer than 10 patients, letters, editorials, conference abstracts, and studies published in abstract form were excluded.

Year of last full review: 2020

Current ILCOR Consensus on Science and Treatment Recommendation for this PICOST:
We suggest using GWR 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.

Database searched: PubMed. The references of full-text articles were screened for additional studies.

Time Frame: (existing PICOST) –Jul 2024 (prior EvUp) to Aug 2025
Date Search Completed: Aug 31, 2025
Search Results (Number of articles identified, and number identified as relevant): 25/4

Summary of Evidence Update:
This update identified **5 relevant studies** that were not included in the 2024 ILCOR evidence update.

Two studies evaluated the ability of the grey matter/white matter ratio (GWR) basal ganglia (BG) on brain CT after ROSC to predict poor neurological outcome in comatose survivors after CA (Czimmeck 2025, Scarpino 2025).

One study (Scarpino 2025) in 65 patients showed that a GWR <1.21 within 6 h after ROSC predicted poor neurological outcome at hospital discharge, with 100% specificity and 45% [28-63] sensitivity.
Another study (Czimmeck 2025) in 69 patients investigated **GWR-basal ganglia at 4 days after ROSC.** In that study, GWR-basal ganglia with a threshold value of 1.10 predicted poor neurological outcome (CPC 4-5) at hospital discharge with 100 [93-100]% specificity and 41 [30-54]% sensitivity. The lower GWR thresholds, compared with the other study, could be at least partly because only CPC 4 and 5 were considered as poor neurological outcomes in the Czimmeck study.

One study (Kenda 2024) in 81 patients assessed the ability of **net water uptake (NWU)** in different brain regions to predict neurological outcome after CA. NWU consists of changes in brain radiodensity over time, and it was calculated as the change in HU
between early and late CT for each anatomical region using the following formula: 1- (HU region late/HU region early), where HU are the Hounsfield units (HU). An NWU greater than 8% in either the caudate nucleus or in the putamen on brain CT performed at 24h-7 days (late) vs. within 6 h (early) predicted poor neurological outcome (CPC 4-5) with 100 [86-100]% specificity and 43 [31-56]% sensitivity (identical values for caudate nucleus and putamen). The area under the curve (AUC) for outcome prediction was 0.81 [0.71–0.90] for the caudate nucleus and 0.78 [0.69–0.88] for the putamen. Sensitivity was lower for thalamic NWU (25 [15–39]%) and pallidus NWU (19 [11–31]%). White matter NWU was not helpful to predict functional outcome (AUC 0.54 [0.40–0.68]).

One study (Lang 2025) evaluated in 140 patients the ability of five **qualitative (visually assessed) signs of hypoxic-ischemic injury on CT performed at 84 (66-109) hours** to predict poor neurological outcome at 6 months. The **loss of grey/white matter distinction** in the corona radiata and the high convexity area predicted poor neurological outcome with 100 [97-100]% specificity and 46 [37-54]% and 51 [42-59]% sensitivity, respectively. The **presence of sulcal effacement** in different regions (basal cisterns, basal ganglia, corona radiata and high convexity) predicted poor neurological outcome at 6 months with specificity ranging from 94 [89-97]% to 100 [97-100]% and sensitivity ranging from 29 [21-37]% and 49 [40-57]%. The **presence of the pseudo-subarachnoid haemorrhage** and **white cerebellum signs** predicted poor neurological outcome at 6 months with 100 [97-100]% specificity
and sensitivity of 8 [4-14]% and 11 [7-18]%, respectively. The **presence of signs of reversal** predicted poor neurological outcome at 6 months with 100 [97-100]% specificity and 9 [5-15]% sensitivity.

Relevant Guidelines or Systematic Reviews: none

RCTs: None

Nonrandomized Trials, Observational Studies

Study Acronym; Author; Year Published	**Study Type/Design; Study Size (N)**	**Patient Population**	**Primary Endpoint and Results (include P value; OR or RR; & 95% CI)**	**Summary/Conclusion Comment(s)**
Grey-White matter Ratio (GWR) - Basal Ganglia (BG)				
Czimmeck et al. 2025	**Study Type:** retrospective, monocentric observational study. One-hundred and fifty-two patients were included in the study. CT scan was performed in sixty-nine patients.	**Inclusion Criteria:** adult OHCA and in-hospital-CA (IHCA) patients with serum NfL testing within 24–96 h after CA. **Exclusion criteria:** N/A	The brain CT accuracy was not the primary endpoint of the study. **1° endpoint:** to evaluate NfL as a biomarker for neuroprognostication after CA in clinical routine. **2° endpoint:** to compare NfL to established prognostication methods. **Results:**	In comatose survivors after CA a GWR-BG <1.10 on brain CT performed on day 4 predicted poor neurological outcome (CPC 4-5) at hospital discharge with 100% specificity and moderate sensitivity.

			A GWR-BG <1.10 on CT performed on day 4 predicted poor neurological outcome (CPC 4-5) at hospital discharge **with 100 [93-100]% specificity and 41 [30-54]% sensitivity.**	
Scarpino et al. 2025	**Study Type:** Prospective single-centre study. Sixty-five patients were included in the study. Brain CT was performed in all patients.	**Inclusion Criteria:** Consecutive comatose (GCS<8) adult patients who were prognostically assessed within 6 hours after CA, except for the NSE, which was measured within 12 hours after CA. **Exclusion criteria:** traumatic or neurological causes of CA, pre-existing neurological disability, regain of consciousness or death before neurophysiological tests.	The brain CT accuracy was not the primary endpoint of the study. **1° endpoint:** the accuracy of short- and middle-latency SSEPs recorded within 6 hours of ROSC in predicting both poor (CPC 3–5) and good (CPC 1–2) neurological outcomes at hospital discharge. **2° endpoint:** the prognostic accuracy of other ERC-ESICM predictors. **Results:** GWR <1.21 within 6 h after ROSC predicted poor neurological outcome at hospital discharge with 100% specificity and 45 [28-63]% sensitivity.	In comatose survivors after CA a GWR <1.21 on brain CT performed within 6 h after ROSC predicted poor neurological outcome at hospital discharge with 100% specificity and moderate sensitivity.
Net Water Uptake (NWU)				
Kenda et al., 2024	**Study Type:** a multicentre observational study. Eighty-one patients were included in the derivation cohort of the study. CT scan was performed in all patients.	**Inclusion Criteria:** Adult, non-traumatic IHCA and OHCA, sustained ROSC, both received a first CT within the first 6 h after CA and a second CT between 24 h and 7 days after CA. **Exclusion criteria:** at least one image containing larger structural lesions that could confound image analysis, presence of residual contrast agent from previous coronary or CT-angiography.	**1° endpoint:** to use automated analysis of consecutive CT imaging to calculate net water uptake (NWU) in different brain regions and assess it as a prognostic marker after CA. **Results:** A NWU of greater than 8% in either the caudate nucleus or in the putamen on brain CT performed within 6 h (early) and at 24h-7 days (late) predicted poor neurological outcome (CPC 4-5) with 100 [86-100]% specificity and 43 [31-56]% sensitivity	In comatose survivors after CA a NWU >8% in different brain regions on early and late brain CT scan predicted poor neurological outcome (CPC 4-5) at hospital discharge with high specificity, but low sensitivity. The study showed that cytotoxic oedema at the

			(identical values for caudate nucleus and putamen). Sensitivity was lower for thalamic NWU (25 [15–39]%) and pallidum NWU (19 [11–31]%). Outcome prediction was not useful using white matter NWU (AUC 0.54 [0.40–0.68].	basal ganglia level increases between six hours and 24 hours – seven days after cardiac arrest. These changes do not occur at the level of the white matter.
Loss of Grey-White matter distinction				
Lang et al., 2025	**Study Type:** in-depth analysis of a prospective observational international sub-study within the TTM2 trial. One-hundred-forty patients were included in the study. CT scan was performed on all patients.	**Inclusion Criteria:** adult, unconscious (not obeying verbal commands) at 48 hours post cardiac arrest, CT >48 hours ≤7 days post-arrest. **Exclusion criteria:** no CT available, withdrawn consent, CT >7days and/or <48h after CA, technical requirements unfulfilled, large ischaemic lesion, intracranial haemorrhage, artefacts interfering with evaluation.	**1° endpoint:** to make improvements in interrater variability of a standardized qualitative CT assessment. **2° endpoint:** to examine which anatomical regions provided the most accurate standardized assessment of loss of grey-white distinction and sulcal effacement. **Results:** **The loss of GW matter distinction at 84 (66-109) h in corona radiata and in high convexity** predicted poor neurological outcome at 6 months with **100 [97-100]% specificity** and **46 [37-54]% and 51 [42-59]% sensitivity,** respectively.	In comatose survivors after CA, the loss of GW matter distinction in the corona radiata and in high convexity at 72-96 h after CA predicted poor neurological outcome at 6 months with 100% specificity and moderate sensitivity.
Sulcal effacement				
Lang et al., 2025	**Study Type:** in-depth analysis of a prospective observational international sub-study within the TTM2 trial. One hundred forty patients were included in the study.	**Inclusion Criteria:** adult, unconscious (not obeying verbal commands) at 48 hours post cardiac arrest, CT >48 hours ≤7 days post-arrest. **Exclusion criteria:** no CT available, withdrawn consent, CT >7days and/or <48h after CA, technical requirements unfulfilled, large ischaemic lesion, intracranial	**1° endpoint:** to make improvements in interrater variability of a standardized qualitative CT assessment. **2° endpoint:** to examine which anatomical regions provided the most accurate standardized assessment of loss of grey-white distinction and sulcal effacement.	In comatose survivors after CA the presence of sulcal effacement in different regions at 72-96 h after CA predicted poor neurological outcome at 6 months with 100% specificity

	CT scan was performed on all patients.	haemorrhage, artefacts interfering with evaluation.	**Results:** **The presence of sulcal effacement at 84 (66-109) h in different regions (basal cisterns, basal ganglia, corona radiata and high convexity)** predicted poor neurological outcome at 6 months with **specificity ranging from 94 [89-97]% to 100 [97-100]%** and **sensitivity ranging from 29 [21-37]% and 49 [40-57]% sensitivity.**	and moderate sensitivity.
Pseudo Subarachnoid Haemorrhage Sign				
Lang et al., 2025	**Study Type:** in-depth analysis of a prospective observational international sub-study within the TTM2 trial. One-hundred-forty patients were included in the study. CT scan was performed on all patients.	**Inclusion Criteria:** adult, unconscious (not obeying verbal commands) at 48 hours post cardiac arrest, CT >48 hours ≤7 days post-arrest. **Exclusion criteria:** no CT available, withdrawn consent, CT >7days and/or <48h after CA, technical requirements unfulfilled, large ischaemic lesion, intracranial haemorrhage, artefacts interfering with evaluation.	**1° endpoint:** to make improvements in interrater variability of a standardised qualitative CT assessment. **2° endpoint:** to examine which anatomical regions provided the most accurate standardized assessment of loss of grey-white distinction and sulcal effacement. **Results:** **The presence of Pseudo Subarachnoid Haemorrhage at 84 (66-109) h** predicted poor neurological outcome at 6 months with **100 [97-100]% specificity** and **8 [4-14]% sensitivity.**	In comatose survivors after CA the presence of Pseudo Subarachnoid Haemorrhage at 72-96 h after CA predicted poor neurological outcome at 6 months with 100% specificity and very low sensitivity.
White Cerebellum Sign				
Lang et al., 2025	**Study Type:** in-depth analysis of a prospective observational international sub-study within the TTM2 trial. One hundred forty patients were included in the study.	**Inclusion Criteria:** adult, unconscious (not obeying verbal commands) at 48 hours post cardiac arrest, CT >48 hours ≤7 days post-arrest. **Exclusion criteria:** no CT available, withdrawn consent, CT >7days and/or <48h after CA, technical requirements unfulfilled, large ischaemic	**1° endpoint:** to make improvements in interrater variability of a standardized qualitative CT assessment. **2° endpoint:** to examine which anatomical regions provided the most accurate standardized assessment of loss of grey-	In comatose survivors after CA the presence of signs of white cerebellum at 72-96 h after CA predicted poor neurological outcome at 6 months with 100% specificity

	CT scan was performed on all patients.	lesion, intracranial haemorrhage, artefacts interfering with evaluation.	white distinction and sulcal effacement. **Results:** **The presence of signs of white cerebellum at 84 (66-109) h** predicted poor neurological outcome at 6 months with **100 [97-100]% specificity** and **11 [7-18]% sensitivity.**	and very low sensitivity.
Reversal Sign				
Lang et al., 2025	**Study Type:** in-depth analysis of a prospective observational international sub-study within the TTM2 trial. One hundred forty patients were included in the study. CT scan was performed on all patients.	**Inclusion Criteria:** adult, unconscious (not obeying verbal commands) at 48 hours post cardiac arrest, CT >48 hours ≤7 days post-arrest. **Exclusion criteria:** no CT available, withdrawn consent, CT >7days and/or <48h after CA, technical requirements unfulfilled, large ischaemic lesion, intracranial haemorrhage, artefacts interfering with evaluation.	**1° endpoint:** to make improvements in interrater variability of a standardised qualitative CT assessment. **2° endpoint:** to examine which anatomical regions provided the most accurate standardized assessment of loss of grey-white distinction and sulcal effacement. **Results:** **The presence of signs of reversal at 84 (66-109) h** predicted poor neurological outcome at 6 months with **100 [97-100]% specificity** and **9 [5-15]% sensitivity.**	In comatose survivors after CA the presence of signs of reversal at 72-96 h after CA predicted poor neurological outcome at 6 months with 100% specificity and very low sensitivity.

Reviewer Comments:
The five studies we included assessed changes on brain CT due to HIBI with different modalities and timings. Three studies assessed the grey matter/white matter ratio (GWR), a measure of cytotoxic brain oedema, within six hours (two studies) or four days (one study) after ROSC. GWR has been employed in several studies included in previous ILCOR reviews and evidence updates. Another study assessed the difference in brain radiodensity over time after ROSC using NWU, a method based on brain mapping, which appears to be suitable for research only at the moment. The last study assessed different qualitative changes in brain CT due to cytotoxic or vasogenic oedema resulting from HIBI. The results of these last two studies deserve further validation.
The task force is planning an updated systematic review on all modalities for neuroprognostication in the near future.

Note on the interpretation of test results
Neuroprognostic tests used in patients who are comatose after resuscitation from cardiac arrest measure the severity of brain injury. An abnormal response from these tests may be classified as “positive,” and a normal

response as “negative,” or vice versa, depending on the prognostic perspective taken. Usually, as in this evidence review, a positive result of these tests indicates that the outcome of that patient will be poor. If this occurs, the prediction is correct, and the test result is a true positive. Conversely, if the outcome is good, the positive test result is a false positive. In this context, the false-positive rate (FPR) of a test is the proportion of patients with good outcome who are assigned a falsely pessimistic prediction. In other words, the FPR is the number of false positives divided by the total number of patients with a good outcome. FPR is also the complement of specificity, i.e., 100% − specificity. Therefore, a test with 100% specificity has 0% FPR. Ideally, all neuroprognostic tests predicting poor outcome should yield 100% specificity. While neuroprognostic tests predicting outcome should also ideally offer a reasonably high sensitivity when “negative” (in this case indicating that the outcome of the patient will be good), this is less important than their having a high specificity (low FPR), since the latter minimizes the risk of incorrectly predicting (and acting upon) a poor prognosis in a potentially viable patient.
In most neuroprognostic studies, as in prognostic studies in general, the treating team is aware of the results of the prognostic tests under investigation. Consequently, these results may affect their treatment decisions, leading to a self-fulfilling prophecy bias that may overestimate the specificity of prognostic tests in predicting poor outcome. This bias contributes to the low certainty of the evidence of most neuroprognostic studies after cardiac arrest. For that reason, the ILCOR 2020 Consensus for this PICOST is that the decision to limit the treatment of comatose post–cardiac arrest patients should never rely on a single prognostication element. The consensus of the task force was that in patients who remain comatose in the absence of confounders (e.g., sedative drugs), a multimodal approach should be used, with all supplementary tests considered in the context of the clinical examination.
For further details on the methodology and interpretation of prognostic tests see Geocadin RG, Callaway CW, Fink EL, Golan E, Greer DM, Ko NU, Lang E, Licht DJ, Marino BS, McNair ND, Peberdy MA, Perman SM, Sims DB, Soar J, Sandroni C; American Heart Association Emergency Cardiovascular Care Committee. Standards for Studies of Neurological Prognostication in Comatose Survivors of Cardiac Arrest: A Scientific Statement From the American Heart Association. Circulation. 2019 Aug 27;140(9):e517-e542.).

Notes on the interpretation of neuroprognostic tests based on brain CT

The grey matter/white matter ratio on brain CT (**GWR**) is calculated by measuring the density of specific regions of interest (ROIs) in the grey matter (most often, the caudate nucleus and the putamen) and dividing it by the density of ROIs in the white matter (most often, corpus callosum and the posterior limb of the internal capsule). Unlike the results of other neuroprognostic tests (e.g., clinical examination), GWR is a continuous rather than dichotomous (categorical) variable. Results are dichotomized to calculate the sensitivity and specificity of GWR by establishing a threshold that divides positive from negative results. Consequently, test sensitivity and specificity depend on the threshold chosen: a high threshold increases the test's specificity and decreases the sensitivity, and vice versa.
A source of heterogeneity for neuroprognostication based on GWR is the presence of different calculation methods. They depend on which and how many regions of the grey or the white matter are sampled. This may create different results across measuring methods. Another potential source of heterogeneity is the use of different equipment and different acquisition techniques.
Net water uptake (**NWU**) measures the changes in brain radiodensity over time, and it is calculated as the change in HU
between early and late CT for each anatomical region using the following formula: 1- (HU region late/HU region early), where HU are the Hounsfield units (HU).
Qualitative, visually assessed signs of HIBI on brain CT detect either early cytotoxic oedema, seen as a reduced distinction between the grey and white matter radiodensity, or later vasogenic oedema with a displacement of cerebrospinal fluid/effacement of sulci and basal cisterns.
The “Pseudo Subarachnoid Haemorrhage Sign” is seen as high radiodensity along sulci and cisterns from distension of superficial veins, while the “White Cerebellum Sign” is seen as decreased radiodensity in the supratentorial brain in comparison to cerebellum, and the “Reversal Sign” is seen as higher radiodensity in white matter in comparison to grey matter.

Reference list: ***(List by ILCOR ref standard (last name first author, year of publication, first page number) and insert hyperlink to all articles identified as relevant (if available on PubMed)***

Czimmeck C, Resuscitation 2025 Aug:213:110650. https://pubmed.ncbi.nlm.nih.gov/40409670/

Kenda M, Resuscitation 2024 Jul:200:110243. https://pubmed.ncbi.nlm.nih.gov/38796092/

Lang M, Resuscitation 2025 Sep:214:110675. https://pubmed.ncbi.nlm.nih.gov/40499676/

Scarpino M, Resuscitation 2025 Sep 4:110801. https://pubmed.ncbi.nlm.nih.gov/40914341/

2026 Evidence Update

ALS 3510 (Part 2) – Prognostication Brain MRI

Worksheet author(s): Claudio Sandroni, Sonia D'Arrigo
External Collaborator (data extraction and management): Sofia Cacciola
Task Force: Advanced Life Support (ALS)
Date Submitted to SAC rep for peer review and approval: September 10, 2025
SAC rep: Eric Lavonas

PICOST / Research Question:
Population: Adults who are comatose after resuscitation from cardiac arrest (either in-hospital or out-of-hospital), regardless of target temperature**.**
Interventions: index test based on imaging: **Magnetic Resonance Imaging (MRI)**
Comparison: none.
Outcomes: poor neurological outcome, defined as Cerebral Performance Categories (CPC) 3-5 or Glasgow Outcome Scale (GOS) 1-3, or modified Rankin Score (mRS) 4-6 at hospital discharge/1 month or later.
Study designs: Prognostic accuracy studies where the 2x2 contingency table (ie, 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 fewer than 10 patients, letters, editorials, conference abstracts, and studies published in abstract form were excluded.

Year of last full review: 2020

Current ILCOR Consensus on Science and Treatment Recommendation for this PICOST:
We suggest using diffusion-weighted brain MRI for predicting neurological outcome of adults who are comatose after cardiac arrest (weak recommendation, very low-certainty evidence).
We suggest using ADC on brain MRI for predicting neurological outcome of adults who are comatose after cardiac arrest (weak recommendation, very low-certainty evidence).

Database searched: PubMed. The references of full-text articles were screened for additional studies.

Time Frame: (existing PICOST) –Jul 2024 (last EvUp) to Aug 2025
Date Search Completed: Aug 31, 2025
Search Results (Number of articles identified, and number identified as relevant): 24/1

Summary of Evidence Update:

This update identified **1 relevant study** that was not included in the 2024 ILCOR evidence update. This study evaluated the ability of **MRI at 96 h after ROSC** to predict poor neurological outcome in comatose patients after CA (Chan 2024). This study assessed a simplified version of a validated qualitative regional MRI scoring system. Twelve predefined regions were scored on an ordinal scale with 0 representing no abnormality, 1 representing focal abnormality (involving <50% of the structure), and 2 representing widespread abnormality (involving >50% of the structure). On MRI performed at 96 (81-110) h, a hypoxic-ischemic brain injury (HIBI) score >19 in the cortex region and >9 in the deep grey nuclei (DGN) predicted poor neurological outcome at hospital discharge with 100% specificity and 34 [28-41]% and 47 [41-54]% sensitivity, respectively. A HIBI score combined cortex-DGN >27 predicted poor neurological outcome at hospital discharge with 100% specificity and 39 [32-46]% sensitivity.

Relevant Guidelines or Systematic Reviews: none

RCT: none

Nonrandomized Trials, Observational Studies published Jun 30, 2024 to Aug 31, 2025

Study Acronym; Author; Year Published	**Study Type/Design; Study Size (N)**	**Patient Population**	**Primary Endpoint and Results (include P value; OR or RR; & 95% CI)**	**Summary/Conclusion Comment(s)**
Hypoxic-ischemic brain injury (HIBI) MRI score				
Chan et al., 2024	**Study Type:** retrospective, single-centre. Two hundred-nineteen patients were included in the study. MRI was performed in all patients.	**Inclusion Criteria:** age >18 years, initially comatose following CA, with ROSC, MRI between 2 days and 7 days post-CA **Exclusion criteria:** N/A	**1° endpoint:** to test a simplified version of a validated qualitative regional MRI scoring system for classification of poor neurologic outcome following CA. **Results:** Twelve predefined regions were scored on an ordinal scale with 0 representing no abnormality, 1 representing focal abnormality (involving <50% of the structure), and 2 representing widespread abnormality (involving >50% of the structure). Abnormalities were tested on both diffusion weighted imaging (DWI) and fluid-attenuated inversion recovery (FLAIR) sequences. On MRI performed **at 96 (81-110) h**, the **HIBI score >19 in the cortex region** and **>9 in the deep grey nuclei (DGN)** predicted poor neurological outcome at hospital discharge with **100% specificity and 34 [28-41]% and 47 [41-54]% sensitivity, respectively. A HIBI score combined cortex-DGN >27** predicted poor neurological outcome at hospital discharge with **100%**	This single-centre study showed that a high score quantifying the severity of HIBI changes on brain MRI can predict poor outcome with 100% specificity. Sensitivity was higher at the level of deep grey nuclei.

			specificity and 39 [32-46]% sensitivity.	

Reviewer Comments: *(including whether this PICOST should have a systematic or scoping review*)
The task force is planning an update of the systematic review of all modalities for neuroprognostication in the near future.

Note on the interpretation of test results
Neuroprognostic tests used in patients who are comatose after resuscitation from cardiac arrest measure the severity of brain injury. An abnormal response from these tests may be classified as "positive," and a normal response as "negative," or vice versa, depending on the prognostic perspective taken. Usually, as in this evidence review, a positive result of these tests indicates that the outcome of that patient will be poor. If this occurs, the prediction is correct, and the test result is a true positive. Conversely, if the outcome is good, the positive test result is a false positive. In this context, the false-positive rate (FPR) of a test is the proportion of patients with good outcome who are assigned a falsely pessimistic prediction. In other words, the FPR is the number of false positives divided by the total number of patients with a good outcome. FPR is also the complement of specificity, i.e., 100% − specificity. Therefore, a test with 100% specificity has 0% FPR. Ideally, all neuroprognostic tests predicting poor outcome should yield 100% specificity. While neuroprognostic tests predicting outcome should also ideally offer a reasonably high sensitivity when "negative" (in this case indicating that the outcome of the patient will be good), this is less important than their having a high specificity (low FPR), since the latter minimizes the risk of incorrectly predicting (and acting upon) a poor prognosis in a potentially viable patient.
In most neuroprognostic studies, as in prognostic studies in general, the treating team is aware of the results of the prognostic tests under investigation. Consequently, these results may affect their treating decisions, leading to a self-fulfilling prophecy bias that may overestimate the specificity of prognostic tests in predicting poor outcome. This bias contributes to the low certainty of the evidence of most neuroprognostic studies after cardiac arrest. For that reason, the ILCOR 2020 Consensus for this PICOST is that the decision to limit treatment of comatose post–cardiac arrest patients should never rely on a single prognostication element. The consensus of the task force was that in patients who remain comatose in the absence of confounders (eg, sedative drugs), a multimodal approach should be used, with all supplementary tests considered in the context of the clinical examination.

Notes on the interpretation of MRI
In patients with hypoxic-ischaemic brain injury (HIBI), diffusion-weighted Imaging (DWI) changes on brain MRI detect reduced water diffusion in the brain tissue due to cellular swelling. Fluid-attenuation inversion recovery (FLAIR) mainly reflects vasogenic oedema, and it is used less often than DWI to assess HIBI after cardiac arrest. The study included in this evidence update assessed a simplified score, based on both DWI and FLAIR, to evaluate the severity of MRI changes from HBI after cardiac arrest and found two different thresholds for 100% specificity: one for the cortical score and the other for the deep grey nuclei. Sensitivity was higher with the deep grey nuclei score. Three previous studies we assessed in the 2024 Evidence Update of imaging studies also found thresholds for 100% specificity for MRI scores (An C. 2020; Keijzer HM, 2022; Vanden Berghe S, 2020). All studies, including the one in the present Evidence Update, employed different methods to calculate the scores, which prevented a direct comparison across study results.

For further details on the methodology and interpretation of prognostic tests see Geocadin RG, Callaway CW, Fink EL, Golan E, Greer DM, Ko NU, Lang E, Licht DJ, Marino BS, McNair ND, Peberdy MA, Perman SM, Sims DB, Soar J, Sandroni C; American Heart Association Emergency Cardiovascular Care Committee. Standards for Studies of Neurological Prognostication in Comatose Survivors of Cardiac Arrest: A Scientific Statement From the American Heart Association. Circulation. 2019 Aug 27;140(9):e517-e542.).

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