**Title: NEUROPROGNOSTICATION IN**

 **CARDIAC ARREST PATIENTS**

**Authors: Ashutosh Kumar 1, Ankur Khandelwal 2**

1. **Dr. Ashutosh Kumar**

**Assistant Professor**

**Department of Anaesthesiology & Critical Care**

**All India Institute of Medical Sciences (AIIMS), Nagpur, India**

**Email:** **neokumar.158@gmail.com**

**Mobile: 91-9686019371**

1. **Dr. Ankur Khandelwal**

**Associate Professor**

**Department of Anaesthesiology, Critical Care and Pain Medicine**

**All India Institute of Medical Sciences (AIIMS), Guwahati, India**

**Email:** **ankurchintus@gmail.com**

**Mobile: 91-7042929671**

**Abstract**

Cardiac arrest (CA) is a life-threatening event associated with high morbidity and mortality rates. Advances in resuscitation science have improved the survival rates of CA patients; however, the majority of survivors often face neurological sequelae, ranging from mild cognitive impairment to severe neurological disability. Neuroprognostication, the process of assessing the likelihood of meaningful neurological recovery in these patients is extremely crucial especially in those who remain comatose despite return of spontaneous circulation (ROSC). Current recommendations advocate prognostication no earlier than 72 hours following ROSC in comatose patients. A multimodal strategy consisting of neurological examination, electrophysiological studies, neuroimaging and biomarkers reduces the likelihood of erroneous outcome prediction. Importantly, ethical considerations and the potential for self-fulfilling prophecies underscore the need for a multidisciplinary approach to neuroprognostication.

***Keywords: Cardiac arrest, coma, neuroprognostication, survivors***

**Introduction**

Hypoxic-ischemic brain injury (HIBI) leaves nearly half of cardiac arrest (CA) survivors comatose 72 hours after return of spontaneous circulation (ROSC) [1]. Neuroprognostication is challenging in these patients since clinical improvement takes time. Failing to recognize a bad prognosis may prolong sufferings secondary to emotional burden and financial loss. On the contrary, premature and erroneous diagnosis might cause a "self-fulfilling prophecy," when removing life-sustaining measures kills even if recovery is feasible [2]. Uncertainty exists over the ideal time to carry out and interpret neurologic testing.

**Timing of Neurological Assessment & Neuroprognostication**

In the current era, the time to neuroprognostication following CA has changed with respect to increased application of Targeted Temperature Management (TTM). Neuroprognostication in the pre TTM era was generally done at 48-72 hours from ROSC. Now, the assessment is not recommended before 72 hours after ROSC (and later if confounding factors are still present) [3, 4]. The effect of hypothermia on the modality being used for making neurological prognosis should be kept in mind. Ideally, neuroprognostication should be done only after achieving normothermia. Current modalities of neuroprognostication include neurological examination, electrophysiology, neuroimaging and biomarkers.

**Neurological Examination**

The neurological examination which reflects the degree of HIBI in Post Cardiac Arrest Syndrome (PCAS) patients remains critical for determining prognosis. As a result, clinicians typically utilize the total neurological symptoms to forecast the results following ROSC. In PCAS patients treated with TTM, the neurological assessment should be deferred until five days after ROSC or three days after normothermia.

Extensor posturing or no motor response is related with poor outcome, although with a lower specificity of around 88% [3]. When hypothermia is used as a part of TTM, the false positive rate (FPR) of a bad motor examination after 72 hours has been demonstrated to be too high for conclusive neuroprognosis [4]. This FPR falls over time. It was 21% (95% CI, 9%-38%), compared to 6% (95% CI, 1%-20%) on day 7 in a study [5]. Another research added flexor posture as a poor motor response predictor of poor outcome, however, this might be mistaken with a withdrawal reaction and has traditionally been eliminated. The Glasgow Coma Scale (GCS) motor score of 2 at the 72-hour mark has minimal specificity in predicting negative neurological prognosis. However, it exhibits a sensitivity ranging from 70% to 80% [3].

Lack of pupillary light reflex (PLR) at 72 hours is highly specific for poor neurologic prognosis [6]. Pupillary function may be quantified using automated pupillometry in order to improve sensitivity and specificity. Better outcomes were predicted by faster conduction velocities and Neurological Pupillary Index (NPI; based on pupillary size, latency, and constriction and dilation velocities) [7]. NPI 3 at any time between days 1 and 3 had 100% specificity (95% CI, 98%-100%) with poor outcome but 32% sensitivity [8]. Another study found that NPI threshold of 3.7 at 6 hours after ROSC indicated a poor outcome with 82% specificity [9]. A bilaterally absent corneal response 72 hours after ROSC also indicates a poor prognosis, albeit with less precision than the PLR [10]. The corneal reflex is more susceptible to sedative and muscle relaxant side effects than PLR.

Myoclonus, characterized by quick, abrupt, involuntary jerks brought on by inhibitions or contractions of the muscles is commonly seen after ROSC from CA. Poor neurological outcome is nearly generally correlated with the early (48 hours) post-anoxic status myoclonus lasting for 30 mins or more. However, myoclonus should only be used in conjunction with other indices since it is seen to be a less reliable predictor than PLR [11]. Electroencephalogram (EEG) recording can be utilised to exclude more benign types of post-anoxic myoclonus, such as Lance-Adams syndrome [12].

When making a prognosis, it is important to rule out any confounding factors such as body temperature and the residual effects of sedatives and/or neuromuscular blocking drugs. Another drawback of clinical examination-based predictors is that their results cannot be hidden from the treating team, which might lead to a self-fulfilling prediction in terms of clinical care.

**Electrophysiology**

1. **Electroencephalogram (EEG)**

The EEG has been used to assess HIBI severity in multiple studies. However, the lack of a clear definition of EEG patterns linked with poor neurological prognosis has hindered its broad use as a predictor [13]. According to the recommendations established by the European Resuscitation Council (ERC) and the European Society of Intensive Care Medicine (ESICM) in 2015, it is recommended to evaluate malignant EEG patterns, such as unresponsive background with burst suppression or status epilepticus following rewarming, in conjunction with other predictive factors. This recommendation is made in light of the existing disparity [14]. Recent research suggests that EEGs collected within 24 hours of ROSC might give crucial prognostic information. Poor neurological prognosis as evaluated by cerebral performance category (CPC 3–5) at 6 months was successfully predicted [specificity 100 % (98–100%)] in 430 comatose resuscitated patients using continuous EEG patterns: isoelectric, low-voltage (< 20 μV), or burst suppression with similar bursts. These indications, however, were shown to have poor sensitivity [29% (22–36%)] [15].

1. **Somatosensory evoked potentials (SSEPs)**

SSEPs assess the dorsal column-lemniscal sensory circuit. The main somatosensory cortex's N20 potential reveals thalamocortical neuron synapse integrity. Absent bilateral N20 potentials reflect thalamocortical link failure, which predicts a poor neurologic prognosis at hospital discharge up to 12 months with an FPR of 2.7% (95% CI, 1.6%-4.4%) [16].

If the N20 cortical wave of SSEP is absent on both sides 72 hours after ROSC, the neurological prognosis is poor [FPR 0.4 % (0-2%)] [3]. However, SSEP sensitivities are often below 50%. For the strongest predictors to meet ERC-ESICM requirements 72 hours after ROSC, the N20 SSEP wave must be missing. In a study conducted by Endisch et al., the authors evaluated the amplitude of N20 SSEP waves in 293 CA survivors from day 1 to day 4 after ROSC. With a specificity of 100% and a sensitivity of 57%, low amplitude (0.62 V) predicted poor neurological results (CPC 4-5) [17].

SSEP works better with less sedation than EEG, though it is susceptible to electrical interference. Since hypothermia reduces conduction velocity, SSEP should be recorded following rewarming.

**Neuroimaging**

1. **Computed Tomography (CT)**

Cerebral edema is the predominant CT finding of HIBI. The ratio of gray matter (GM) and white matter (WM) densities i.e., GWR is routinely collected at three levels: basal ganglia, centrum semiovale, and high convexity. Changes occur soon after CA. In comatose survivors of CA between 1- and 24-hours following ROSC, a GWR between 1.16 and 1.22 predicted a poor neurological prognosis (CPC 3–5) with 0% FPR and sensitivities of 28 to 76% on brain CT [18, 19]. A single-center analysis of 240 patients with brain CT within 24 hours of ROSC found that a GWR <1.22 accurately predicted hospital mortality [98 % (91–100%], but did not differentiate between survivors with poor or excellent outcomes [20]. In comatose ROSC patients, current guidelines advocate brain CT within 72 hours as part of a multimodal neuroprognostication strategy [21].

1. **Magnetic Resonance Imaging (MRI)**

HIBI following CA causes diffusion-weighted imaging (DWI) hyperintense regions on brain MRI. The changes are quantified using apparent diffusion coefficient (ADC). The whole-brain ADC, the fraction of brain volume with low ADC, and the lowest ADC value in HIBI-prone brain regions have been used to predict poor neurological prognosis following CA [22]. Hypothermia also reduces ADC values, thus, MRI should be ideally done after achieving normothermia. Wu et al. examined 80 of 200 prospectively collected CA patients who had at least one MRI scan. Out of 80 patients, 14 had therapeutic hypothermia (TH). Patients with mean whole-brain ADC depression <665 × 10–6 mm2/s did not recover from moderate to severe impairment [23]. Wijman et al. found that individuals with ADC values <650 × 10–6 mm2/s and >10% brain volume had poor results in 51 patients (31 of whom had TH) [24].

Brain MRIs should be performed 2-5 days after ROSC, if at all possible, though MRI might predict neurological outcomes as early as 3 h following ROSC [25, 26]. Due to the small number of patients investigated, current guidelines advise utilizing brain imaging following CA only in conjunction with other predictors and in centers with specialized experience. Also, MRI is impractical in the most unstable patients, which may bias prognostic analyses.

**Biomarkers**

Numerous biomarkers have been studied for neuroprognostication. These include neuron specific enolase (NSE), S-100B, glial fibrillary acidic protein (GFAP), neurofilament light (NFL) and tau -proteins. These protein biomarkers are secreted after neuron and glial cell damage and thus reflect hypoxic damage to brain during CA. Their blood levels are thought to correlate with HIBI following CA [27, 28]. Advantages of using biomarker concentrations is that they are straightforward to measure and are not altered by sedatives like clinical examination and EEG. However, no single biomarker can accurately and consistently predict bad outcomes. Thus, unlike prior recommendations, current guidelines do not prescribe a precise biomarker level to predict poor outcome with 100% specificity due to multiple reasons [11]. Firstly, the time of sampling affects biomarker thresholds. Secondly, the variability of biomarker measurement methods can also generate systemic errors. Thirdly, biomarkers may yield false positives from extracerebral sources (e.g., NSE extracerebral resources include red blood cells, neuroendocrine tumors, and small cell carcinoma).

Recently, microRNAs (miRNAs) have been discovered as potential CA outcome biomarker. miRNAs influence gene expression using 20–22 nucleotides. Neuronal miRNAs pass the blood–brain barrier and may be quantified in plasma after global brain ischemia. Their benefit is that they can assess degree of brain injury in addition to neuronal cell function. Comatose CA patients' mortality and neurological outcomes are independently predicted by miRNAs, according to preliminary research [29, 30].

**Prognostication strategy**

The strongest predictors (FPR < 5% for poor outcome prediction with narrow CI) should be assessed first. These include bilaterally absent pupillary reflexes at ≥72 h post-ROSC and/or N20 SSEP wave following rewarming. In the absence of such signals, we may resort to less reliable predictors, such as unresponsive EEG pattern after achieving normothermia (status epilepticus, burst suppression), diffuse ischemic lesions on brain CT or MRI within 24 hours or 2-5 days after ROSC or early status myoclonus (48 h) **[Figure 1]**. If none of these criteria are met or prognostic test findings are discordant, the prognosis is uncertain and prolonged monitoring and therapy should be maintained to identify late awakeners. After ceasing sedation, 15–30% of patients with a satisfactory result awaken within 48 h and 10–12 days [31, 32]. Renal insufficiency, age, and post-resuscitation shock enhance delayed awakening. Meanwhile, predictors of good neurological recovery should also be examined. Combining at least two predictors is recommended.

**Conclusion**

Neuroprognostication in CA patients is a complex and evolving field that significantly influences treatment decisions and patient outcomes. Clinical examination, electrophysiology, neuroimaging and biomarkers are often utilised to prognosticate CA survivors. Current guidelines advocate a multi-modal strategy, incorporating different prognostication tests to reduce the possibility of an overly negative prognosis. However, ongoing research, standardization of protocols, and ethical guidance are essential to optimize the precision and ethical application of neuroprognostication in this critical patient population.

**References:**

1. Laver S, Farrow C, Turner D, Nolan J. Mode of death after admission to an intensive care unit following cardiac arrest. Intensive Care Med. 2004 Nov;30(11):2126-8.
2. Elmer J, Torres C, Aufderheide TP, Austin MA, Callaway CW, Golan E, et al. Association of early withdrawal of life-sustaining therapy for perceived neurological prognosis with mortality after cardiac arrest. Resuscitation. 2016 May; 102:127-35.
3. Sandroni C, Cavallaro F, Callaway CW, D'Arrigo S, Sanna T, Kuiper MA, et al. Predictors of poor neurological outcome in adult comatose survivors of cardiac arrest: a systematic review and meta-analysis. Part 2: Patients treated with therapeutic hypothermia. Resuscitation. 2013 Oct;84(10):1324-38.
4. Mulder M, Gibbs HG, Smith SW, Dhaliwal R, Scott NL, Sprenkle MD, et al. Awakening and withdrawal of life-sustaining treatment in cardiac arrest survivors treated with therapeutic hypothermia\*. Crit Care Med. 2014 Dec;42(12):2493-9.
5. Matthews EA, Magid-Bernstein J, Sobczak E, Velazquez A, Falo CM, Park S, et al. Prognostic Value of the Neurological Examination in Cardiac Arrest Patients After Therapeutic Hypothermia. Neurohospitalist. 2018 Apr;8(2):66-73.
6. Levy DE, Caronna JJ, Singer BH, Lapinski RH, Frydman H, Plum F. Predicting outcome from hypoxic-ischemic coma. JAMA. 1985 Mar 8;253(10):1420-6.
7. Tamura T, Namiki J, Sugawara Y, Sekine K, Yo K, Kanaya T, et al. Early outcome prediction with quantitative pupillary response parameters after out-of-hospital cardiac arrest: A multicenter prospective observational study​. PLoS One. 2020 Mar 19;15(3): e0228224.
8. Oddo M, Sandroni C, Citerio G, Miroz JP, Horn J, Rundgren M, et al. Quantitative versus standard pupillary light reflex for early prognostication in comatose cardiac arrest patients: an international prospective multicenter double-blinded study. Intensive Care Med. 2018 Dec;44(12):2102-2111.
9. Riker RR, Sawyer ME, Fischman VG, May T, Lord C, Eldridge A, et al. Neurological Pupil Index and Pupillary Light Reflex by Pupillometry Predict Outcome Early After Cardiac Arrest. Neurocrit Care. 2020 Feb;32(1):152-161.
10. Sandroni C, Cariou A, Cavallaro F, Cronberg T, Friberg H, Hoedemaekers C, et al. Prognostication in comatose survivors of cardiac arrest: an advisory statement from the European Resuscitation Council and the European Society of Intensive Care Medicine. Resuscitation. 2014 Dec;85(12):1779-89.
11. Nolan JP, Soar J, Cariou A, Cronberg T, Moulaert VR, Deakin CD, et al. European Resuscitation Council and European Society of Intensive Care Medicine Guidelines for Post-resuscitation Care 2015: Section 5 of the European Resuscitation Council Guidelines for Resuscitation 2015. Resuscitation. 2015 Oct; 95:202-22.
12. Aicua Rapun I, Novy J, Solari D, Oddo M, Rossetti AO. Early Lance-Adams syndrome after cardiac arrest: Prevalence, time to return to awareness, and outcome in a large cohort. Resuscitation. 2017 Jun; 115:169-172.
13. Rundgren M, Rosén I, Friberg H. Amplitude-integrated EEG (aEEG) predicts outcome after cardiac arrest and induced hypothermia. Intensive Care Med. 2006 Jun;32(6):836-42.
14. Hirsch LJ, LaRoche SM, Gaspard N, Gerard E, Svoronos A, Herman ST, et al. American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology: 2012 version. J Clin Neurophysiol. 2013 Feb;30(1):1-27.
15. Sondag L, Ruijter BJ, Tjepkema-Cloostermans MC, Beishuizen A, Bosch FH, van Til JA, et al. Early EEG for outcome prediction of postanoxic coma: prospective cohort study with cost-minimization analysis. Crit Care. 2017 May 15;21(1):111.
16. Benghanem S, Nguyen LS, Gavaret M, Mira JP, Pène F, Charpentier J, et al. SSEP N20 and P25 amplitudes predict poor and good neurologic outcomes after cardiac arrest. Ann Intensive Care. 2022 Mar 15;12(1):25.
17. Endisch C, Storm C, Ploner CJ, Leithner C. Amplitudes of SSEP and outcome in cardiac arrest survivors: A prospective cohort study. Neurology. 2015 Nov 17;85(20):1752-60.
18. Jeon CH, Park JS, Lee JH, Kim H, Kim SC, Park KH, et al. Comparison of brain computed tomography and diffusion-weighted magnetic resonance imaging to predict early neurologic outcome before target temperature management comatose cardiac arrest survivors. Resuscitation. 2017 Sep; 118:21-26.
19. Lee BK, Kim WY, Shin J, Oh JS, Wee JH, Cha KC, et al. Prognostic value of gray matter to white matter ratio in hypoxic and non-hypoxic cardiac arrest with non-cardiac etiology. Am J Emerg Med. 2016 Aug;34(8):1583-8. doi: 10.1016/j.ajem.2016.05.063.
20. Metter RB, Rittenberger JC, Guyette FX, Callaway CW. Association between a quantitative CT scan measure of brain edema and outcome after cardiac arrest. Resuscitation. 2011 Sep;82(9):1180-5.
21. Primary Panel; Fordyce CB, Kramer AH, Ainsworth C, Christenson J, Hunter G, et al. Neuroprognostication in the Post Cardiac Arrest Patient: A Canadian Cardiovascular Society Position Statement. Can J Cardiol. 2023 Apr;39(4):366-380.
22. Hirsch KG, Mlynash M, Eyngorn I, Pirsaheli R, Okada A, Komshian S, et al. Multi-Center Study of Diffusion-Weighted Imaging in Coma After Cardiac Arrest. Neurocrit Care. 2016 Feb;24(1):82-9.
23. Wu O, Sorensen AG, Benner T, Singhal AB, Furie KL, Greer DM. Comatose patients with cardiac arrest: predicting clinical outcome with diffusion-weighted MR imaging. Radiology. 2009 Jul;252(1):173-81.
24. Wijman CA, Mlynash M, Caulfield AF, Hsia AW, Eyngorn I, Bammer R, et al. Prognostic value of brain diffusion-weighted imaging after cardiac arrest. Ann Neurol. 2009 Apr;65(4):394-402.
25. Mlynash M, Campbell DM, Leproust EM, Fischbein NJ, Bammer R, Eyngorn I, et al. Temporal and spatial profile of brain diffusion-weighted MRI after cardiac arrest. Stroke. 2010 Aug;41(8):1665-72.
26. Park JS, Lee SW, Kim H, Min JH, Kang JH, Yi KS, et al. Efficacy of diffusion-weighted magnetic resonance imaging performed before therapeutic hypothermia in predicting clinical outcome in comatose cardiopulmonary arrest survivors. Resuscitation. 2015 Mar; 88:132-7.
27. Humaloja J, Ashton NJ, Skrifvars MB. Brain Injury Biomarkers for Predicting Outcome After Cardiac Arrest. Crit Care. 2022 Mar 22;26(1):81.
28. Rajajee V, Muehlschlegel S, Wartenberg KE, Alexander SA, Busl KM, Chou SHY, et al. Guidelines for Neuroprognostication in Comatose Adult Survivors of Cardiac Arrest. Neurocrit Care. 2023 Jun;38(3):533-563.
29. Beske RP, Bache S, Abild Stengaard Meyer M, Kjærgaard J, Bro-Jeppesen J, Obling L, et al. MicroRNA-9-3p: a novel predictor of neurological outcome after cardiac arrest. Eur Heart J Acute Cardiovasc Care. 2022 Aug 9;11(8):609-616.
30. Oh SH, Kim HS, Park KN, Ji S, Park JY, Choi SP, et al. The Levels of Circulating MicroRNAs at 6-Hour Cardiac Arrest Can Predict 6-Month Poor Neurological Outcome. Diagnostics (Basel). 2021 Oct 15;11(10):1905.
31. Paul M, Bougouin W, Geri G, Dumas F, Champigneulle B, Legriel S, et al. Delayed awakening after cardiac arrest: prevalence and risk factors in the Parisian registry. Intensive Care Med. 2016 Jul;42(7):1128-36.
32. Gold B, Puertas L, Davis SP, Metzger A, Yannopoulos D, Oakes DA, et al. Awakening after cardiac arrest and post resuscitation hypothermia: are we pulling the plug too early? Resuscitation. 2014 Feb;85(2):211-4.

**Figure 1**: **Algorithm for Neuroprognostication**

