

Systemic Review

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Systemic Review of Current Strategies for Predicting Neurological Outcomes in Post-Cardiac Arrest Patients

Arnav Mana¹, Susan X. Zhao, MD^{2*}

¹Los Gatos High School, Los Gatos, CA, USA

²Santa Clara Valley Medical Center, San Jose, CA, USA

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*Correspondence:

Dr. Susan X. Zhao, Santa Clara Valley Medical Center, San Jose, CA, USA, Email: susanzhao@gmail.com

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Out-of-Hospital Cardiac Arrest (OHCA)
Return of Spontaneous Circulation (ROSC)
Targeted Temperature Management (TTM)

Abstract

Despite significant advances in cardiopulmonary resuscitation (CPR) and post-cardiac arrest care, out-of-hospital cardiac arrest (OHCA) remains a major public health problem, with high rates of death and severe long-term neurological impairment among survivors. This systematic review addresses the current methods in predicting poor neurological outcomes in comatose OHCA survivors, including both pre- and post hospital factors, neurophysiological tests, neurological exam, biomarkers, and neuroimaging. A multimodality, multidisciplinary approach incorporating these factors as well as the OHCA survivors and their surrogate decision makers' values is proposed (WEMuV) to guide neuroprognostication and counseling. The review also identifies emerging technologies such as artificial intelligence and machine learning as promising innovations that could integrate and automate complex patient data analysis to provide more accurate, personalized risk assessments and improve outcomes in OHCA patients.

Introduction

Cardiac arrest (CA), particularly out-of-hospital cardiac arrest (OHCA) is a major public health issue, with an estimated 350,000 occurrences each year in the United States alone.¹ Despite advances in cardiopulmonary resuscitation (CPR), public health campaign in raising awareness, promoting bystander action, and making automatic external defibrillators available in public places, as well as post arrest hospital care (particularly targeted temperature management/TTM), the OHCA survival to discharge rate remains low at around 10% and essentially unchanged over the past 30 years.¹ Survival to hospital discharge is certainly not the end point, as an overwhelming 32% of survivors experience permanent neurological impairment, which is a leading cause of long-term disability and death.²

The Cerebral Performance Category (CPC) scale is a 5-point instrument used to assess a person's neurological status after a cardiac arrest, ranging from good cerebral performance (CPC 1) to brain death (CPC 5).³ The CPC is typically dichotomized at the ability to perform activities of daily living or work in a sheltered environment (CPC 1-2 vs. 3-5). While CPC is widely regarded as the gold-standard for post CA neurological assessment, it has been shown to have a poor to fair correlation with long-term quality of life.⁴ For the purpose of this review, CPC is used as an outcome measure for neuroprognostication. CA and OHCA are used interchangeably throughout this review.

Caring for OHCA patients requires a multidisciplinary team

that often includes Critical Care, Neurology, Nephrology and Cardiology specialists to implement TTM, stabilize cardiovascular function, ensure oxygenation and ventilation, manage seizures, and most importantly address underlying causes such as urgent coronary angiography for acute myocardial infarction-related CA.⁵ These interventions strongly influence neurological recovery by limiting factors that worsen brain injury and by reducing secondary injury from recurrent CA or global hypoperfusion due to hemodynamic instability. Both the underlying cause of OHCA and the combination of pre-hospital/pre-EMS factors play a vital role in survivors' ultimate neurological outcomes.⁵ A comprehensive and dynamic integration of both pre- and post-hospital factors will be instrumental in arriving at a neuroprognostication to guide clinicians to provide effective care and compassionate counseling to families of OHCA survivors.

Despite decades of clinical progress, reliable neuroprognostication after cardiac arrest remains a major challenge. Accurate prediction of neurological recovery is essential for guiding post-arrest management, resource allocation, and counseling of families. This systematic review aims to synthesize current evidence on prognostic indicators of neurological outcome after OHCA, incorporating both objective measures and patient-centered values to guide decision-making, while highlighting emerging tools such as artificial intelligence and machine learning that may advance individualized prognostication in the future.

Methods

Search Strategy

A comprehensive literature search was conducted in PubMed, PubMed Central (PMC), and the NCBI Bookshelf from January 2014 to July 2024 (with the exception of older landmark studies) to capture the most recent decade of evidence. Controlled vocabulary terms and corresponding free-text keywords were used in combination with Boolean operators. The full PubMed search equation was:

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["cardiac arrest"[tiab] OR "heart arrest"[tiab]] AND ["neurological outcome"[tiab] OR "neuroprognostication"[tiab] OR "hypoxic-ischemic brain injury"[tiab]] AND ["biomarkers"[MeSH Terms] OR "EEG"[tiab] OR "electroencephalography"[tiab] OR "somatosensory evoked potentials"[tiab] OR "neuroimaging"[tiab] OR "machine learning"[tiab]]
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Equivalent search strategies were adapted for other databases using their respective controlled vocabulary systems. Reference lists of key articles and recent review papers were hand-searched to identify additional studies not captured in the database search.

Eligibility Criteria

Studies were included if they met the following criteria:

Population

Adult patients (≥ 18 years) who experienced out-of-hospital cardiac arrest.

Intervention/Exposure: Any clinical, biochemical, electrophysiologic, or imaging assessment used for neurological prognostication.

Outcomes

Neurological outcomes as measured by the Cerebral Performance Category (CPC) or equivalent validated neurological scales.

Study Design

Original clinical studies (randomized, observational, or cohort), meta-analyses, and systematic reviews.

Studies were excluded if they were: (1) non-human or pediatric studies, (2) case reports or conference abstracts, (3) not in English, or (4) lacking defined neurological outcomes.

Screening and Selection

All records retrieved from database searches were imported into Zotero for deduplication. Full-text screening was then conducted by the two reviewers by applying the predefined PICO elements—specifically confirming the Population (adult OHCA survivors), Intervention (prognostic modality), and Outcome (CPC score)—to confirm final study eligibility.

A total of 504 records were initially identified and screened by title and abstract. 422 studies were excluded at this stage due to poor relevance or similar content. Of the remaining, 82 full-text articles were assessed for eligibility. During full-text assessment, 54 articles were excluded because they were review articles, guidelines, or contained previously synthesized data and did not provide a new, unique lens. This left 28 unique studies that underwent final screening. A total of 4 additional articles were then excluded: pediatric cohorts ($n = 3$) and absence of neurological outcome reporting ($n = 1$). This resulted in 24 studies ultimately included in the final synthesis. Please refer to the PRISMA flow diagram (Figure 1).

Data Synthesis

Given the heterogeneity of outcome measures and prognostic tools, findings were synthesized qualitatively. Evidence was grouped by prognostic modality (clinical examination, EEG, biomarkers, neuroimaging, and emerging machine learning models) to highlight methodological consistency, predictive performance, and gaps in knowledge. Please refer to Table 1 for summary of included studies.

Key Elements of Post OHCA Neurological Damage and Assessment

Pathophysiology of Brain Injury Following Cardiac Arrest

The primary cause of illness and death after CA is hypoxic-ischemic brain injury (HIBI), as proposed by the

“two-hit” model. The first hit occurs during CA: the brain’s extreme sensitivity to hypoxia means even two minutes without blood flow can damage cortical and hypothalamic neurons, while the brainstem is more resilient. Oxygen and glucose deprivation rapidly depletes cellular energy, causing excitotoxic glutamate release. Excess calcium influx activates destructive enzymes, leading to neuronal death and lasting cognitive deficits.⁶ The second hit, reperfusion injury, occurs after ROSC (Return of Spontaneous Circulation) and can unfold over hours or days. Sudden oxygenated blood triggers reactive oxygen species, oxidative stress, and inflammation (TNF- α , IL-6), which further damage brain tissue and the blood-brain barrier. This secondary injury often contributes more to long-term neurological deficits than the initial ischemia.⁶

Current Approaches to Neurological Prognostication Post-OHCA

Pre-ROSC Factors

The first few minutes after cardiac arrest are crucial for a patient’s neurological outcome. For shockable rhythms such as ventricular fibrillation, the time to defibrillation is a very strong predictor of survival and good neurological function. Studies have shown that every minute of delay to the first shock significantly reduces the chance of a successful outcome.⁷

The promptness and quality of bystander CPR are also reliable predictors of a positive neurological outcome.⁸ Effective chest compressions can maintain some blood flow to the brain, lessening the impact of the first “hit” of hypoxic-ischemic injury. The total “downtime,” which is the time from cardiac arrest to ROSC, is a combined measure

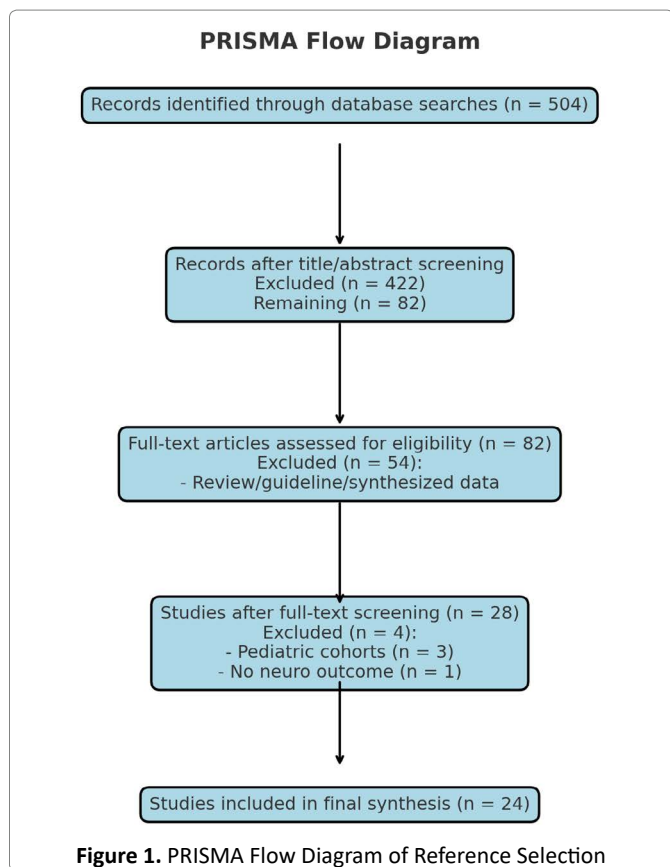


Figure 1. PRISMA Flow Diagram of Reference Selection

Table 1. Summary of Characteristics for Included Studies

Prognostic Factor	Study Design	Setting	Notes	Reference
Pre-ROSC: Time to defibrillation & CPR quality	Observational cohort / registry studies	OHCA	Shockable rhythms; shorter downtime and prompt, high-quality CPR linked to better neurological outcomes	7, 8, 9
Post-ROSC: Targeted temperature management (TTM)	RCT/ observational	ICU	Preventing fever >37.5 °C beneficial; aggressive cooling <33 °C not consistently advantageous	10
Post-ROSC: Seizure management	Observational / case series	ICU	Clinical or electrographic seizures treated with antiseizure medications; routine prophylaxis not recommended	11
Post-ROSC: Oxygenation / ventilation / MAP targets	Observational / guideline-based	ICU	O2 saturation 94-98%; PaCO2 35-45 mmHg; MAP >65 mmHg; individualized targets improve outcomes	12
Neurological examination	Observational / prospective	ICU	Absence of pupillary/corneal reflexes >72h and motor response predictive of poor outcome	13
Neuroimaging: MRI-DWI/ ADC values	Observational / prospective cohort	ICU	MRI 3-5 days post-arrest; lower ADC values associated with poor outcomes	14
Serum biomarkers: NSE, Tau	Prospective cohort	ICU / Lab	NSE levels on day 3-4 strongly predict poor neurological outcome; tau protein shows promise	17
EEG	Observational / prospective	ICU	Burst suppression or status epilepticus predictive; continuous patterns indicate better outcome; interpretation expertise matters	19, 20
SSEP (N20 potentials)	Observational / prospective	ICU	Bilateral absence after 48h ROSC predicts poor outcome; adjunct to EEG	21

that shows the impact of both CPR quality and the time it takes to get to definitive care. Shorter downtime is linked to better survival and neurological recovery.^{8,9}

Post-ROSC Factors

Early post-ROSC care is crucial for reducing secondary brain injury and improving neurological outcomes. Evidence shows that TTM aimed at preventing fever above 37.5 °C is beneficial, whereas aggressive cooling below 33 °C has not consistently improved outcomes.¹⁰ Seizures are common in comatose post-arrest patients and increase brain metabolic demand; clinical or electrographic seizures are treated with medications such as levetiracetam or sodium valproate, while routine prophylaxis is not recommended.¹¹

Proper oxygenation and ventilation are essential. Oxygen saturation should be maintained at 94-98% to prevent hypoxic or hyperoxic injury, and arterial carbon dioxide at 35-45 mmHg to preserve cerebral blood flow without worsening edema. Maintaining mean arterial pressure above 65 mmHg and adjusting targets individually may improve outcomes, as many patients have impaired cerebral autoregulation. Together, these measures form the core of post-ROSC care for brain protection and survival.¹²

Neurological Examination

A comprehensive clinical neurological exam remains the foundation of prognostication. Specific signs, especially after a patient has been warmed and sedatives have worn off, are reliable indicators. The absence of pupillary light reflexes and corneal reflexes on both sides more than 72 hours after cardiac arrest is a strong sign of a poor outcome. Similarly, a motor response that is absent or shows extensor posturing is a worrisome sign. When these signs are persistent and not affected by medications or other factors, they can be a reliable predictor of poor outcomes.¹³

Neuroimaging

Neuroimaging offers invaluable information to assess the extent of brain injury. Brain MRI with diffusion-weighted imaging (DWI), done within 3-5 days after cardiac arrest, can be a moderately reliable prognostic tool.¹⁴ DWI is very sensitive to acute ischemic injury, showing areas with reduced water movement that indicate cellular damage. Quantitative analysis of DWI, using apparent diffusion coefficient (ADC) values, can further refine prognostic predictions: patients with poor outcomes exhibited lower mean whole-brain ADC values (729.1×10^{-6} mm/s) compared with those with favorable outcomes (787.1×10^{-6} mm/s).¹⁴

Serum Biomarkers

Serum biomarkers provide measurable indicators of

brain injury and are widely used to predict outcomes after OHCA. Neuron-specific enolase (NSE), an enzyme involved in glucose metabolism, and tau protein, associated with neurodegeneration, are highly specific for detecting neuronal damage.¹⁵ While tau protein is not yet part of standard clinical practice guidelines, studies have shown a strong association between elevated levels of total tau (t-tau), and sometimes phosphorylated tau (p-tau) with poor neurological outcome.¹⁶ NSE, on the other hand, has been well established as part of the standard neuroprognostication post OHCA. In a cohort of 153 OHCA survivors (mean age 64.2 years), NSE levels strongly predicted poor neurological outcome (CPC 3-5), with the highest predictive value observed on day 4 after arrest. NSE level above 20 µg/L on day 4, particularly if rising from day 3, predicted a poor outcome with 100% specificity and 73% sensitivity.¹⁷ Extremely elevated NSE (>50 µg/L) on day 4 was also associated with poor outcome with high specificity, though lower sensitivity.¹⁷ NSE levels additionally predicted 12-month mortality, with the highest accuracy on day 3.¹⁷ Despite their utility, these biomarkers are limited by availability, timing of measurement, and potential confounding from other medical conditions.

Neurophysiology

The electroencephalogram (EEG) is another widely used tool for predicting outcomes. This non-invasive method records the electrical activity of the brain, providing data for analysis.¹⁸ Highly abnormal EEG patterns, such as burst suppression or status epilepticus, done 72 hours after ROSC, without other confounders like sedation or hypothermia, are considered reliable indicators of a poor outcome, while more normal patterns with continuous background activity often predict a better neurological outcome.¹⁹ In expert hands, EEGs provide invaluable prognostic insights in the ICU, yet their reliability is often overestimated due to institutional expertise and inter-reader variability.²⁰

Additionally, somatosensory evoked potential (SSEP) tests, which measure electrical signals in the spinal cord and brain in response to a sensory stimulus, are commonly used as adjunctive tests in OHCA comatose patients. N20 potential is the best studied and obtained after applying stimulus to the median nerve. They can add value in prognostication in patients with unfavorable EEG patterns. Bilateral absence of N20 potentials done after 48 hours of ROSC are considered an indicator of poor outcomes.²¹

Discussion

In this review, we propose the WEMuV framework to guide neuroprognostication of comatose survivors after OHCA (Figure 2). The first step, Wait (W), emphasizes postponing prognostic evaluations for at least 72 hours in patients without TTM, or 72 hours after rewarming to 36 °C in those treated with TTM. The second, Exclude (E),

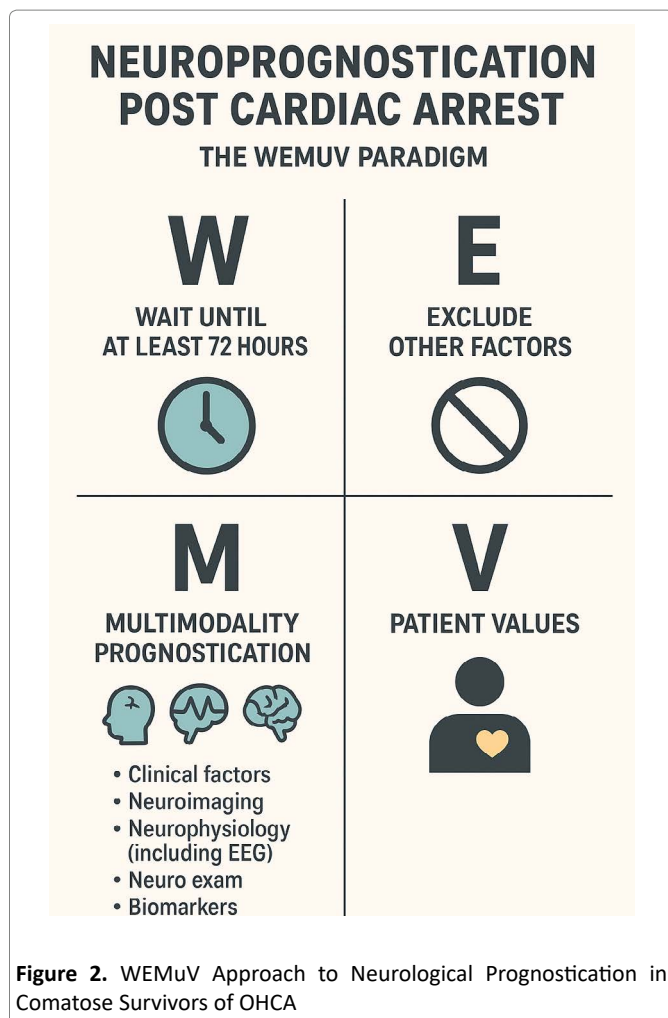


Figure 2. WEMuV Approach to Neurological Prognostication in Comatose Survivors of OHCA

recommends eliminating confounders such as sedative or toxic drug effects, electrolyte disturbances, hypothermia, or other metabolic derangements, as these can confound neurological assessment. Delayed recovery may occur once such disturbances are corrected; in fact, 29% of survivors who ultimately awoke did so more than 48 hours after rewarming and cessation of sedation.²² The third component, Multimodality (Mu), highlights the need to integrate multiple prognostic domains, including clinical and demographic factors (age, initial rhythm, downtime, access to timely resuscitation and defibrillation, vasopressor requirements), neurophysiological modalities (EEG, SSEPs), standardized neurological exams, neuroimaging, and biomarkers such as NSE. No single parameter is definitive; all must be interpreted together, accounting for interactions and limitations. Finally, Values (V) underscores incorporating patient-specific considerations such as comorbidities, life expectancy, and preferences about quality of life. Integration of these elements ensures prognostication is evidence-based, ethically sound, and patient-centric.^{5,23}

Artificial intelligence (AI) offers a promising avenue for improving neuroprognostication. Machine learning

can analyze large patient datasets, including biomarkers, EEG patterns, and clinical history, to detect patterns not apparent to standard methodologies. Models trained on thousands of records can link age, cardiac arrest duration, EEG features, and NSE levels to generate comprehensive risk assessment algorithms. This approach can improve prediction accuracy and guide individualized treatment plans, supporting families in decisions about continuing or withdrawing life-sustaining therapies.²⁴

Conclusion

Despite major advances in cardiopulmonary resuscitation and post CA care, death and major neurological injury-related morbidity and disability after OHCA remain significant and stubbornly unchanged over the decades. As illustrated by the “two-hit” model, the underlying pathophysiological processes are complex and vary greatly among individuals. This review highlights the importance of a multimodal approach for neurological prediction and shared decision making for counseling. The emerging technologies such as artificial intelligence and large language models also bring promise to enhance the predictive accuracy of existing prognostic tools. The proposed WEMuV model offers a focused guidance on multimodality prognostication.

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